

YOUR BRAIN FN F D

How Chemicals Control Your Thoughts and Feelings

Third Edition

GARY L. WENK

YOUR BRAIN ON FOOD



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on

FOOD

HOW CHEMICALS CONTROL YOUR
THOUGHTS AND FEELINGS

Third Edition

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For Jane

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PREFACE

Various writers throughout the past century have compared the human brain to an elegant machine. Imagine that this machine is full of wires and that the wires are different colors. Some are blue, some are red, some are green, and so on, but they all convey information from one part of the machine to another. Now imagine that the blue wires are organized differently than the red wires, that the red wires are organized differently than the green wires, and so on. If you were to look inside your brain, you would discover that although its pathways are organized like the colored wires in your telephone or computer, it does not actually use wires at all but instead uses cells, or neurons, to process information: One neuron is connected to the next and to the next, and so on. Indeed, this

elegant machine, your brain, is composed of approximately 100 billion neurons, and within a single structure, the cortex, these neurons make an estimated 0.15 quadrillion connections with each other. These billions of neurons are not uniquely colored, but they do release unique chemicals, called neurotransmitters, onto each other. What happens when molecules of a foreign substance—for example, a drug or a morsel of food—interact with the balance of neurotransmitters in this chemical soup? The balance of flavors in this soup will determine what happens to you.

The major point that I make in this book is that anything you consume—the drugs you take, the foods you eat—can affect how your neurons behave and, subsequently, how you think and feel. In the course of illustrating this point, I examine what neuroscientists currently know about the actions of specific drugs and food in the brain and seek to advance your understanding of your own brain by demonstrating how its workings can be altered by what you “feed” it. I describe several neurotransmitter systems, including their basic role in the brain, and explore how various substances—be they plant extracts, nuts, mushrooms, spices, chocolate, or medicinal and recreational drugs—can influence these neurotransmitters in terms of their production, their release from the neuron, and their ultimate inactivation and excretion from the body. I also discuss the brain’s role in certain experiences—for example, hallucinations, religiosity, pain, and the aging process—and the extent to which these experiences are influenced by what we consume. In

addition, I consider the role of evolution in determining the brain's responses to the food and drugs that we consume and place the use of some of these substances in cultural history.

The brain contains more than 100 known, or suspected, neurotransmitter chemicals and probably many more that scientists have yet to discover. I have chosen to focus on those neurotransmitter systems most commonly associated with the psychoactive effects of drugs and nutrients that, in many cases, are regularly consumed today.

This book is intended not as an exhaustive review of all that is known about the topic of food and drugs and the brain but, rather, as a brief—and, I hope, enjoyable—introduction to it. By the end of the book, you will know more than just how a select group of drugs or food works in your brain; you will be able to predict how substances that I did not discuss, and those that have not even been discovered yet, might also affect your brain. Even better, you may look back on the chapters you have read and discover that they are much too simplistic for you now and that you want to learn more about greater complexities of brain function than this book covers. If reading this book motivates you to learn more about neuroscience and its associated topics, then I will have succeeded in my goal to advance your understanding of your brain. The suggested readings that I have listed at the end of the book offer an excellent next step in that advancement.

This book could not have been written without the encouragement and generosity of my mentors, colleagues, family, and

friends—particularly David Olton, who patiently motivated my curiosity in the effects of drugs on the brain; James McGaugh, who inspired my interest in behavioral pharmacology; Giancarlo Pepeu, who has continued to nurture my interest in the role of drugs in the history of culture; Peabo Bryson, a man with an exquisite voice who challenged me to explore the role of neuroscience in religion; Paul Gold, for the many perspicacious discussions on the Utah slopes; and Jacqueline Crawley, for her boundless enthusiasm and stimulating insights into the function of the brain. Their wisdom helped focus my fanciful ideas into rational theories. The insights are theirs; the errors are mine.

I will always be grateful to Joan Bossert and Catharine Carlin at Oxford University Press for their unflagging support and optimism at every step of this long journey. I also feel very privileged to have worked with Marion Osmun, a brilliant and talented editor, who provided a nurturing combination of advice and encouragement. I am also grateful to the thousands of students who have taken my psychopharmacology classes and whose personal stories enliven these pages.

During every stage of the writing, the text benefited immeasurably from the wonderful editorial suggestions of my wife, a woman of unrivaled intelligence and uncommon patience. She shaped my concept of my audience and how to reach them and skillfully converted my jargon into intelligible prose. I have learned to trust her judgment and insight more than my own; if there is wisdom in my writing, it has evolved under her guidance. This book is dedicated to Jane.

CHAPTER I

FOOD, DRUGS, AND YOU

A long time ago, our ancestors discovered that ingesting some plants or the body parts of certain animals produced effects that were rather unpleasant or even lethal. Reference to these substances appeared in a collection of prayers of comfort for the dying and referred to a type of spiritual medicine, at the time called a *pharmakon*, that was used principally to alleviate suffering near the end of life. Simply stated, a *pharmakon* was a poison. Originally, the term *pharmakos* (φάρμακος) referred to a human scapegoat who was sacrificed, sometimes literally by poisoning, as a remedy for the illness of another person, usually someone far more important in the local society. Later, around 600 BCE, the term came to refer to substances used to cure the sick. It is, of

course, related to two terms in use today: *pharmacology*, the scientific investigation of the mechanisms by which drugs affect the body, and *psychopharmacology*, the study of the effects of drugs on the brain—effects that in turn are defined as “psychoactive.”

This book explores not only several drugs but also a range of foods with these effects. In fact, the single unifying property of these substances is that they are all psychoactive in some way, which means they can affect your brain and therefore your behavior. By the end of the book, I hope that you will appreciate that the distinction between what is considered a drug (i.e., something that your brain wants or needs to function optimally) and food (i.e., something that your body wants or needs to function optimally) is becoming increasingly difficult to define. Indeed, the routine use of some substances, such as stimulants and depressants, is so universal that most of us do not even consider them to be drugs but, rather, actual food. Is coffee, tea, tobacco, alcohol, cocoa, or marijuana a nutrient or a drug? For many people, the distinction has become rather blurred. I suggest that anything you take into your body should be considered a drug, whether it is obviously nutritious or not. As you will see, even molecules that are clearly nutritious, such as chocolate or essential amino acids like lysine and tryptophan (which can be purchased in any grocery store today), exhibit properties that many of us would attribute to a drug.

PLANTS ARE THE SOURCE OF FOOD AND DRUGS: WHY?

The foods we eat and many of our most popular psychoactive drugs often come from plants. Humans consume plants, either directly in their natural form or after they have been transformed into the flesh of a vertebrate, such as a cow, pig, or bird. This book discusses how the contents of plants directly or indirectly influence our brains. We all intuitively know that what we eat can alter how we feel. Nutritional neuroscientists and psychopharmacologists have been investigating the mechanisms that underlie how the contents of plants specifically alter brain chemistry and thus brain function. Basically, plants contain chemicals that are nutritious, psychoactive, or both. That is why the title of this book is *Your Brain on Food*. Everything that humans consume can, and often does, affect brain function in subtle and profound ways and influences how we think and feel.

Why do plants have such profound effects upon us? Are plants trying to control humans? After reading the chapters on tobacco and caffeine, you might conclude that plants have almost succeeded in taking over the world. In truth, plants have no interest in humans at all. For the past 100,000 years since the origin of our species, we have been, and will likely remain despite our role in global warming, almost entirely irrelevant to them.

Earth is home to more than 1 trillion different species; invertebrates such as insects, spiders, and mollusks make up

80% of all of those species, and plants make up approximately 17%. In terms of the number of species and total biomass, plants and insects are the dominant two species on the surface of the planet (single-celled organisms are the dominant species in Earth's crust). For the past 400 million years, plants and insects have had a complicated symbiotic relationship: Plants both need the insects for their own survival and procreation and also must avoid being eaten by the insects. The problem for plants is that they are not mobile; they cannot simply run away from the bugs or swat them with a limb. Their solution has been to produce a large variety of chemicals to influence the insects' behavior to serve the needs of the plants. These chemicals are called secondary metabolites because they do not play a primary role in a plant's own biological processes related to its own daily existence—they are produced simply for the plant's interactions with insects. Plants do not produce these secondary metabolites for our benefit or entertainment. Humans are simply bystanders to the tug-of-war between plants and insects; we can either benefit from their battle or become casualties.

Why do our brains respond so profoundly to the chemicals in plants? To discover the answer, we need to go back in time to approximately 1.3 billion years ago when the last common ancestor of both plants and animals lived on the planet. Humans and plants still share more than 3,000 genes that are critical to our survival that were bequeathed to us by this creature. This shared genetic message due to a shared evolutionary history

explains why our human brains respond to the contents of plants. Plants, insects, and human brains all produce and utilize chemicals that are the basis for the chapters that follow, including acetylcholine, dopamine, serotonin, γ -aminobutyric acid, glutamate, opiates, and prostaglandins. Human brains synthesize many of the same psychoactive chemicals that exist in plants, including morphine and the hallucinogens dimethyltryptamine and bufotenin. All of these chemicals already existed more than 1 billion years ago in the last common ancestor of plants, insects, and humans. When we consume these ancient molecules, they can influence our brain function because of our shared genetic history.

Even primitive one-celled organisms produce many of the same chemicals that are in our brains. Therefore, whether you choose to eat a bunch of broccoli or a large pile of amoebas, the chemicals they contain may alter how your neurons function and, therefore, how you feel or think. The lowly plants, fungi, algae, and others that live at the bottom of the food chain continually convert sunlight into all of the critical nutrients, including carbohydrates, proteins, fats, and vitamins, that humans require for survival.

We have all experienced the consequences of our shared evolutionary history with the plants we eat. For example, unripe bananas contain high levels of the neurotransmitter serotonin. When you eat an unripe banana, its serotonin is free to act upon the serotonin neurons within your intestines. The consequence is likely to be increased activation of the

muscles in the wall of your intestines, usually experienced as diarrhea. Plants are not the only source of chemicals that can act upon your brain. The fact that you share an evolutionary history with insects and reptiles also underlies the ability of venoms, which often also contain serotonin, to produce the unpleasant effects you would feel if you were stung by a bee or bitten by a snake. Our shared history with plants and animals on Earth leads to some interesting predictions. For example, consider the following science fiction scenario: A spaceman is walking on an Earth-like planet and is suddenly bitten by an unfriendly and grizzly looking creature. The spaceman can see that he is injured and that a liquid substance was injected under his skin by the beast. Does he die? No, he does not die because his species and that of the creature on this foreign planet do not share an evolutionary past or a common ancestor. Although their amino acids might have first evolved in space, as is now believed, since that distant time, their independent evolutionary paths have made it highly improbable that they use similar neurotransmitter molecules within their respective brains and bodies. Thus, every spaceman, from Flash Gordon to Captain Kirk and Luke Skywalker, should feel safe walking around any planet (except their own) with impunity from animal and plant toxins. For this same reason, the intoxicating drinks and powerful medicines that always seem to be popular in these foreign worlds in science fiction movies would also be completely without effect on the brains of our plucky spaceman.

DRUGS AND THE ORGAN OF THE MIND

Back on Earth, people in ancient cultures were certainly very aware of the unique properties of certain plants and of the consequences of consuming them on the body and brain; indeed, they often sought them out as remedies for a variety of physical illnesses. This ancient use of plant extracts as medicines was also likely the beginning of a long series of upheavals in our concept of how the brain functions and what its role is as the organ of the mind. For millennia, people believed that mental illness was caused by evil spirits or was a punishment delivered by an angry deity rather than as the result of a brain disease or dysfunction, as we now realize. Only comparatively recently, in the mid-20th century, have effective drugs been introduced for the treatment of mental illness. The realization that it might be possible to treat mental illness in the same way that one treats physical illness—that is, medically—was slow to gain general approval in part because of the wide-ranging, and for some still quite frightening, implications about what this meant regarding the nature of the human mind. What if all mental activity is biochemical in nature? What if our cherished thoughts, such as of God, and our deepest emotions, such as love, are simply the result of biochemical reactions within one of the organs of our body? What does this say about the soul or romance? Will we one day have drugs to treat the broken soul or the broken heart similar to the drugs we use now to treat serious mental illness? It is probably not too farfetched to expect that yes, in the future,

drugs will be invented to enhance our romantic urges (Viagra aside) and assist our communication with our deity of choice. Our grandchildren will likely have a whole host of drugs to enhance a broad range of mental functions.

In fact, we already do have a vast pharmacopeia, legal and otherwise, that affect the brain and no end of debate about their value and effectiveness. This leads me to several basic principles that apply to any substance you ingest that might affect your brain.

First, these substances should not be viewed as being either “good” or “bad.” Drugs and nutrients in your diet are simply chemicals—no more, no less (see Figure 1.1). They have actions within your brain that you either desire or would like to avoid.

Second, every drug has multiple effects. Because your brain and body are so complex and because the chemicals you ingest are free to act in many different areas of your brain and body at the same time, they will often have many different effects—both direct and indirect—on your brain function and behavior.

Third, the effect of a drug or nutrient on your brain always depends on the amount consumed. Varying the dose of any particular drug changes the magnitude and the character of its effects. This principle is called the dose–response effect—that is, in general, greater doses lead to greater effects on your brain, although sometimes greater doses produce completely opposite effects of those with low doses. For example, aspirin reduces body temperature when taken at normal therapeutic doses but increases body temperature when taken at high doses.

Finally, the effects of a drug on your brain are greatly influenced by your genes, the nature of the drug-taking experience, and the expectations you have about the consequences of the experience. For example, if you respond strongly to one drug, you are likely to respond strongly to many drugs, and this trait is likely shared by at least one of your parents.

Sometimes the contribution of your genes to your drug experience can be dangerous. One young man in my class wanted to pledge to a popular fraternity, but he was rather awkward socially and had trouble making friends. He began attending fraternity parties, and against the warnings of his parents, he started drinking alcohol and smoking marijuana. He reported that he became paralyzed after he drank alcohol. It was an odd paralysis that would disappear after a few hours. In the meantime, other students at the party would place his limbs in odd positions, where they remained until the paralysis passed. I asked a physician friend about his condition and learned that the student had probably inherited a disorder of alcohol metabolism. His body converted alcohol into a derivative that was quite toxic to his muscles and so irritating to them that they produced a tightened grip on his body. If he had continued drinking alcohol, then the cellular debris from his degenerating muscles would slowly have collected inside his kidneys, causing them to fail as well. The interaction of his genes and alcohol was going to have devastating effects on his health if he did not quickly change his behavior. There are at least two lessons we can take from this student's nearly disastrous experience. First,

get to know your genetic history—you might have some hidden surprises waiting to be uncovered. Second, sometimes, a little basic knowledge about how the things we consume can affect our bodies can actually save our lives.

REALLY BASIC NEUROSCIENCE AND PHARMACOLOGY

Just how food and drugs affect the brain is the focus of this book, and in subsequent chapters, I provide you with details underlying the specific mechanisms involved in this process. But to ground that discussion, here I present some very basic anatomy and brain chemistry so we can examine the key mechanisms involved in brain–drug interactions.

Why are our brains located in our heads? Wouldn't they be safer if they were deep in our chest, similar to the location of our hearts? Brains, regardless of how small or simple, have evolved at the best possible location to perform their principal function: survival of the individual and the species. For the past 600 million years, since they first appeared in a single-celled common ancestor of the human and *chronoflagellate*, brains have always been located at the front end of the feeding “tube,” which in humans and many other organisms is the tubular system (the alimentary canal) that extends from the mouth to the anus. Worms, fish, birds, reptiles, dogs, and you—all simple feeding tubes. Your brain makes it possible for you to find food by sight, sound, and smell and then to organize your behavior so that the front end of your feeding tube can get close enough to taste the

food and check it for beneficial or potentially harmful contents before you ingest it. Once the food is in your feeding tube, it is absorbed and becomes available to the cells of your body. Your entire feeding tube and associated organs, also known as the gastrointestinal system, use nearly 70% of the energy you consume just to make the remaining 30% available to the rest of your body. Your brain uses approximately 25% of the available consumed energy, and your other organs that allow you to reproduce and move around your environment (including your muscles and bones) utilize approximately 15%. As you can see, very little energy is left over for other tasks in the body. These percentages give you some idea of the priorities—thinking, sex, and mobility—that billions of years of evolution have set for your body to achieve.

THE EVOLUTION OF THE GUT–BRAIN RELATIONSHIP

Brains use a lot of energy, and with the evolution of bigger brains, organisms depended on building longer feeding tubes in order to optimize the extraction of more energy from whatever entered the front end of the feeding tube. For mammals, the length of the gut is significantly correlated with the total body mass as well as with the size of the brain. Over time, as the relative size of the brain became larger compared to total body size, the forces of evolution changed strategies and developed a more efficient and shorter feeding tube that relies on a high-quality diet (after all, the gut can only be increased

in length until there is insufficient room to contain it). There were also some significant genetic changes in the expression of some gut enzymes that allow us to extract more energy from our diet. Despite these modifications in the gut, a study of more than 100 different mammals did not find any correlation between the size of the brain and the length of the gut. Surprisingly, there is a negative correlation between brain size and total body fat, except for humans. Therefore, humans have a big brain, a relatively low mass of body fat (except for modern humans consuming the standard Western diet), and a gastrointestinal system that is fairly efficient at extracting energy for itself and its principal customers—the reproductive system and the brain. But there was a surprising trade-off during evolution: As brains became bigger, reproductive success failed. One might predict that having a larger brain would allow greater reproductive success. After all, you would expect that animals with bigger brains would find more food, avoid predators more successfully, and find more mates. This prediction is based on the assumption that bigger brains are smarter, but this is not always the case. Animals with smaller brains and bodies often demonstrate impressive cognitive abilities, whereas some large-brained species do not. The critical factor is not size but, rather, the sophistication of the wiring between individual neurons.

The primate body spends nearly 25% of its food budget on brain metabolism compared to only approximately 5% spent by most other mammals. Our brains use most of this energy

to organize our behavior to socialize with others in our species in order to find a mate with whom to reproduce. That is our inherent biological imperative, regardless of whether or not everyone responds to it. You know one manifestation of this imperative as dating, and it requires a very large and complex brain to pull this off successfully. Meanwhile, your brain has evolved some interesting neurotransmitter chemicals that allow you to enjoy dating—two, in particular, are dopamine and an opium-like chemical. Both play a critical role in rewarding your brain—and, therefore, you—for consuming high-calorie food, such as the quintessential dating meal of cheeseburgers and French fries at the local diner, and for having sex, often the quintessential dating result. Eating and having sex are obviously excellent ideas if your purpose is to maintain and propagate your species. But these two neurotransmitters, as you will learn in later chapters, play a larger role in allowing you to experience happiness or euphoria through various behaviors, whether you are eating donuts, having sex, or shooting heroin.

Let's return to the anatomy lesson. At this point, you need only appreciate that your brain is composed of neurons and some supporting cells, called glia. If you were to extract a very small cube of brain tissue (Figure 1.1b), you would find it densely packed with cells, blood vessels, and very little else. The neurons are organized into columns of cells and small gatherings, called nuclei or ganglia, which tend to be involved in related functions. For example, some ganglia control movement, some control body temperature, and some control your mood.

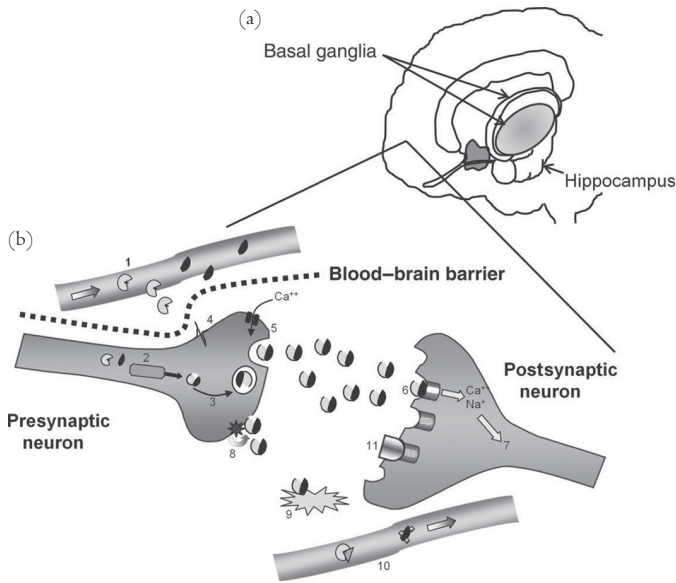


Figure 1.1 The anatomy of a few brain regions that are discussed later in the book (a). How individual neurons communicate with each other (b).
See text for details.

Overall, your brain is organized so that the back half receives incoming sensory information and then processes and organizes it into your own very personal experience of the here and now. The front half of your brain is responsible for planning and movement, usually in response to some important incoming sensory stimulus, such as someone's voice telling you that it is time for dinner. You hear the voice, smell the aroma of food cooking, feel a craving for food as your blood sugar levels fall, sense that it is late in the day and the sun is setting, and so on; thus, it must be dinnertime. This information is funneled into the front of your brain, which then makes a decision to move

the front end of your feeding tube toward the smell and the voice to obtain a reward—the food and survival for another day!

To facilitate the process between your sensing the external world and deciding how to interact with it and to elicit useful behaviors that will improve your chances of survival, propagate your species, and make you happy, the neurons in your brain must communicate with each other. They do this mostly by releasing neurotransmitters onto each other, including the two neurotransmitters just mentioned as well as others that will be introduced soon. Most of them can be found in just about every brain structure. Moreover, their function depends entirely on the function of the structures in which they are located.

Let's consider a few examples. First, find the basal ganglia in the center of Figure 1.1a. The nuclei that compose the basal ganglia are responsible for allowing normal movement. The level of the neurotransmitter dopamine in these nuclei is much higher than in most surrounding brain regions. Therefore, scientists have concluded that dopamine within the basal ganglia is involved in the control of movement. Furthermore, if we expose your brain to a drug that impairs the function of dopamine or the neurons that produce and release it, then your ability to move will be impaired. But it would be incorrect to assume that dopamine is always involved with movement—it is not. You can also find dopamine in the retina of your eye and in your hypothalamus, structures that have nothing to do with movement. Similarly, the neurotransmitter norepinephrine can be found in the hippocampus, a structure critical for forming new

memories. Thus, norepinephrine influences the formation of memories. But norepinephrine also plays a role in other brain regions that have nothing to do with making memories. The takeaway point is that there is no such thing as a specifically unique “dopamine function” or an exclusively distinct “norepinephrine function.” The brain region in which the neurotransmitter is found defines its function, not the neurotransmitter itself. In fact, neurotransmitters exhibit a complex array of actions in different brain regions, and so we can rarely make a single universal statement about their role in brain function.

Neurotransmitters are produced in our brains from the contents of our diets by means of a many-step process. First, nutrients (labeled 1 in Figure 1.1b), such as amino acids, sugar, fats, and peptides (strings of amino acids bound together), are extracted and absorbed from the food we eat and are transported out of the arterial blood supply to the brain—that is, they are actively carried through the blood–brain barrier and transported into the neurons. Enzymes (labeled 2) convert these nutrients into different neurotransmitters. The neurotransmitter molecules are then actively transported into synaptic vesicles (labeled 3), or very tiny spheres with hollow centers into which approximately 10,000 molecules of a typical neurotransmitter can be stored for later release from a neuron.

The arrival of an electrical signal (labeled 4 in Figure 1.1b) then initiates a series of further steps. This electrical signal is called an action potential. It is a very small electrical disturbance that moves quickly along the axon away from the cell

body. The axon is a long, straight extension of the neuron that carries the action potential and allows one neuron to communicate with other neurons. Axons are rather like electrical wires that connect the different parts of the brain. The arrival of the action potential at the end of the axon induces the entry of calcium ions, which initiate the next step in the communication of one neuron with the next: A synaptic vesicle merges into its cell wall (imagine two soap bubbles coming together) and releases (labeled 5) the neurotransmitter into a very small space between neurons, called a synaptic cleft. The junction at which two neurons communicate via the release of a neurotransmitter molecule is called a synapse. The neurotransmitter molecule briefly interacts or binds with a protein, called a receptor (labeled 6), on the surface of the neuron on the other side of the synapse. One consequence of this binding action is that some ions, such as calcium (Ca^{2+}) or sodium (Na^{+}), move into the downstream neuron to induce secondary biochemical processes (labeled 7), which may have long-term consequences on the neuron's behavior.

Meanwhile, after interacting with the receptor, the actions of the neurotransmitter must be terminated by means of its reabsorption (labeled 8 in Figure 1.1b) back into the neuron that originally released it. This is called reuptake. A secondary method of neurotransmitter inactivation is by local enzymes (labeled 9) into a chemical that can no longer interact with the brain. Once the neurotransmitter is enzymatically inactivated, it is removed from the brain into the bloodstream (labeled 10).

Such by-products of the ordinary hustle and bustle of the brain can be easily monitored in many of our body fluids, and this information can be used to determine whether our brains are functioning normally.

Drugs and the contents of our diet can interact with any of these various processes and impair, or even sometimes enhance, the production of neurotransmitters, as well as impair their storage into synaptic vesicles, alter their release from neurons, modify their interaction with receptor proteins (labeled H in Figure 1.1b), slow their reuptake, and possibly even stop their enzymatic inactivation. Because your brain is the organ of the mind, drugs and foods that do any of these things can have a profound influence on how you think, act, and feel.

How do drugs and chemicals in our diet actually affect our brains? Most influence the transmission of chemical signals between neurons. The part of your brain or body in which a chemical acts to produce its effect is called its “site of action.” The behavioral effects of a chemical can provide clues to its site of action within your brain. For example, nutrients or drugs that affect your sleep or your level of arousal usually alter activity of neurons within a region of your brain called the brainstem-activating system. Another clue to a drug’s site of action is provided by the unequal distribution of neurotransmitters in the brain. For example, as mentioned previously, dopamine is highly concentrated in the basal ganglia, a part of the brain that controls movement. Therefore, drugs that affect the dopamine system often impair movement.

Why do some chemicals in our diets affect our brains and how we feel while others have no effect on us? Many drugs or nutrients that might potentially influence brain function are never able to enter the brain because of the presence of a series of barriers, the most important of which is the blood–brain barrier. This barrier allows the easy entry of drugs that are lipid (fat)-soluble and restricts the entry of drugs that are water-soluble. Because the brain is composed of so many lipids, the tendency of a drug to dissolve into lipid and water phases of the brain tells us much about how a drug achieves its effects. Very lipid-soluble drugs enter the brain rapidly; they also tend to exit rather rapidly, which reduces the duration of their action. Some familiar examples of lipid-soluble drugs are the vitamins A, D, E, and K. Nicotine and caffeine are also quite lipid-soluble and enter the brain easily; if they did not, then it is highly unlikely that anyone would abuse them. Take a moment to appreciate how this fact has been an incredible boon to the evolutionary success of tobacco and coffee plants: Their discovery by our species led to their widespread cultivation and protection as two of the most important plants on Earth.

Once a drug has entered the brain, what happens next? Most of the time, the site of action is a receptor protein, which floats on the surface of a neuron. Chemicals that bind to receptors and produce a reaction by the neuron are typically called agonists; chemicals that bind to receptors and effectively block the action of a neurotransmitter or agonist are called antagonists. In other words, agonists usually stimulate a response from the

neuron, and antagonists usually prevent or reduce the response of neurons. These two terms are used frequently throughout this book.

Some chemicals that you might consume are never completely metabolized or inactivated after they have entered your body and are therefore available to re-enter your brain and continue to affect brain function. In contrast, some chemicals that you ingest are actually metabolized by your body into quite powerful psychoactive drugs. For example, a small percentage of the codeine in cough syrups is converted into morphine, a far more powerful painkiller; psilocybin, from the hallucinogenic mushroom of the same name, is converted into the equally hallucinogenic psilocin; and heroin is inactive in your brain and must be converted into morphine before it can produce its euphoric effects. Usually, however, a drug is converted by enzymes to make it inactive in your brain and body and is subsequently excreted in the urine, feces, sweat, breast milk, or expired air from the lungs.

Sometimes the effects of some chemicals are present for so long that the brain slowly adjusts to their presence. Over time, the brain acts as though the drug or nutrient had become a necessary component of normal brain function. You experience your brain's adjustment to the eventual absence of this substance as craving.

CRAVING AND ADDICTION

What does craving feel like? Consider, for example, the very powerful drug sugar. Your brain needs sugar (usually in the

form of glucose) to function normally. The many billions of neurons in your brain require a constant supply of glucose to maintain their ability to produce energy and communicate with other neurons. These neurons can only tolerate a deprivation of glucose for a few minutes before they begin to die. Therefore, as blood levels of sugar decrease with the passage of time since your last meal, you begin to experience a craving for food, preferably something sweet. The presence of sugar in your brain is considered normal, and its absence leads to the feeling of craving and the initiation of hunting or foraging behaviors, such as seeking out a vending machine for a Hershey bar. If you wish to experience the truly overwhelming and powerful nature of drug craving, stop eating for a full day.

A second, and far less familiar, example of craving is the response of the brain to long-term exposure to the drug amphetamine. This drug increases the release of the neurotransmitters dopamine, norepinephrine, and serotonin from neurons. The constant presence of these neurotransmitters within the synapse modifies the number and behavior of neuronal protein receptors. Over time, and with daily exposure to amphetamine, the behavior of various neurons may change in profound ways. These compensatory changes partly explain why people who use amphetamine often require increasingly larger amounts of the drug to experience a consistent feeling of euphoria. After a few hours, when amphetamine levels in the brain decrease, the individual experiences a lack of euphoria, or dysphoria, which is experienced as depression and a craving for the return of

amphetamine back into the brain. The brain, in short, craves chemicals that it “thinks” it needs to function normally; continued craving is called an addiction.

The constant consumption of caffeine, nicotine, or almost any chemical can produce similar types of compensatory changes within your brain and lead to craving with their absence from the brain. This kind of response is exactly what your brain evolved to do for you: Its purpose is to be flexible and learn how to survive—to be plastic or adaptive to a changing environment and to the variety of chemicals that enter your feeding tube. When this situation of “normalcy” is lost because of the absence of something that your brain has become accustomed to having regularly available (e.g., sugar, amphetamine, or anything else that you are accustomed to consuming), your brain reacts by creating in you the urge to replenish its supply. You experience this feeling as craving, regardless of the legality, safety, or cost of the substance being craved.

Craving is also associated with another interesting expression of brain function. The removal of a drug or a chemical from the brain is frequently accompanied by biological and behavioral changes that are opposite those produced by the drug: This is rebound. I like to say that the brain always “pushes back.” For example, the rebound from the euphoria induced by the stimulants cocaine and amphetamine is the depression that follows once the drugs have left the brain. This interesting brain response is apparently only unidirectional. What I mean by this is that we often observe depression following stimulant-induced

euphoria, but we never see euphoria as part of the rebound experience following use of depressants such as alcohol and barbiturates. No one ever experiences happiness as part of a hangover from a night of binge drinking.

Many biological factors, such as age and weight, play a crucial role in the way that drugs affect the brain and influence behavior. So, too, does the unique neural circuitry that you inherited from your parents and that sometimes influences whether a drug will be exciting or depressing to you. This concept was probably best described as the law of initial value, which states that each person has an initial level of excitation that is determined by his or her genetics, physiology, sickness or health status, drug history, and environmental factors; the degree of response to a psychoactive drug depends on how all of these factors affect one's current level of excitation or melancholy. For example, patients suffering from pain, anxiety, or tension experience euphoria when they are given small doses of morphine. In contrast, a similar dose of morphine given to a happy, pain-free individual often precipitates mild anxiety and fear. If you have a fever, aspirin lowers your body temperature, but aspirin cannot cool your body on a hot day—you must first have the fever for it to work. Coffee produces elation and improves your ability to pay attention if you have been awake for a long period of time or had poor sleep the night before; in contrast, the same dose of coffee is likely to produce much less arousal if you are well rested. Catatonic patients may respond with a burst of animation and spontaneity to an intravenous

injection of barbiturates, whereas most people would simply fall asleep. Sedative drugs create more anxiety in outgoing, athletic people than they do in introverted intellectual types.

The law of initial value is a fascinating concept worthy of additional discussions that are beyond the scope of this book. Indeed, the various basics of neuroscience and pharmacology just summarized barely scratch the surface of all that has been learned throughout the years about the brain and its response to the food and drugs we consume every day. The chapters that follow build on these basics to examine the intersection of brain and body chemistry and the co-evolution of our gut and brain within our changing culture. Along the way, some of the major neurotransmitter systems are examined in detail, including those shown in Figure 1.2.

Almost everything you choose to consume will directly or indirectly affect your brain. Obviously, some things we consume affect us more than others. I assume that spices, plants, animal parts, drugs of any kind, coffee, tea, nicotine, and chocolate are all just food, and I define food as anything we take into our bodies, whether it is nutritious or not. In order to better understand how food and drugs affect the brain, it is helpful to divide them into three categories.

First, there are chemicals we consume in high doses with acute dosing—for example, coffee, sugar, heroin, alcohol, nicotine, marijuana, some spices, and a few psychoactive plants and mushrooms. Their effects are almost immediate and depend on how much reaches the brain. In this group, the most important

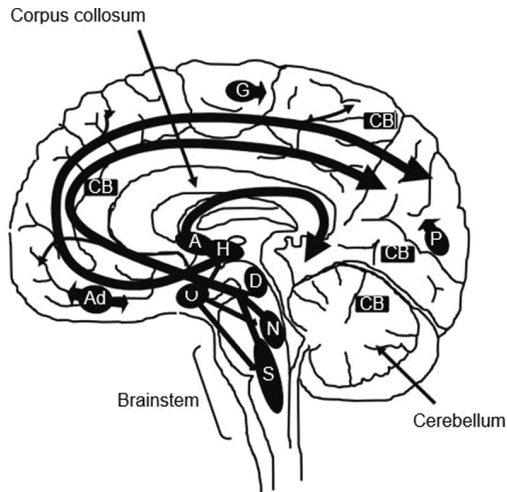


Figure 1.2 Schematic anatomy of neurotransmitter systems. A, Acetylcholine neurons mostly originate within the basal forebrain region and project to the cortex, hippocampus, amygdala, and olfactory bulbs. Ad, Adenosine can be released by virtually every cell in the brain. CB, Cannabinoid neurons are scattered throughout the brain and cerebellum. D, Dopamine neurons originate within the midbrain and project into the basal ganglia and frontal lobes. G, GABA neurons are found throughout the brain as small interneurons and also project from one brain region into another. H, Histamine neurons mostly lie near the bottom of the brain and project diffusely into most brain regions. N, Norepinephrine neurons originate within the locus coeruleus in the floor of the fourth ventricle, under the cerebellum, and project virtually everywhere in the brain. O, Orexin neurons project onto acetylcholine, dopamine, histamine, serotonin, and norepinephrine neurons to promote wakefulness. P, Peptide-containing neurons tend to be diffusely scattered, although there are notable exceptions. S, Serotonin neurons originate with a scattered group of nuclei that lie along the midline of the brainstem and project downward into the spinal cord and upward into all regions of the brain. Glutamate neurons are found everywhere in the brain; they are not represented in the figure.

consideration is to get enough of the chemical to its site of action in the brain to actually produce some kind of effect that we can notice and associate with consuming that particular food or drug.

Most of the time, this simply does not happen. For example, consider nutmeg: Low doses will be in pies next Thanksgiving, and most of us will not notice that it contains the chemicals myristicin and elemicin, which our bodies convert into the popular street drug Ecstasy. Yet, if we consume the entire canister of the spice, our guts will notice (with a terrible diarrhea), and there is a good chance that we will hallucinate for approximately 48 hours. According to my students, the experience is quite unpleasant. I will return to nutmeg and other spices later.

Second, there are foods that affect our brain slowly over a period of a few days to many weeks. This is usually called precursor loading, and it includes many different amino acids (tryptophan and lysine are good examples); carbohydrates that have a high glycemic index, such as potatoes, bagels, and rice; fava beans; some minerals (particularly iron and magnesium); lecithin-containing products such as donuts, eggs, and cakes; chocolate; and the water-soluble vitamins. The purpose of these foods is to bias the function of a specific transmitter system, usually to enhance its function in the brain. For example, scientists once thought that drinking a glass of warm milk before bed or eating a large meal of protein made us drowsy

because of tryptophan loading. Current evidence does not support this explanation, but the claim makes my major point: We must get enough of any particular nutrient or chemical to the right place and at the right dose in our brains in order for us to notice any effects. Unfortunately, tryptophan has difficulty getting into our brains, particularly when consumed within the context of a large variety of other amino acids, as are present in meat.

So, what is the scientific evidence for considering the cognitive effects of these foods? Mostly, it is related to what happens when we do not get enough of them. For example, studies have shown that consuming too little tryptophan makes us depressed and angry; historians now attribute multiple wars and acts of cannibalism to low-tryptophan diets. Too little of water-soluble vitamins (the B's and C) in the diet will induce changes in brain function that we will begin to notice after a few weeks of deprivation. Many authors naively jump to the conclusion that giving high doses of such nutrients will rapidly improve our mood or thinking. Unfortunately, this is rarely the case. Some vitamin supplementation does positively alter brain function; the few scientifically reliable examples of these benefits are discussed later. Ordinarily, the foods in this category require more time to affect our brains than do those foods in the first category.

The third category includes the slow-acting, lifetime dosing nutrients that are regularly discussed in the popular

press. This category includes antioxidant-rich foods such as colorful fruits and vegetables; fish and olive oils; fruit juices; anti-inflammatory plants and drugs such as aspirin; some steroids; cinnamon and some other spices; nicotine, caffeine, and chocolate; the fat-soluble vitamins; nuts; legumes; and beer and red wine. People who eat these foods positively benefit from consuming them regularly over their life span. The benefit derives from the fact that all these foods provide our brains with some form of protection against the most deadly thing we expose ourselves to every day—oxygen. Because we consume food, we must consume oxygen. Because we consume oxygen, we age. Thus, people who live the longest tend to eat foods rich in antioxidants or simply eat much less food. Although nicotine and caffeine prevent the toxic actions of oxygen in our brain, I am not suggesting that you should start having a cigarette with your morning coffee. However, if you are already addicted to both nicotine and caffeine, you need to weight the benefits of stopping versus the potential benefits to your brain.

You can see that depending on the way in which you frame the question about how food affects the brain, you get a different list of foods and a different reason for consuming them. If you wish to alter your current brain function or slow your brain's aging, you need to eat specific foods. In truth, most of us never consider these distinctions when eating—we just eat what tastes good. Unfortunately, our brains powerfully reward us when we eat sugar, fat, and salt; thus, we have obesity and the oncoming

epidemic of obesity-related illnesses. Consequently, like drugs, food has both negative and positive effects, depending on what you take, how much you consume, and for how long. In later chapters, I discuss the neurological mechanisms that control our urge to keep eating tasty foods.

CHAPTER 2

NEUROBIOLOGY OF FEEDING: HORMONES, OVEREATING, AND AGING

The brain receives a steady stream of varied hormonal signals about the stored energy status of the body. After careful consideration of environmental factors, such as when another food source might next be available, consideration of anticipated energy needs during that time period, and the current social situation, the brain attempts to influence food choices according to the food's nutritional value, how pleasurable it tastes, and past experience with the source—and then eating begins. But the real challenge for the brain is how to stop eating.

This decision is partly determined by how fat we are. The brain learns about this through the action of two hormones—leptin and insulin—and responds by reducing food consumption. The blood levels of insulin and leptin are continuously

elevated in the brains of obese people, but their brains ignore these hormonal signals and so eating continues. The effectiveness of these hormones is influenced by fluctuating levels of estrogen; this leads to the gender dichotomy that females are more sensitive to the appetite-suppressant action of leptin (initiated by their body fat), whereas males are sensitive to the appetite-suppressant action of insulin (induced by eating).

FEMALE BRAINS ON FOOD DO NOT FOLLOW THE SAME RULES AS MALE BRAINS ON FOOD

The brain also gets sensory feedback from the mouth and nose about the smell, taste, and feel of the food, as well as the expansion of the stomach. Unfortunately, these signals can easily be ignored by the brain—and so we keep eating. New research on how the brain gets us to stop eating has led to the development of drugs designed to reduce food intake by mimicking one or more of these feedback signals. But each time, the same thing happens—caloric intake decreases for a short time and then the brain learns to ignore the false signal so that caloric intake is restored. Why? Because not ingesting a sufficient number of calories has dire consequences for our survival. There is no evolutionary advantage to trying to lose weight by restricting eating. Four billion years of evolution have led to the following simple directive: Find and consume the energy within food, repeat often. Think about this the next time you contemplate taking a diet aid.

When an energy source is on your tongue, the brain is informed via six quite simple molecular interactions within the taste buds that lead to the activation of reward pathways in the brain that utilize the neurotransmitters dopamine, endorphins, endocannabinoids, and orexin. Orexin influences both our level of arousal and our craving for food. Take a moment to appreciate how this system optimizes your daily existence and survival. These orexin neurons wake you in the morning and then make you crave food.

Once food reaches the gut, it encounters still more receptors that detect sweetness, fattiness, and bitterness. It appears as though the entire gut is a continuation of the tongue with specialized taste receptors. The activation of these receptors slows the intestinal transit of the food, providing a greater opportunity for nutrient extraction within the limited length of the intestines.

BIORHYTHMS AND DIET EFFECTS ON THE BRAIN

Is there a good time of day to eat? What would happen if you could only eat between the hours of 9 a.m. and 4 p.m.? Would you gain less weight and be healthier overall even if you ate a high-fat diet? The answer is yes and is based on how the body is influenced by daily rhythms of eating and sleeping. We are already well aware of the negative consequences of ignoring the role of our biorhythms: Nightshift work, and the odd patterns of sleeping and waking that this lifestyle involves, has

many negative health consequences, including insomnia, high blood pressure, obesity, high triglyceride levels, and diabetes—collectively known as the metabolic syndrome.

In a recent series of studies, mice were given free access to a nutritionally balanced diet or a diet that was high (61% of calories) in fat. Some mice were allowed total access to the food at all times; others were only allowed access for an 8-hour window during the early phase of their normal active period. Mice given total all-day access to a high-fat diet (the standard American diet) developed obesity, diabetes, and metabolic syndrome and poor sleep–wake rhythms. A high-fat diet also led to the degeneration of the olfactory system and as a consequence food would lose much of its sensory allure. The mice that had time-restricted access to the high-fat diet were significantly healthier than the mice given all-day access to the same diet. These lucky mice lost body fat and had normal glucose tolerance, reduced serum cholesterol, improved motor function, and normal sleep cycles. Most surprising, the daily caloric intake of all groups did not differ, regardless of their diet or feeding schedule. Therefore, it truly does matter when you eat. The take-home message is eat early, skip dinner, and never have late-night snacks. Skipping breakfast and overeating in the evening play a significant role in weight gain and obesity. Furthermore, people who skip breakfast report not feeling as satisfied by their food and being hungry between meals. If this sounds like you, then it is time to change your mealtimes.

WHEN GOOD FOOD TURNS BAD

Our body's reaction to the food we eat can sometimes warn us that something is wrong. One day we are eating our favorite food without consequence; the next day, the same food produces nausea, dizziness, and mental confusion. Why? Sometimes the constituents of our diet can induce toxic reactions when they are not being properly metabolized and excreted. For example, star fruit (*Averrhoa carambola*)—small, waxy-skinned fruit whose name originated from the star-like shape produced when the fruit is cut in cross section—contains an impressive variety of vitamins, minerals, and dietary fibers and is a rich source of antioxidants. But it poses a serious risk for individuals with kidney failure. The consequences of eating star fruit when the kidneys are not functioning adequately include several symptoms that might easily be ignored or misinterpreted as unrelated to eating the fruit, such as vomiting, hiccups, mental confusion, and seizures. Overall, this is a very important warning: How we respond to the components of our diet is greatly influenced by the status of our health.

ACIDIC DIETS AND BRAIN FUNCTION

Is it true that the foods and beverages you consume can cause your blood to become more alkaline or acidic? Contrary to popular hype, the answer is no, not to any significant degree. The pH of your blood is tightly regulated by a complex system of buffers that are continuously at work to maintain a normal level

that is slightly more alkaline than pure water. The bottom line is that if you are breathing and going about your daily activities, your body is doing an adequate job of keeping your blood pH under control and your diet is not causing any wild deviations in your blood pH.

Your blood (plasma) needs to maintain a pH of 7.35 to 7.45 for your cells to function properly. Although the various reasons your cells require your blood to maintain a pH in this range to stay healthy are beyond the scope of this book, it is worth mentioning the most important reason: All of the proteins that work in your body have to maintain a specific geometric shape in order to function, and the three-dimensional shapes of the proteins in your body are affected by the tiniest changes in the pH of your body fluids.

When people encourage you to “alkalize your blood,” they mean that you should eat plenty of foods that have an alkaline-forming effect on your entire body. The reason is that the vast majority of highly processed foods—such as white flour products and sugar—have an acid-forming effect on your system, and if you spend years eating a poor diet that is mainly acid-forming, you will overwork some of the buffering systems to a point where you could create undesirable changes in your health. In general, most vegetables and fruits have an alkaline-forming effect on your body, whereas most grains, animal foods, and highly processed foods have an acid-forming effect. Your health is best served by a mixture of nutrient-dense, alkaline- and acid-forming foods that

include carbohydrates, fats, and proteins. Let's take a look at these foods.

CARBOHYDRATES AND BRAIN FUNCTION

A carbohydrate is a molecule made of carbon, hydrogen, and oxygen. Glucose is a carbohydrate and is commonly called "sugar." The adult brain has a very high energy demand requiring continuous delivery of glucose from blood. The brain accounts for approximately 2% of the body weight but consumes approximately 20% of glucose-derived energy, making it the main consumer of glucose. The largest proportion of energy in the brain is consumed for neuronal computation and information processing.

Obviously, our brains need a lot of sugar; without it, we quickly lose the ability to think and slip into a coma. We must obtain the sugar from our diet. Unfortunately, somewhere in our evolutionary history, we lost the ability to convert fat into sugar; unlike a few lucky animals, humans cannot perform this metabolic trick. So, in the morning when you wake up from a long period of fasting, your brain wants you to eat lots of sugar and other simple carbohydrate sources, such as a donut.

Sometimes, what your brain wants is not always good for your body. Donuts are a good example. It is early morning and you are driving to work after a nice breakfast of black coffee and two eggs, over easy, with bacon. Yet, you are still hungry and having difficulty paying attention to the traffic. Why? Your brain

is not cooperating because it is not satisfied with that breakfast because it lacked one critical ingredient that your brain urgently needs—sugar. You have been fasting since dinner last night and your blood levels of sugar have fallen. From your brain's perspective, sugar is indispensable. It will do whatever is necessary to convince you to eat sugar as often as possible. Why? Your brain needs sugar (usually in the form of glucose) to function normally. The billions of neurons in your brain require a constant supply of sugar to maintain their ability to produce energy and communicate with other neurons. Your neurons can only tolerate a total deprivation of sugar for a few minutes before they begin to die. Therefore, as blood levels of sugar decrease with the passage of time since your last meal, you begin to experience a craving for food, preferably something sweet. Essentially, the presence of sugar in your brain is considered normal, and its absence leads to the feeling of craving and the initiation of foraging behaviors, such as seeking out a vending machine for some cupcakes or a candy bar. There is a reason that donut shops and sugar-laden cereals are so popular, and you can lay the blame on neurons within the feeding center of your hypothalamus. If your brain did not want those donuts so badly, the donut shops would not be so densely distributed along your route to work.

Once inside the brain, sugar is also used to produce a very important neurotransmitter chemical called acetylcholine. Acetylcholine allows you to learn and remember, to regulate your attention and mood, and to control how well you can move.

Your brain makes acetylcholine from choline, which is obtained from the diet, and from acetyl groups that originate from the metabolism of sugar. We frequently obtain choline in our diet by eating lecithin. Lecithin can be found in many different bakery goods, such as donuts and cupcakes, and is commonly added to chocolate. Thus, a tasty chocolate-covered donut first thing in the morning is going to provide your brain with everything it wants and needs to pay attention and learn new things. Unfortunately, those eggs and bacon that you had for breakfast were completely insufficient for the task of preparing your acetylcholine neurons for a day of thinking and learning. In one day, your active brain utilizes the equivalent of 10 donuts of sugar! So, tomorrow morning, without doubt, you are going to eat a donut because it is what your brain wants.

GOOD FAT AND BAD FAT

We also need fat. Fat frequently takes up more territory than any other organ in our bodies. A long time ago, our ancestors needed fat deposits because food was not always available. Fat can accommodate wide swings in nutrient availability because it is capable of rapid changes in size, especially subcutaneous fat, which is not subject to size constraints. We can simply keep packing on the fat cells for a future time when less food might be available—thus improving our chances of survival.

In humans, fat is purposefully located beneath the skin and around vital organs, where it can protect the body against infection and trauma. Bacterial and fungal infections of fat are

uncommon, and cancer metastases into fat pads are rare; this is likely related to the high local concentrations of fatty acid that are lethal to pathogens and non-fat cells. Fat is also critical for thermoregulation because it prevents heat loss and acts as insulation and also generates heat in brown fat—a specialized fat deposit that lies between the shoulder blades and is rich in mitochondria. Fat provides physical protection and forms a buffer that dissipates pressure over skeletal prominences such as elbows and knees, thus preventing the skin from collapsing at vulnerable spots on our limbs.

Our fat mass increases throughout middle age; then, it starts being redistributed. It moves from subcutaneous deposits to visceral deposits around our vital organs. Given this redistribution, waist size tends to increase. To make matters worse, as we age, our fat is also redistributed into bone marrow, muscle, and liver. This loss of subcutaneous fat is often associated with the development of metabolic syndrome, characterized by glucose intolerance, insulin resistance, visceral obesity, and hypertension. When present in the elderly, this condition impairs cardiovascular function and accelerates cognitive decline. Some of us inherit a tendency to redistribute our fat at an earlier age and at a faster rate; when this happens, it is associated with a reduced life span.

All fat deposits do not behave similarly; visceral fat is more pro-inflammatory than subcutaneous fat. Obesity and aging are both associated with chronic, low-grade, body-wide inflammation and insulin resistance. Fat dysfunction associated with

obesity is now thought to reproduce many of the same metabolic conditions that underlie the normal aging process. Essentially, obesity accelerates the aging of our organs and predisposes us to diseases that are common in old age. But you do not have to be obese in order to suffer from the consequences of excess fat cells. Even skinny older people with relatively more visceral fat than subcutaneous fat are at increased risk for mortality.

THE BENEFITS OF LIPOSUCTION ON BRAIN FUNCTION

Obesity, especially excessive belly fat, increases the risk of numerous diseases, including diabetes, atherosclerosis, and especially cancer. In addition, the cytokines associated with the widespread inflammation related to excessive belly fat directly impair cognitive function. Many laboratories throughout the world, including my own, have documented the molecular mechanisms that explain how excessive body fat impairs brain function. Worse, the effect of excessive belly fat ultimately increases the risk of developing Alzheimer's disease.

What would happen if these harmful fats cells were simply removed? Exercise can shrink fat cells, but only liposuction can remove them from the body. A group of scientists recently investigated this novel question by conducting three very clever experiments on obese and normal-weight mice. First, a group of obese mice were forced to exercise on a treadmill. Unlike the millions of Americans who own treadmills, these mice had no choice but to run. As expected, the daily treadmill

exercising reduced belly fat; reduced the level of inflammation in their bodies; and significantly restructured how their brains functioned at the cellular level, leading to greatly improved memory. In a parallel study, the scientists surgically removed fat pads from a similar group of obese mice—that is, they underwent a standard liposuction procedure. The results were identical to those produced by running on the treadmill: Inflammation was reduced, and the mice became significantly smarter. These findings confirm results from many recent studies that have documented the ability of fat cells to impair brain function and accelerate aging. Then the scientists did something truly astonishing: They transplanted fat pads into normal, healthy-weight mice. The impact of the fat cells was immediately obvious: The mice showed increased signs of brain and body inflammation, and they developed deleterious changes in brain structure and function that led to reduced memory performance (i.e., the rats became stupid).

Today, an overwhelming body of scientific evidence across a wide spectrum of medical disciplines strongly suggests that obesity accelerates the aging process, impairs overall cognitive function, and ultimately is responsible for numerous processes that kill us. The previously discussed mice experiments suggest that the simple removal of excess fat cells can produce significant positive health benefits.

In contrast, the surgical removal of visceral fat is not an easy option; the only solution available is to eat less food. Caloric restriction is the only valid, scientifically proven dietary

intervention that has been shown to slow the aging process and improve overall health. The reason we hear so little about this approach is because no one stands to make a profit on all of us eating less food.

DIETARY FATS THAT IMPROVE BRAIN FUNCTION

We have a fatty brain, and fat plays many vital roles in brain function. In the past, very little attention was given to the influence of dietary fats on our mental state. Recent evidence indicates that it might be possible to manipulate our dietary fat intake to treat or prevent disorders of cognitive function.

A recent study compared the effects of monounsaturated fats from olive and canola oils with polyunsaturated fats from meat, fish, and vegetable oils on a variety of biochemical changes and electrical properties of cells within a brain region that is critical for learning and memory. After 11 months, a diet high in monounsaturated fats, often referred to as the Mediterranean diet, altered brain chemistry in such a way that learning was enhanced, age-related cognitive decline slowed, and the risk of getting Alzheimer's disease was reduced. These findings support the addition of canola, olive, and fish oils containing omega-3 fatty acids to our diet and further demonstrate that sensible nutritional choices are vital for optimal brain function and good mental health. However, are omega-3 fatty acids as favorable for the brain as the some people claim?

THE DUBIOUS BENEFITS OF OMEGA-3 FATTY ACIDS

Omega-3 fatty acids, the key components of fish and flaxseed oils, are a family of fats that occur naturally; three of them— α -linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid (DHA)—are important components of the human diet. Some recent studies have concluded that being deficient in omega-3 fatty acids may affect brain physiology and increase the risk of cognitive decline. Superficially, this claim makes sense. After all, DHA is abundant in the brain and is involved in numerous critical functions. It may also enhance learning and memory processes in the brain.

Omega-3 fatty acids play multiple critical roles in the growth and development of the infant brain. Maternal fish consumption or fish oil supplementation during pregnancy was associated with improved neurodevelopmental outcomes, such as language and visual motor skills, in infants and young children, as well as better eye and hand coordination. Omega-3 fatty acid intake was also associated with improved academic performance in adolescents. Sometimes, preliminary studies make headlines because their results seem so sensible and obvious that we forget to question their validity. For example, a recent study in China identified a significant dose-response relationship between the consumption of fish and IQ scores: Children who always or sometimes consumed fish had higher IQ scores compared to children who rarely ate fish. The authors concluded that

improved sleep quality partially facilitated the association between fish consumption and IQ. Unfortunately, the authors failed to consider whether other contents of the children's diet might have contributed to the benefits. Their study was too narrowly focused on fish and thus likely missed the benefits of other nutrients.

Dietary intake of omega-3 fatty acids has been claimed to slow cognitive decline and the incidence of dementia. The problem is that thus far, clinical trials have either included too few patients or have been conducted for quite brief periods of time. Thus, the results tend to be rather variable and potentially misleading. Recently, a study investigating the potential benefit of omega-3 fatty acids followed almost 3,000 people, aged 60–80 years, for 40 months. Their daily diets, medications, and health status were carefully monitored. Patients and controls were carefully matched for education level, smoking habits, and alcohol use, among other features. Simply stated, omega-3 intake (as fish or a pill supplement) provided no benefits. Cognitive decline was unaffected. The implications of this study cannot be overstated: A single, good dietary habit is never going to be enough to provide protection for your aging brain.

In contrast to their lack of benefit for age-related cognitive decline, omega-3 fatty acids may have a beneficial influence on the outcome in depressive disorders. Chronic diet supplementation with omega-3 fatty acids has produced antidepressant-like effects similar to those of common antidepressant drugs. The therapeutic approach of combining omega-3 fatty acids

with low doses of antidepressants might lead to benefits in the treatment of depression, especially in patients with depression resistant to conventional treatments or by decreasing the magnitude of some antidepressant dose-dependent side effects.

Physicians are increasingly recommending very high doses of omega-3 fatty acids for their potential ability to treat hypertriglyceridemia. However, numerous studies have shown that these compounds are immunosuppressive and may increase susceptibility to infection or reduce the body's ability to defend against certain cancers. Again, too much of a good thing can become a bad thing—even fatty acids.

HOW FAT IMPAIRS BRAIN FUNCTION

Obesity is associated with hypertension, diabetes, sleep apnea, and numerous arthritic disorders. Unfortunately, obese individuals also perform worse on neurocognitive tests even when controlling for education level and evidence of depression. Furthermore, women who eat an unhealthy high-fat diet prior to and during pregnancy are more likely to give birth to children, particularly males, who are at risk of abnormal behaviors, predominantly anxiety, during adulthood. Physicians frequently warn pregnant women to monitor their caloric intake and maintain a healthy weight before and during pregnancy. Maternal nutritional status, infection, and physical or psychological trauma during pregnancy can all increase the risk of obesity, diabetes, and mental disorders in offspring. In the past, the concern was maternal

malnutrition—that is, the developing fetus might lack critical nutrients for normal growth. Today, in the United States, the concern has shifted to overnutrition and obesity and the risks faced by the developing fetal brain.

Another study of maternal obesity reported serious inattention problems and a twofold increase in the incidence of impaired emotional regulation that was still evident 5 years after birth. Maternal obesity also causes abnormalities in areas of the brain responsible for feeding behavior and memory. All these changes were most noticeable in male offspring. How does maternal obesity impair fetal brain development? Again, the damage is due to the fact that fat cells release inflammatory proteins, called cytokines, into the body and brain. The more fat cells the mother has, the more cytokines get released into her blood.

Obesity also increases the likelihood of becoming depressed. Depression is often referred to as “the common cold of mental illness.” This reference reveals some fundamental insights into why we become depressed when we are suffering with the flu or a bacterial infection. Bacteria induce our bodies to release cytokines; depressive behaviors are now thought to be caused by elevated levels of cytokines in the brain. The additional inflammation may also explain why many antidepressant drugs are less effective in obese or elderly people: Their brains have elevated levels of cytokines. Exercise can modestly reduce the level of cytokines in the brain, and depressed obese people often find some relief by exercising. Overall, staying thin means a person

will be less depressed and live longer and be in less chronic pain while enjoying life.

WHY DOES OBESITY CAUSE CHRONIC BODY PAIN? THE ROLE OF NEUROINFLAMMATION

Numerous studies have documented a consistent association of obesity with chronic pain. Essentially, obese individuals are more likely than non-obese to report recurring pain. Furthermore, the level of pain experienced increases in parallel with the degree of obesity. The link between obesity and body pain is apparent across age groups, ranging from children to older adults. It is painful to be obese at any age.

Currently available evidence indicates that the direction of the relationship leads from increases in body weight to elevated pain symptoms. This means that people do not gain weight in response to chronic body pain; rather, the pain develops as a consequence of the extreme weight gain. Therefore, in contrast to what many people assume, the increasing pain level is not simply due to increased loading on the joints leading to arthritis-related pain.

How does obesity produce so much pain? A recent study demonstrated that obesity induces body pain by potentiating inflammatory responses. Indeed, it is now understood that obesity reflects a state of chronic systemic inflammation. This is likely the best explanation for why obesity and pain are so strongly associated.

What is the best way to counteract this painful situation? Eating anti-inflammatory foods, such as fish, nuts, and beans, lowered the levels of inflammatory markers and reduced body pain levels regardless of body weight. Thus, a healthy diet can help reduce the pain associated with being obese even before losing the excess weight. Another powerful anti-inflammatory food to consider adding to your diet if you are obese is pond scum.

DIETARY POND SCUM CAN REDUCE NEUROINFLAMMATION

Spirulina is a far more attractive name for the biomass of edible blue-green algae that forms a green slimy film on the surface of stagnant water ordinarily called pond scum. Spirulina is typically home to two species of algae: *Arthrospira platensis* and *Arthrospira maxima*. Why should you eat it? Spirulina is an excellent source of highly potent antioxidants and anti-inflammatory chemicals that can benefit your brain health across the entire life span as well as protect from the consequences of obesity.

A recent study investigated whether it was possible to treat severe neonatal infection by administering a spirulina-enriched diet to nursing mothers. Severe infection, and the associated brain inflammation, can cause long-term changes to the developing brain due to oxidative stress even after the original infection has been adequately treated by antibiotics. A spirulina-enriched diet given to lactating mothers reduced the level of brain inflammation and provided an antioxidant defense for the developing

neonatal brain. These studies are interesting because they clearly demonstrate that the addition of specific plant-based chemicals to a nursing mother's diet can counteract ongoing disease mechanisms in the child by reducing the prolonged negative effects on the brain and the body's antioxidant system that are produced by neonatal systemic inflammation.

At the other end of the life span, the brain inflammation that develops with normal aging is poorly understood and usually challenging to treat. Some neurons are exceptionally vulnerable to the consequences of brain inflammation and oxidative stress. One of the most vulnerable groups of neurons produces the neurotransmitter dopamine; the death of these dopamine neurons is associated with Parkinson's disease. Thus, there is considerable interest in finding ways to reduce brain inflammation in order to prevent or slow the onset of the symptoms of Parkinson's disease. A recent study examined the beneficial effects of a diet enriched with spirulina in an animal model of Parkinson's disease. The results demonstrated that spirulina supplementation prevented the death of dopamine neurons. Clinical trials in humans need to be conducted to confirm the results of this study.

Given the broad range of obesity-induced health problems attributed to inflammation, another study investigated the potential protective actions of spirulina in obese adults. Fifty subjects received 2 g of spirulina or a placebo daily for 3 months. Spirulina supplementation significantly lowered low-density lipoprotein cholesterol and interleukin-6 (a pro-inflammatory

protein) concentration and considerably improved total antioxidant status compared to placebo.

Unfortunately, very few clinical trials using spirulina supplementation to treat neurological conditions in humans have been performed. Despite our current ignorance about the specific therapeutic actions of these algae, the previously mentioned preliminary studies strongly indicate that dietary spirulina supplementation may be quite beneficial, particularly for people who enjoy eating too much.

THE PLEASURE OF OVEREATING

Two different neurotransmitter systems, endogenous opioid peptides called endorphins and cannabinoids, make eating pleasurable. Endorphins enhance the sensory pleasure derived from food, and the consumption of food high in fat and sugar stimulates the release of endorphins. Endorphins enable us to experience the deliciousness of food and ensure that we do not stop eating too soon, but they do not influence our decision to eat. Drugs that selectively block the action of endorphins reduce the intake of foods that are quite sweet or have a high fat content. Interestingly, these drugs that block endorphins, called antagonists, only reduce the pleasure of eating these foods; they do not reduce the feelings of hunger. Endorphins drive us to overconsume palatable foods by blunting the impact of feeling full. For example, while standing next to the buffet table, many of us will engage in mindless eating. We know that we should stop eating and move away from the buffet line and let someone

else get at the food. Our bellies are full to the point that it hurts to breathe. Belts are loosened another notch. Why can't we stop eating?

Neuroscientists have some interesting explanations. One of these is called "ingestion analgesia," and it involves endorphins. The role of ingestion analgesia is to keep you eating. Even though continued eating has become unpleasant because the stomach is painfully stretched to its full capacity and we have reached the point where we cannot unbutton anything else in public, and even though we have embarrassed ourselves in front of relatives or co-workers by our voracious appetite, we still keep noshing. Essentially, we block out the painful feedback from these feelings by releasing endogenous opiates into our brain and body. Not surprising, our reaction to pain is significantly reduced when eating tasty foods, such as chocolate. This explains why we can indulge in a decadent dessert even after we have become fully satiated by a large meal. We have basically become insensitive to the pain of continued eating.

WHY DO WE LIKE TO OVEREAT SO MUCH?

Our brains evolved when food was scarce; thus, we are compelled by our genetic legacy to eat whatever and whenever possible. Animals have a tendency to eat a great deal of food when palatable food is readily available. In addition we also subconsciously prevent others from taking our food source. We defend our access to tasty food when it is within easy reach and is at risk

of being consumed by other humans. Studies have shown that humans will eat more when more food is available even when the food is stale or otherwise unappealing (which is good news for bad cooks!). Furthermore, even if you point out to others that the food is stale or that they have eaten more than their fair share, they will continue to eat. Our biological drive to consume tasty food to completion outweighs any opposing cognitive or motivational factors. Even after we have gained a lot of weight, our bodies want to gain more.

Research indicates that obese humans have elevated levels of endogenous endocannabinoids—marijuana-like chemicals—in the blood and brain. Remember the munchies? When we become overweight, our bodies induce a constant state of the munchies by bathing our brain in endocannabinoids.

The endogenous marijuana neurotransmitters, the endocannabinoids, also contribute to the pleasurable aspect of eating. Scientists have discovered that marijuana increases the pleasurable response to eating sugar but has no effect on how much we dislike the taste of other types of foods. For example, if you hate eating peas or broccoli, smoking marijuana will not induce you to like eating them. The ability of sugar to induce a rewarding feeling is caused by the release of dopamine in the brain's reward center. This brain region informs you that your brain likes this food and wants you to consume it more often. In the presence of marijuana, significantly more dopamine is released in response to the same amount of sugar-enriched food. What does this mean? The brain's endogenous marijuana

system ordinarily modulates how good a particular food tastes to us; smoking marijuana simply enhances this natural mechanism in the brain.

The brain's main purpose is to help us survive and pass on our genes. Eating is a critical and necessary behavior that the brain organizes and controls that allows daily survival. Therefore, the brain rewards itself for successfully consuming enough calories to survive by releasing these two powerful neurotransmitters—endorphins and endocannabinoids. As a consequence of the manner in which evolution has shaped the response of our brains to food, overeating of calorie-dense food has become a major health problem in the developed world. Our brains were shaped by evolution to be very efficient at instructing us to eat but quite inefficient at stopping us from eating.

WHY DOES FAT TASTE SO GOOD?

One of the best things about the taste of chocolate is its wonderful creamy smoothness. That feeling is due to the presence of fats. Despite the universal feeling that fatty foods produce on the tongue, scientists have long claimed that we do not actually possess the ability to taste fat. Textbooks mention only our ability to taste sour, salty, sweet, bitter, and, rather recently, umami (which is the taste produced by the additive monosodium glutamate [MSG]). A recent study demonstrated that humans and other animals exhibit a protein on their tongue that can sense the presence of fat. If there is a protein for tasting fat, then there must be a gene responsible for this protein. Indeed,

this gene has been identified, and it appears as though variations in this gene explain why some people are far more sensitive to fat in their food than others.

The amount of the fat-tasting protein on the tongue varies. If you have inherited a tendency to have fewer of these receptors, then your response to fat is muted and you are more likely to be obese. Obese people do prefer food with higher fat content and consume fat as a larger percentage of their overall calorie intake. Even if you have not inherited this tendency, if you consume lots of fatty foods, you will modify the activity of this gene and subsequently make less of the fat-tasting protein. Unfortunately, as a consequence, you become less sensitive to the taste of fat and begin to prefer foods that contain higher levels of fat in order to obtain the same pleasurable sensation when eating. Essentially, you start eating more fatty foods but enjoy their taste much less.

WHY IS OBESITY SO DIFFICULT TO DEFEAT?

Most of us are aware that diets high in fat and sugar will lead to obesity. The problem is that fat and sugar are raved like heroin or methamphetamine. Why is this so? The answer is that these foods actually change how the brain functions. Day after day, year after year, the constant bathing of the brain in fats and sugar slowly changes how the DNA in the cells of the brain's feeding center behaves. With these gradual modifications in gene function, our brain circuitry also changes; ultimately, it

rewires itself. Eventually, we eat more fat and sugar every day in order to feed this ever-more-powerful new reprogramming that is evolving inside the brain.

Scientists once assumed that obese people were simply addicted to food in the same manner that someone becomes addicted to heroin—that is, food produces happy, pleasant feelings, and therefore eating lots of food would produce extremely pleasant feelings. Not so. A few years ago, scientists discovered just the opposite was true: The brain's reward center *decreased* its response to eating tasty food. In obese humans, dopamine function becomes significantly impaired in response to many years of a poor diet. Consequently, people consume ever-greater quantities of fat and sugar in order to compensate for the diminished rewards that were once experienced by consuming only one scoop of ice cream or a small donut.

BLAME IT ON YOUR GENES

Are we born destined to become obese? Apparently, yes. Many studies have shown that children who have two obese or overweight parents are four times more likely to become obese themselves. To be considered low risk, the parents of the adolescents needed to be lean, with a body mass index less than 25. When the children in the high-risk group were shown pictures of tasty-looking, high-calorie foods, the dopamine-dependent pleasure centers in their brains became highly activated, especially compared to the response of the same brain regions in the low-risk children. Children who are destined to become obese

apparently inherit a dopamine system that becomes much more excited at the sight of a chocolate milkshake than does the dopamine system in the brain of a child who is not destined to become obese as an adult.

BUGS TO THE RESCUE

Stand naked in front of a mirror. Look closely—really closely! Put on a pair of magic glasses that allow you to see the immense multitude of creatures looking back at you. For every one of your big human cells, roughly two little bugs live inside of you. If you were to count all of the cells on and inside of you that are not actually *you*, they would number in the trillions. You are never really alone. These bugs were not simply along for the ride; they made the journey possible. Despite our focus on all things human, such as politics, war, and love, these microscopic single-celled organisms have remained the dominant species on this planet. Whether we acknowledge it or not, according to the evolutionary biologist Stephen Jay Gould, we live in age of bacteria, “as it was in the beginning, is now, and ever shall be.”

As soon as individual cells evolved into fully multicellular organisms during the Cambrian period approximately 500 million years ago, they quickly discovered the fantastic survival benefits of fully integrating themselves; once there, they never left. The total weight of the many trillions of bugs that reside in your gut is more than 2 pounds, and they are multiplying constantly due to all of the nutrients you are providing them; they are also in a constant battle for survival. The viruses in your gut

kill so many bacteria every minute that their carcasses account for approximately 60% of the dry mass of your feces (now you know what is in there).

Probiotics are popular today. The logic is that we can somehow modify the population of bugs that live in our guts, which weighs 2 pounds and contains trillions of bacteria and viruses, by taking one little pill that weighs a fraction of an ounce and that contains a billion bacteria. This is total nonsense. Taking that little pill to modify the balance of bugs in the gut is like adding a drop of water to the ocean! Unless you are a child suffering with diarrhea due to an infection by a rotavirus, there is no good scientific evidence that probiotics will make you healthier. Prebiotics are an even bigger waste of money. Prebiotics are simply fiber foods that are meant to feed the bacteria that already live in your gut. Beans, pears, and nuts are prebiotics. If you wish to change the balance of bugs in your gut, just change your diet.

The bacteria and viruses that have hitched their fortunes to you contribute to your good health as well as to your sickness. As our species and theirs evolved, we established some rules to govern our cohabitation, and most of the time everything works out well. But like an unpredictable roommate, these bugs can turn against us, and their impact on brain function can be profound because they share our body's exposure to the drugs and foods we consume. Obesity induces an imbalance in the body's intricately choreographed dance with these little creatures. Why? Because during the process of depositing and

filling fat cells, another cell type, called a macrophage, becomes embedded among our fat cells. Macrophages are part of the body's immune defense system. When they are surrounded by fat cells, these macrophages start releasing chemicals that impair the body's ability to regulate glucose and fat metabolism while also making the body insensitive to insulin—this is known as the metabolic syndrome.

How can we turn off these nasty macrophages? The hero of our story is a cell called an eosinophil. The more of these eosinophils you have in your body, the better able you are to reverse the negative effects of macrophages. One of the most effective signals for inducing your body to produce more eosinophils (and you are not going to like this) is infection by parasitic worms. After a group of scientists at the University of California at San Francisco infected obese mice on a fatty diet with a parasitic worm, the body fat disappeared and glucose tolerance was restored. I realize that this idea sounds disgusting, but just keep in mind that your new parasitic companion would have lots and lots of company, you would lose lots of weight, and after a little while you would become accustomed to those subtle undulations within your abdomen as the worm grew ever larger while consuming all of your body fat. Fortunately, these scientists also determined that the worm need only spend a week within your gut in order for you to benefit from its ability to activate your eosinophils. Fat farms and health spas would be able to offer some interesting package deals! This study has some broad implications related to our overly hygienic lifestyle

in developed countries that often have the greatest percentage of obese citizens. We co-evolved with many different parasitic species; we still carry many of them around with us all of the time. Thus, inviting into our bodies just one more parasitic worm could become an integral part of a new Paleolithic diet plan.

Your brain lives in a symbiotic relationship with the bugs in your gut. Whatever you eat, they eat. Indeed, they are also adept at adjusting to our diets. If you consume lots of carbohydrates, they will adjust their numbers to produce more bacteria that can metabolize sugar. In return for our feeding them, they help our brains function optimally in a variety of ways. During the past few years, it has become increasingly apparent that in the absence of bacteria, humans would never have evolved to our current level of cognitive performance. Our brains are profoundly dependent on a wide range of chemicals produced by these gut bugs. For example, without these gut microbes, our brains do not correctly develop the serotonin neurons that play a key role in the control of emotion. A shift in the mixture of these bugs can lead to poor health, including heart disease, inflammatory bowel diseases, high cholesterol, obesity, and cancer. One recent study discovered that our gut biome does not like us to indulge in a high-salt diet. For many years, physicians have wondered why a high-salt diet is so detrimental to normal brain function. Apparently, eating too much salt for too many years leads to the increased production of pro-inflammatory proteins that directly damage the brain. Given these recent discoveries, it is easy to appreciate how the health of our gut bacteria can influence

how we feel and think and our vulnerability to certain mental and physical disorders.

For example, members of the Lachnospiraceae family of gut bacteria may protect against colon cancer in humans by producing butyric acid. Butyric acid may also benefit people with ulcerative colitis and Crohn's disease due to its ability to reduce inflammation in the gut. Interestingly, butyric acid is the chemical present in some popular chocolates, vomit, and parmesan cheese that gives these substances their familiar odor. OK, stop reading and go and compare the odors of chocolate and parmesan cheese—I know you want to.

Ordinarily, we live in harmony with the trillions of little creatures that share our bodies. Thank goodness, since there are so many more of them than us. In general, we would like them to stay out of our brains, but unfortunately, they rarely follow orders, particularly a one-celled parasite known as *Toxoplasma gondii*. You have heard about this one before because it has been blamed for various illnesses and cancers associated with handling cat litter. *Toxoplasma gondii* is everywhere. Statistically speaking, you and I are both infected but are simply not aware of it. Without a doubt, the presence of *T. gondii* in your brain affects your behavior. Indeed, the evolution of our genus probably owes much to the influence of this parasite in our brains during the past few hundred thousand years. *Toxoplasma gondii* possesses genes that are capable of causing the brain to greatly increase its production of the neurotransmitter dopamine. People infected with *T. gondii* exhibit many of the symptoms

expected of someone whose brain contains far too much dopamine. For example, men infected with *T. gondii* tend to be more extroverted, more aggressive, more suspicious, and more prone to jealousy. In contrast, infected women tend to be more warm-hearted and easy-going and much less prone to jealousy or suspicions. However, infected women both attempt and complete suicide more often than do women who do not harbor the parasite in their brains.

It is thought that this parasite has been living in the brain, and thus influencing behavior, for as long as the *Homo* genus has existed. Its presence can predispose someone to schizophrenia or drive large groups of infected people to go to war. Did possessing this parasite make it more likely for one group of garrulous people to triumph over another uninfected population? Its continued presence might explain why war and suicides are still with us today.

THE SUICIDAL BRAIN

Numerous factors may induce people to think about suicide (the ideators) and actually attempt suicide (the attempters). For example, the traditional risk factors for suicide, such as depression, hopelessness, many psychiatric disorders, and impulsivity, strongly predict suicide ideation but weakly predict suicide attempts among ideators. Alternatively, a diminished fear of pain, injury, and death can increase one's probability of attempting suicide and facilitate the progression from suicidal thoughts to suicidal acts.

Out of the approximately 120 successful suicides that occur each day in the United States, 70% are committed by White, mostly middle-aged, males. Fifty percent of all successful suicides are achieved using firearms, which are chosen, mostly by males, for their extreme efficacy. In contrast to the certainty of using a firearm, each year thousands of people deliberately inhale carbon monoxide (CO) in order to end their lives, usually via the exhaust fumes from their own vehicles while sitting in them in their own garages. For example, 70% of all fatal CO poisonings in Utah between 1996 and 2013 were due to suicides. The incidence of successful CO-induced suicide has actually declined due to strict federal CO emissions standards for motor vehicles following the Clean Air Act of 1970 and the widespread presence of catalytic converters. One recent study examined the CO levels in a standard-sized garage after 20 minutes. The CO level was 253 parts per million (ppm) for a car without a catalytic converter and 30 ppm for the car equipped with one. Emissions controls on automobiles have thus significantly reduced the success rates of CO-related suicides. Subsequently, although thousands of people every year attempt suicide by this widely familiar method, a greater percentage of them survive the attempt.

Following a failed suicide attempt, acute CO poisoning causes serious mental health problems due to the death of neurons in vulnerable brain regions such as the hippocampus, a brain structure that is critical for learning and memory abilities, and the basal ganglia, a brain region that controls

normal movement. Most of these neurological changes develop over a period of many days and occur due to extensive oxidative stress and brain inflammation induced by CO poisoning. The brain is particularly vulnerable due to its constant high demand for oxygen, which is denied to it by CO-enriched blood. During the first few days and weeks after the failed attempt, the initial symptoms include headaches, dizziness, fainting with loss of consciousness, and, following severe poisoning, seizures. Later, after many weeks, survivors often report significant learning and memory impairments, movement disorders that resemble Parkinson's disease, depression, psychosis, and even symptoms of dementia. The degree and number of neurological symptoms depend on the extent and location of the most severe oxygen deprivation inside the brain.

Two therapies are often used for these patients. The first is hyperbaric oxygen therapy. The second is a drug that is commonly given to patients with Alzheimer's disease, Aricept, whose mechanism is discussed in Chapter 3. The benefits provided by this drug suggest that neurons that release the neurotransmitter acetylcholine are likely injured by CO poisoning. Aricept enhances the function of this neurotransmitter in the hippocampus and frontal lobes. A recent study discovered that survivors of CO poisoning also have reduced numbers of receptors for the drug nicotine in their brains. This knowledge about the role of acetylcholine neuronal damage may lead to the development of better therapies for survivors of failed

suicide attempts as well as for people who have experienced a severe brain trauma.

WHAT TO FEED AN INJURED BRAIN

You have just experienced a traumatic injury to your head; a series of changes are about to occur in your brain that will have short- and long-term negative consequences. You just joined the ranks of 1.7 million other people living in the United States who experience a traumatic brain injury (TBI) every year. TBI is an alteration of brain function caused by external forces leading to loss of consciousness, temporary memory loss, and alterations in mental state at the time of the injury.

A study by the Mayo Clinic found that one-third of patients whose brains showed pathology and evidence of chronic degenerative diseases had participated in contact sports. The popular press has published numerous stories about retired players of the National Football League who have a threefold increased risk of developing depression as well as a variety of worsening cognitive impairments. Indeed, all athletes, especially young adults, exposed to repetitive concussions are at increased risk of developing cognitive deficits.

In the hours, days, and weeks following an initial TBI accident, a series of secondary biochemical changes develop that lead to a progressive degeneration within vulnerable brain regions. Many of these changes are also commonly associated with advanced normal aging and are thus rather well studied. One of the initial changes involves a dysfunction

of the mitochondria inside of the neurons of the brain. Mitochondria are responsible for energy production and are critical to the survival of neurons, which use a lot of energy. The injury to the mitochondria leads to a condition called oxidative stress, in which individual atoms of oxygen that we inhale become very toxic to the brain. Next, the oxidative stress induces brain inflammation, which leads to an assortment of degenerative diseases, particularly during the years following the TBI event. These three critical events following the TBI—that is, loss of normal energy production, oxidative stress, and long-term brain inflammation—underlie the development of seizures, sleep disruption, fatigue, depression, impulsivity, irritability, and cognitive decline. Although no effective treatments are available to alleviate these biochemical events in the brain, research has advanced sufficiently to understand how specific chemicals in the diet can target the negative effects of oxidative stress and inflammation.

A series of recent studies, conducted, for obvious ethical reasons, primarily using animal models, have discovered that adding certain vitamins and minerals to the diet may alleviate some of the long-term consequences of TBI. I would never recommend taking mega-doses of any supplement; thus, I list the dietary sources of these nutrients. It is always most effective, and considerably cheaper, to obtain nutrients via their natural sources. Supplementation with vitamins B₃ (found in white meat from turkey, chicken, and tuna), D (most dairy products and fatty fish such as salmon, tuna, and mackerel), and E (nuts and

seeds, spinach, and sweet potatoes) improved cognitive function following repetitive concussive brain injury.

Magnesium and zinc are both depleted following TBI. Zinc supplementation for 4 weeks reduced inflammation and neuronal cell death and decreased the symptoms of depression and anxiety in rats following TBI. Both zinc and magnesium can be obtained by eating nuts, seeds, tofu, wheat germ, and chocolate. The omega-3 fatty acids DHA and α -linolenic acid were also shown to be neuroprotective in animal studies, whether taken prior to or after the injury. Thus, people who participate in contact sports might want to add these fats to their regular diet. However, do not waste your money on α -linolenic acid or DHA supplements; adequate amounts are easily obtained via a diet containing fatty fish, flaxseeds, canola oil, soybeans, pumpkin seeds, tofu, and walnuts.

Sulforaphane was shown to improve blood–brain barrier integrity, reduce cerebral edema, and improve cognition in a rodent model of TBI. Sulforaphane can be obtained via a diet containing Brussels sprouts, broccoli, cabbage, cauliflower, kale, broccoli sprouts, turnips, and radishes. Finally, enzogenol improved cognition when administered to TBI patients in a randomized, controlled study. Enzogenol is a water extract of the bark from *Pinus radiata* that contains high levels of proanthocyanidins. Again, do not waste your money; proanthocyanidins are easily obtained by consuming grapes (seeds and skins), apples, unsweetened baking chocolate, red wines, blueberries, cranberries, bilberries, black currants, hazelnuts, pecans, and pistachios.

Interventional studies with natural antioxidants and anti-inflammatories via the diet are becoming attractive options for patients with TBI. Unfortunately, very few clinical trials to treat this neurological condition have been performed. Preliminary evidence clearly suggests that what a person eats following a brain injury can have significant long-term consequences.

HOW MUCH YOU EAT MATTERS MOST

The trainer for the popular NBC television show *The Biggest Loser* used to think that more exercise was all that was necessary in order to lose weight. After many years of helping severely obese people lose weight, however, Bob Harper has concluded that exercise is not the key; one's diet matters the most.

Not only is Harper helping his clients feel better and achieve their personal goals but also he is helping them live longer, healthier lives. Excess body fat accelerates aging and increases the risk of dying because, as previously discussed, fat cells produce inflammation. Researchers recently investigated whether diet or exercise most effectively reduced the levels of inflammation in overweight or obese women. After 12 months, the scientists concluded that the greatest weight loss and most significant reduction in the level of inflammatory protein reduction came only from dieting. The women who participated in an exercise-only program showed no reduction in inflammatory proteins. Essentially, unless one is a marathon runner or swimmer, the activity of one's musculature is not a major player in calorie consumption.

A large group of monkeys, ranging in age from middle-aged to quite elderly, were fed only 70% of their free-feeding diet for approximately 15 years. For someone eating a 2,000-calorie-per-day diet, this would be approximately 600 fewer calories per day. As a result of eating just 30% fewer calories, the brains of the monkeys on the restricted diet aged significantly more slowly, developed far fewer age-related diseases, had virtually no indication of diabetes and almost no age-related muscle atrophy, and lived much longer. Most important, and consistent with Bob Harper's conclusion, these monkeys did not exercise the weight off; they simply consumed fewer calories.

Simply stated, caloric restriction is the only valid, scientifically proven dietary intervention that can slow the aging process, reduce the risk of cancer, and improve health. It is also much cheaper—you will save money by eating much less food and paying for fewer tennis shoes, workout clothing, and gym memberships. The sooner one loses the fat, the sooner the brain and body can begin to recover. This risk factor is preventable.

THE JANUS EFFECT OF FOOD

The food we eat must be metabolized, a process that requires the oxygen in the air we breathe. Unfortunately, our most basic acts of survival, breathing and eating, are what age our bodies and our brains. If this sounds like the proverbial damned-if-you-do, damned-if-you-don't scenario, well, it rather is, and yet somehow our species has managed to survive this challenge for several hundred millennia.

Like most other animals on Earth, we humans acquire energy for our biochemical machinery by breaking down the carbon bonds found in fats, sugars, and proteins and then gobbling as much energy from the process as possible. The fact that we do this so inefficiently means that much of the energy in our food is lost as heat. This process also leaves our cells with leftover carbon atoms. The problem is what to do with all of the carbon waste. More than 2 billion years ago, the solution for a small, independently living single-celled organism, which might have closely resembled our own mitochondria (the furnace that handles almost all of our cells' energy production needs), was to combine these leftover carbons with a readily available gas, oxygen, and to expel the product as a gas called carbon dioxide. Thus, thanks to our current symbiotic relationship with the descendants of these ancient bacteria, our mitochondria, our bodies obtain energy to live as follows: Carbon bonds come into the front end of our feeding tubes in the form of fats, carbohydrates, and proteins; we then extract energy and excrete the residue as carbon dioxide and water vapor.

Because oxygen is also exceedingly toxic to cells, it must be used very carefully and conservatively. Indeed, scientists have recently discovered that the genes that control energy metabolism have been highly conserved across millions of years of evolution, from yeast to humans, and that these genes influence the rate of the aging process. Essentially, the better we negotiate our energy–oxygen exchange with our indwelling mitochondria, the longer and healthier we live as single individuals and as a

species. Disrupt the balance in this exchange, and the impact can be harmful.

In general, the hemoglobin in our blood does a decent job of regulating the oxygen levels near the individual cells of our bodies so that those cells have the oxygen they need for respiration but not too much to kill them outright. These cells have also evolved numerous antioxidant systems that would allow us live to be 115 years old if we were lucky and ate very little food. But most of us are not that lucky, and most of us eat frequently and just keep on breathing, making ourselves vulnerable to the consequences of oxygen. Thus, our bodies and our brains age more rapidly.

With normal aging, because we insist on eating and breathing, tissue-damaging molecules called oxygen free radicals are formed by our mitochondria. Free radicals are not always harmful, but they become more prevalent with age and may slowly overwhelm our natural antioxidant systems, destroying our neurons and just about every other cell in our bodies. According to another recent discovery, the overproduction of these oxygen free radicals may encourage cancer cells to metastasize and move around the body. Think about the unbelievable irony of this process: The mitochondrial power plant that resides in quite large numbers in every cell of our bodies is actively injuring those cells by the very process of trying to keep them alive. It turns out that each species' maximum life span may be determined by how many free radicals are produced by the hundreds of mitochondria that live in each of their cells.

We are, indeed, our own worst enemy. Unless you listened to your mom's advice and you are eating your fruits and vegetables regularly.

PROTECTING THE BRAIN FROM AGING WITH FRUITS AND VEGETABLES

Sometimes scientists tell us things that we are fairly certain we already believe. Still, it is always nice to know that what we believe to be true is in fact true. A group of scientists investigated whether eating fruits and vegetables for 13 years would actually protect against a decline in cognitive abilities that humans commonly experience with normal aging. It does, and the following discussion details how they proved it.

Approximately 2,500 subjects finished the study and adequately completed all the dietary and cognitive evaluations. The subjects were between the ages of 45 and 60 years at the beginning of the 13-year study, and they were required to maintain careful and detailed records of their daily diets. The subjects were evaluated at the beginning and end of the study for a variety of cognitive abilities, including verbal memory and higher executive functions such as decision-making and mental flexibility, among many other tests. There is good news and bad news in the results.

First, their diet was composed of a variety of fruits and vegetables but specifically excluded potatoes, legumes, and dried fruits (each of these foods introduces specific complications that might interfere with the outcome). The adults were divided

into groups according to the following diets: folate-rich diets containing fruits and vegetables, β -carotene-rich diets containing both fruits and vegetables, vitamin C-rich diets containing both fruits and vegetables, and vitamin E-rich diets containing both fruits and vegetables. The individual consumption of specific nutrients—folate, β -carotene, and vitamins C and E—was also monitored. The subjects were allowed to choose how much of each diet they wished to consume each day; therefore, daily intakes of each nutrient varied. This was allowed in order to more closely reproduce how most of us actually select our daily intakes. At the end of the study, the scientists found that eating fruits and vegetables has differential and significant beneficial effects on different aspects of brain function. When the specific diets were examined more closely, diets that consisted of only fruits or diets with fruits and vegetables rich in vitamins C and E selectively benefited only verbal memory scores. This test involved being told to remember 48 different words and then recalling them after a delay with distractions. The surprising finding was that eating fruits and vegetables had no significant benefit on other types of tasks that required alternative types of memory, such as learning motor tasks or recognizing familiar objects. Clearly, each component of one's diet may influence how well one's brain works in unique ways.

Natural antioxidants found in fruits, seeds, beans, and vegetables, such as polyphenols, provide protective effects for the brain through a variety of biological actions. Polyphenols are abundant in nature; more than 50 different plant species and

more than 8,000 such compounds have been identified in plant extracts. Obviously, investigating the multiple health benefits of these natural chemicals poses an enormous challenge that may have significant health benefits. For example, the consumption of polyphenols is inversely proportional to the incidence of cardiovascular disease. Probably the most thoroughly investigated polyphenols are quercetin, found in apples, tea, and onions, and resveratrol, found in the skin of grapes. Grapes use resveratrol to defend against fungus.

Tea contains a number of beneficial chemicals. In neurodegenerative diseases, administration of tea extracts reduces the production of mutant proteins and may prevent neuron cell death in Alzheimer's disease. Although tea is not a cure for Alzheimer's disease, its use is certainly justified given its safety and potential for long-term benefits. In general, tea, chocolate, and red wine consumption among the elderly are inversely proportional to the incidence of cognitive impairment. A recent epidemiological study also discovered another benefit: Tea drinkers tended to be thinner than coffee drinkers.

Recently, a friend who has been trying to lose weight for many years indicated that her new diet requires that she eat only meat. When I asked whether she was also eating fruits, she answered that fruits are full of sugar and thus not part of her new healthy diet. This is a common recommendation for many of the new, popular diets—avoid carbohydrates in any form. There are some good arguments to be made about avoiding sugar, but if this approach takes fruits out of your

diet, you may be missing important nutrients that might make you healthier in the long term. I want to introduce you to one of these nutrients: ursolic acid.

Ursolic acid is found in apples (mostly in the skin), cranberries, and prunes, as well as in elderflower, basil, bilberries, peppermint, rosemary, thyme, and oregano. Although a considerable number of studies have already documented the ability of this chemical to inhibit the growth of various types of cancer cells, that is not why I mention it here. Eating fruits and spices that contain ursolic acid might also enhance brain function and reverse some of the negative effects of obesity on the brain as one gets older. Studies have shown that ursolic acid can improve cognitive functioning by increasing the brain's and the body's sensitivity to insulin. The biological mechanisms have been fairly well investigated, and it appears that ursolic acid is able to correct the errors in metabolism induced by long-term obesity. The challenge is to discover how many apples, prunes, and cranberries one needs to eat in order to achieve these benefits. Studies on humans have not been performed. Again, the diet that optimizes benefits for the brain is the Mediterranean diet.

Will you lose weight by eating only fruits? Maybe; it depends on what else you are eating. Will you lose weight avoiding fruits and berries while only eating meat? Yes. However, over the long term, it is unwise to do so. A study of 16,000 nurses found that eating blueberries and strawberries was associated with lower rates of cognitive decline. If you are trying to lose weight, the benefits of an all-meat diet are more immediate than the

benefits of eating apples, cranberries, and prunes because their benefits on your health take longer to notice. Essentially, all-meat fad diets have not been around long enough for medical science to determine the long-term risks. Caloric restriction is the only valid, scientifically proven dietary intervention that has been shown to slow the aging process and improve health. The reason we hear so little about this approach is because no one stands to make a profit on all of us eating less food and more apples, cranberries, and prunes.

IS A VEGETARIAN DIET ALWAYS HEALTHY?

I have discovered that most people are usually judicious in how they administer medicines to themselves; in contrast, people are often cavalier in their decisions about which foods they consume. Thus, the average person is unlikely to abruptly stop taking his or her medicine, in contrast, many people decide, usually without much forethought, that they are going to stop eating red meat. Is this always a good decision?

When humans consume diets that are low in tryptophan, a condition often seen when someone first goes on a vegetarian diet, the brain produces much less serotonin and humans display many of the symptoms of depression, such as anxiety, irritability, and difficulty thinking. I have seen the same thing happen to many of my students who decided to become vegetarians without considering the consequences of such a drastic change to their nutrient intake. Historians now blame low-tryptophan

diets (e.g., due to crop failure) for multiple wars and acts of cannibalism (which would have the benefit of restoring their protein intake). Scientists once thought that drinking a glass of warm milk before bed, or eating a lot of turkey meat during the holidays, made people drowsy because of tryptophan loading. However, the current evidence does not support this explanation (turkey meat is actually quite low in tryptophan), but the claim makes an important point: We must get the right balance of any particular nutrient into our brains in order for us to notice any effects.

Some dietary regimens may be beneficial over the long term; for example, it is widely known that the Mediterranean diet is associated with a lower risk of depression. In contrast, a poor diet that is high in saturated fats and caloric levels leads to depression. In one study, subjects who consumed more water, insoluble fiber, ascorbic acid, tryptophan, magnesium, and selenium reported a better mood overall. A diet high in legumes, fruits, and vegetables, such as a typical vegetarian diet, easily provides these nutrients. Thus, a well-balanced vegetarian diet can be quite beneficial to one's health. The most important aspect to consider when converting to a vegetarian diet is where you will get the nutrients that others easily obtain from red meats. Good sources for protein with a complex blend of amino acids, long-chain omega-3 fatty acids, and bioavailable iron and zinc are frequently missing from vegetarian diets. Furthermore, vitamin B₁₂ deficiency often develops with normal aging; thus, being an elderly vegetarian might make obtaining this vitamin

more problematic. As long as a vegetarian obtains sufficient quantities of these essential nutrients, there is no reason to expect any negative health consequences. Indeed, there are many positive benefits for the brain (and body of course) in following a vegetarian diet. For example, vegetarians are less likely to develop type 2 diabetes, which is a risk factor for dementia and Alzheimer's disease.

Several studies of people who do not pay attention to their nutrient balance have reported that vegetarian diets are associated with a higher prevalence of major depression. This mood change can be attenuated by eating a whole egg, which often exerts an antidepressant-like effect for vegetarians. In contrast to all of these wonderful indicators is a study published in the journal *PLoS One* that reported some conflicting findings. First, the good news: A vegetarian diet was related to a lower body mass index and less frequent alcohol consumption. However, the authors also discovered that a vegetarian diet was associated with higher incidences of mental health disorders. Why? One study discovered that the adoption of the vegetarian diet tends to follow the onset of certain mental disorders. These authors concluded that a vegetarian diet is associated with an elevated risk of mental disorders. However, it remains to be determined which came first, a mental disorder or becoming a vegetarian.

DON'T FORGET THE SPICE

My grocery store stopped selling an excellent margarita mix because its label states that it contains the preservative sodium

benzoate. Sodium benzoate prevents food from molding and can be found in many foods and popular soft drinks. The label on the drink mix claimed that it contained only “natural ingredients.” There were complaints from some consumers that inclusion of this preservative violated that claim. Is sodium benzoate truly unnatural? Certainly not. Is it harmful? The answer for sodium benzoate, as for so many ingredients in the foods we consume, is yes and no . . . and it depends. In order to answer this question, we need to consider the natural source of sodium benzoate—cinnamon. Cinnamon is a spice obtained from the bark of the *Cinnamomum verum* tree. Since antiquity, cinnamon has had many uses. Moses included it as an ingredient of the holy anointing oil. The Chinese knew it as Gui Zhi and recommended it for its antibacterial and antipyretic properties. Medieval physicians included cinnamon in their preparations to treat arthritis and infections. Our ancestors were clearly onto something worthwhile.

Today, scientists know that cinnamon is converted in the body to sodium benzoate, which has powerful anti-inflammatory and antioxidant actions. Many of this spice’s benefits likely derive from these actions in the body. Sodium benzoate is frequently added to foods and beverages. However, as is true for so many chemicals in our diet, a little bit of sodium benzoate is good; too much can be harmful. Finding the best daily dose of this ancient spice requires careful investigation.

A recent study found detailed evidence that the benefits of cinnamon, via its metabolite sodium benzoate, may also

produce very specific changes in how memories are made in the brain. Similar to the benefits of many other molecules found in nature, cinnamon only improved brain function in subjects who had existing problems with learning. If we only focus on the effects of cinnamon in the learning-impaired subjects, the changes observed were quite impressive: The basic architecture of the individual components of the brain, the neurons, was significantly transformed by cinnamon. The scientists discovered that the physical connections between neurons were altered so that memories could form more easily.

The doses for humans, scaled up from those of the animals used in this study, would be approximately 1 g per day. I realize that seems like a lot of cinnamon. The problem is that most of the cinnamon we consume is not completely absorbed within the intestines: Either it is utilized for its benefits by the trillions of bacteria (approximately 5 pounds worth) that live within the gut or it is destroyed by enzymes within the body. Fortunately, a sufficient amount of sodium benzoate that is produced from the cinnamon does cross the blood–brain barrier fairly well to gain access to the brain.

Cinnamon has also been shown to protect the brain in many other conditions. It protected mice from a form of multiple sclerosis, it increased chemicals in the brain that protected dopamine neurons in an animal model of Parkinson's disease, and it reduced the formation of reactive oxygen molecules that accelerate the effects of aging in the brain and body. The sodium benzoate produced in the body after eating cinnamon induces

significant increases in the levels of a variety of chemicals in the brain called neurotrophic factors. These factors stimulate the birth of new neurons in the brain and encourage the survival of existing neurons. These two processes are critical for the maintenance of a healthy brain. During the past decade, many scientific studies have discovered that these neurotrophic factors can prevent, or greatly slow, the progression of a variety of degenerative diseases of the brain, including Alzheimer's and Parkinson's disease. Cinnamon has also been shown to reduce blood sugar levels in people with type 2 diabetes and reduce cholesterol levels by up to 25%. Thus, cinnamon is good for your brain and body. When Hippocrates wrote, "Let food be thy medicine and medicine be thy food," he was likely thinking about cinnamon.

Curcumin, derived from the spice turmeric, the powdered rhizome of the medicinal plant *Curcuma longa*, has been used for many centuries throughout Asia and India as a food additive and a traditional herbal remedy. I have published studies showing that curcumin has potent antioxidative and anti-inflammatory proclivities that may be beneficial for patients with either Alzheimer's or Parkinson's disease. Curry containing curcumin is eaten virtually daily in India. The consumption of curry is thought to underlie the very low incidence of Alzheimer's disease in India. Unfortunately, the introduction of the Western diet may be undermining the benefits of this traditional spice. A recent epidemiological study discovered that each time a McDonald's fast-food restaurant opened for business in India,

the incidence of Alzheimer's disease increased significantly in the population of people living within a 30-km radius of the restaurant.

Overall, the solution to aging well is exactly what you may have heard from your mother: Eat healthy and in moderation; exercise a little and in moderation; and, finally, avoid eating anything from a cow.

NOW FOR SOMETHING TRULY WILD

Alternatively, you might consider heterochronic parabiosis. The name sounds complicated, but the method is really quite simple. You can do it at home using a simple two-step process: First, find a young person; second, attach your circulatory system to that of the young person—permanently. This rather gruesome technique was first studied during the Civil War by Dr. Paul Bert. Essentially, the blood from young people can rejuvenate old people, leading to greatly improved brain function and improved regenerative capacity throughout the body. Studies on old mice have shown that sharing blood with young mice leads to reduced signs of aging of the heart, bones, liver, and digestive system. Sharing your cardiovascular system with a younger person can also reverse the age-related decline in pancreatic β cell function that may underlie type 2 diabetes. These studies indicate that converting the composition of aged blood into a youthful composition can reverse, not just slow, the functional decline of the aged body and brain. The challenge is to identify the array of pro-youthful and anti-aging factors that exist in the

blood of young people so that these might be administered to old people. A few of these factors have already been identified; one is oxytocin, which is better known as the “trust hormone” or the “love hormone” because its level in the blood rises after hugging or kissing someone we love or experiencing social bonding or sexual pleasure. More recently, oxytocin has been posited to help us manage both emotional and physiological responses during life-altering events. The simple lesson here is that rather than attaching yourself to an unwilling teenager for blood rejuvenation, it might be easier, and far more enjoyable, to just give and accept hugs freely and often.

FLAVINOIDS TO THE RESCUE

“Let food be thy medicine and medicine be thy food,” said Hippocrates. During the past 2,500 years since he made that statement, science has made significant progress in understanding how food exerts its beneficial effects on health. We now have solid proof that the foods and beverages that are consumed by humans, particularly those derived from tea leaves, coffee and cocoa beans, celery, grapes, mangos, berries, hops, and other grains, have clearly defined beneficial actions on brain function. Although these foods and drinks have quite different chemical compositions, they all contain compounds called flavonoids. Flavonoids are not nutritious, but they are believed to be responsible for the beneficial effects of many foods on the brain.

For many decades, the biochemical benefits of flavonoids were attributed to their ability to confer protection from

oxygen—they are antioxidants. Although flavonoids are capable of acting in this fashion in laboratory experiments, it is unlikely that they can provide this benefit within the brain. The reason is that the flavonoids obtained from the diet do not achieve an adequate level in the brain that would allow them to act as effective antioxidants. So how do they benefit us?

In order to answer this question, scientists have investigated what flavonoids can do when their concentration in the brain is extremely low, at levels that might be achieved by a diet rich in these fruits. The flavonoids directly induce neurons in the brain to become more plastic—that is, more capable of forming new memories. The flavonoids achieve this by directly interacting with specific proteins and enzymes that are critical for learning and memory. They also induce the birth of new neurons, a process that is critical for recovering from injury, exposure to toxins, and the consequences of advanced age, such as increased levels of brain inflammation. Finally, some recent studies have shown that flavonoids actually enhance blood flow to active brain regions.

So how much is enough? Let us consider two of my favorites: wine and chocolate. If you consumed approximately 200 ml (6.7 oz) of Cabernet Sauvignon or approximately 50 g (1.7 oz) of dark chocolate (71% cocoa powder), you would intake nearly identical quantities of flavonoids; 200 ml is the daily wine intake recommended to produce the most health benefits in a typical adult. When young adult females were given flavonoid-rich chocolate drinks, blood

flow to their brains was significantly increased within just 2 hours, and their performance on a complex mental task was greatly improved.

No one is certain whether all flavonoids are capable of producing these benefits. But recent investigations have suggested that it does not matter which type of food provides the flavonoids, only that they are eaten as often as possible. In addition to those edibles mentioned previously, studies to date have also identified benefits from black currants, pears, blueberries, strawberries, and grapefruit. One final caveat: No studies have yet proven a true cause-and-effect connection between the lifelong consumption of flavonoid-rich diets and a reversal of age-related deterioration in learning or general mental function. Still, I think that we should all be willing to make a leap of faith that the connection is real and modify our diets accordingly, such as eating more chocolate!

MORE ON CHOCOLATE AND ITS ACTION IN THE BRAIN

In 1648, according to the diary of English Jesuit Thomas Gage, the women of Chiapas Real arranged for the murder of a certain bishop who forbade them to drink chocolate during mass. In an ironic twist, the pontiff was ultimately found murdered after someone had added poison to his daily cup of chocolate. Was this an act of blind rage by the women of Chiapas Real or justifiable homicide? For a small percentage of the population, eating chocolate can produce rage, paranoia, and anger

that occur without warning. Fortunately, for most of us, this is not the typical reaction to eating chocolate.

In order to understand why chocolate is so enjoyable for some while it induces uncontrollable rage in others, we need to consider the contents of most dark chocolates. Chocolate contains an array of compounds that contribute to the pleasurable sensation of eating it. Many of these compounds are quite psychoactive if they are able to get into our brains. Are they the reason we love chocolate so much? Are they the reason some people fly into fits of anger? The answer to both questions is, of course, yes. However, as is true for so many of the things we eat that affect our brain, it is not that simple.

Chocolate usually contains fats that may induce the release of endogenous molecules that act similarly to heroin and produce a feeling of euphoria. German researchers reported that drugs that are able to block the actions of this opiate-like chemical produced by eating chocolate prevented the pleasure associated with eating chocolate. Chocolate also contains a small amount of the marijuana-like neurotransmitter called anandamide. Although this molecule can easily cross the blood–brain barrier, the levels in chocolate are probably too low to produce an effect on our mood by itself.

Chocolate contains some estrogen-like compounds, a fact that may explain a recent series of reports showing that men who eat chocolate live longer than men who do not eat chocolate. The effect was not seen for women, who have an ample

supply of their own estrogen until menopause. However, estrogen is not likely to cause rage.

Let's focus on the women of Chiapas Real again. In contrast to its effects on men, women more often claim that chocolate can lift their spirits. In a study of college students and their parents, 14% of sons and fathers and 33% of daughters and mothers met the standard of being substantially addicted to chocolate. Women seem to have very strong cravings for chocolate just prior to and during their menstrual cycle.

Women eat more and crave more foods in the days before the start of their period when progesterone levels are low. This is when premenstrual symptoms tend to appear as well. Chocolate may provide an antidepressant effect during this period. In one study, researchers found that women in their 50s often developed a sudden strong craving for chocolate. It turns out that most of the women had just entered menopause and were on a standard form of estrogen replacement therapy consisting of 20 days of estrogen and 10 days of progesterone. The chocolate cravings developed during the days on progesterone. Why?

Chocolate contains magnesium salts, the absence of which in elderly females may be responsible for the common postmenopausal condition known as chocoholism. Approximately 100 mg of magnesium salt is sufficient to remove any trace of chocoholism in these women; but who would want to do that? Finally, a standard bar of chocolate contains as many antioxidants as a glass of red wine. Clearly, there are many good

reasons for men and women to eat chocolate to obtain its indescribably soothing, mellow, and yet euphoric effect.

What about the anger? How might that happen? Chocolate contains phenethylamine (PEA), a molecule that resembles amphetamine and some of the other psychoactive stimulants. PEA often appears in foods as a result of microbial metabolism related to bacterial contamination. When chocolate is eaten, PEA is rapidly metabolized by the enzyme monoamine oxidase (MAO). Fifty percent of the PEA a person consumes in a chocolate bar is metabolized within only 10 minutes. Therefore, very little PEA usually reaches the brain, thus contributing little or no appreciable psychoactive effect without the use of a drug that can inhibit MAO. Could this happen? Possibly yes. MAO levels are at their lowest level in premenstrual women, which is the time when women most crave the soothing effects of chocolate.

In addition, chocolate also contains small amounts of the amino acid tyramine. Tyramine can powerfully induce the release of adrenaline, increase blood pressure and heart rate, and produce nausea and headaches. Usually, the nasty effects of tyramine are prevented because it, too, is metabolized by MAO. You can see the problem: The tyramine and PEA in chocolate may slow each other's metabolism. The consequence is that if both of these chemicals remain in the body too long, high blood pressure, a fast-beating heart, heightened arousal, racing thoughts, anger, anxiety, and rage would ensue. One rather controversial study claimed that inhibitors of MAO were able to increase PEA levels in the brain by 1,000-fold. That is a lot, and

the consequences of this actually happening could be lethal. But the potential exists for some vulnerable people to experience significant shifts in mood after eating chocolate with high cocoa powder levels.

The main point to take away from this discussion about chocolate is that plants, such as the pods from the cocoa tree, contain a complex variety of chemicals that, when considered individually, are not likely to impact our brain function. However, when considered in aggregate, they may exert compound effects throughout the body; some of those effects may be desirable, whereas others may not. Chocolate is an excellent example of how difficult it is to differentiate food from drugs. In some countries, there is ample reason to believe that chocolate is a powerful cognitive stimulant. In 2012, the prestigious *New England Journal of Medicine* reported that there is a significant correlation between the annual per capita consumption of chocolate and the number of Nobel laureates per capita.

CHAPTER 3

MEMORIES, MAGIC, AND A MAJOR ADDICTION

What causes memory loss in patients with Alzheimer's disease? Why did witches once believe that they could fly? Why is it so difficult to stop smoking? The answers to these questions can be found by understanding the function of acetylcholine, a neurotransmitter chemical that exists almost everywhere in nature. Acetylcholine was discovered by the pharmacologist Otto Loewi a couple days after Easter Sunday in 1920 while working at University College, London. His equipment was simple, but his insights demonstrated true genius. Loewi shared the Nobel Prize for Physiology or Medicine in 1936 with Henry Dale, also a pharmacologist, for their work on chemical neurotransmission. Acetylcholine has been found in both uni- and multicellular

organisms, including the bacterium *Pseudomonas fluorescens*, isolated from the juice of fermenting cucumbers, as well as in the blue-green algae *Oscillatoria agardhii*, in which it may be involved with photosynthesis.

Acetylcholine stimulates silk production in spiders and limb regeneration in salamanders. In humans, acetylcholine enables movement by stimulating the muscles to contract, and it plays an important role in the action of the parasympathetic and sympathetic nervous systems, which are part of the autonomic nervous system (ANS). The ANS maintains homeostasis, or a balance of forces or equilibrium, for your entire body. Among other functions, it controls the rate at which your heart beats, how fast you breathe, how much saliva your mouth is making, the rate of movement of material in your gut, your ability to initiate urination, how much you are perspiring, the size of your pupils, and the degree of visible sexual excitation you might experience. Within the human brain are numerous acetylcholine pathways that influence the function of the cortex, hippocampus, and many other regions. Within these various regions, the actions of acetylcholine enable you to learn and remember, regulate your attention and mood, and control how well you can move. Thus, anything that affects the function of acetylcholine neurons has the potential to affect all of these brain and body functions. That “anything” could be a certain drug or a disease.

A CASE IN POINT: ALZHEIMER'S DISEASE

Sometimes we can learn much about the role of a particular neurotransmitter system by investigating what happens when it is injured or diseased. In the brains of people with Alzheimer's disease, for example, acetylcholine neurons that project into the hippocampus and cortex very slowly die. The effects of this neuronal death have been the subject of research in my laboratory for more than 25 years. The loss of normal acetylcholine function in the cortex may be why patients with Alzheimer's disease have difficulty paying attention to their environment. The loss of acetylcholine projections to the amygdala, part of the brain's limbic system, may underlie the emotional instability, such as irritability and paranoia, that is sometimes observed in these patients. And the loss of acetylcholine projections into the hippocampus may underlie the profoundly debilitating memory loss that is the major hallmark of this disease.

Let me illustrate the effect of at least one of these losses by first describing the role of acetylcholine in the cortex of a normal brain (yours). Imagine that, using an electroencephalogram (EEG), I have attached some electrodes to the front half of your head to record the electrical activity occurring inside your brain. Next, I calmly inform you that as soon as I ring a bell (at the point in time shown by the number 1 in Figure 3.1), a masked gunman will enter the room and start shooting. You

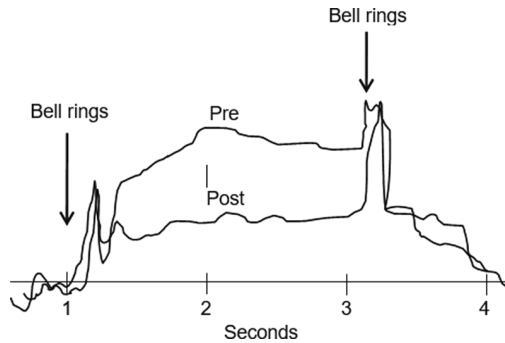


Figure 3.1 Electroencephalogram recorded over the frontal lobes showing the presence of an “anticipation wave” with an intact acetylcholine system (Pre) and without a functioning acetylcholine system (Post). The sharp vertical spikes are associated with a bell ringing at the beginning and end of the recording.

must also believe that I am telling the truth for this to work. Okay, now I ring the bell. Take a look at the EEG recording labeled “Pre” in Figure 3.1. It shows that an electrical wave quickly appears within the frontal lobes of your brain that began as soon as I rang the bell. The bell ringing causes the sharp spikes prior to the formation of the wave. This electrical pattern, also known as an EEG wave, will continue to live in your brain until one of two things happens: either someone runs into the room with a gun (at the point in time shown by the number 3 in Figure 3.1) or the bell rings again or you decide nothing is going to happen after all. At that point, the EEG wave will disappear. This “pre-wave” indicates that you were paying close attention to what you thought was about to happen. It is an expression of your brain experiencing anticipation.

Experiments in my laboratory and in others have demonstrated that the appearance of this wave of electrical activity requires the normal function of acetylcholine within your frontal cortex. If the acetylcholine neurons that project into your frontal cortex are destroyed, then this wave cannot fully form and you will have great difficulty paying attention to important things, such as the impending appearance of a masked gunman. An example of such a wave is labeled “Post” in Figure 3.1. In this case, the absence of acetylcholine does not allow the wave to fully develop. This research has demonstrated that acetylcholine’s function is to instruct the neurons in one’s frontal cortex to pay attention to important information and be vigilant to impending danger. If acetylcholine function is impaired, this ability is lost. These results provide valuable insight into why patients with Alzheimer’s disease have trouble paying attention to things that might be important, or even harmful, to them. Indeed, during the later stages of their disease, when most of these acetylcholine neurons have disappeared, patients have difficulty paying attention to anything at all.

KEEP THE ALUMINUM COOKWARE— IT DOES NOT CAUSE ALZHEIMER’S DISEASE

Aluminum is everywhere around us all of the time. It is the most abundant metal in the Earth’s crust. Yet, somehow, we have become fearful of it when it is used as cookware or as cans for beer or soda. No life form uses aluminum for any biological

process. The reason is that aluminum is highly reactive and easily combines with other metals and oxygen to form hundreds of different minerals. Aluminum, in scientific terms, is not bioavailable to humans—usually. It depends on what chemical form the aluminum takes. Usually, because aluminum is so tightly bound within minerals, animals have no chance to absorb it into their tissues.

Plants do not use aluminum, but they are capable of absorbing it. Grains harvested to make bread and cereals often contain a few parts per million (ppm) of aluminum. This aluminum exists within a bioavailable form that humans can absorb into their bodies. Animals that eat plants have concentrations of aluminum in their tissues, too. Thus, meats obtained from cows may contain up to 1,000 ppm of aluminum. This is where things get a little dicey. Are we at risk from the aluminum in our diet? It depends entirely on how much a person consumes. Some people are vulnerable to its presence in the body. Aluminum has also been found in the brains of Alzheimer's disease patients who have died. Although this seems suspicious, aluminum salts will deposit in any soft tissue that has cell loss due to injury or degeneration. Thus, aluminum salts also deposit in the hearts of people with coronary disease. Aluminum does not cause Alzheimer's disease.

What about antiperspirants? The aluminum salts used in these products do one thing—they irritate our sweat glands to the point that they swell and close the pores that allow perspiration to reach the surface of our skin. The real risk

from antiperspirants comes from using sprays that produce a cloud of aluminum salts that can be inadvertently inhaled. Thus, keep using your aluminum cookware—it poses no risk to health. The real risk comes from the food we cook in those pots and pans.

ACETYLCHOLINE PRODUCTION AND RELEASE

Sometimes the severity of the cognitive symptoms in Alzheimer's disease can be reduced, at least to some degree, by drugs and dietary nutrients that enhance the function of acetylcholine neurons in the brain. To understand how this is possible, we need to examine how acetylcholine is produced in the brain in the first place.

Neurons synthesize acetylcholine from choline, which is obtained from the diet, and from acetyl groups that originate in mitochondria from the metabolism of sugar. Here is yet another example of the importance of sugar for your brain's normal function. The synthesis of acetylcholine occurs within the cytoplasm of your neurons, and the product is stored in synaptic vesicles, those small, round packets that neurons release to communicate with each other. Neurons pay a lot of attention to the shelf life of their neurotransmitters; they prefer to release the most recently produced neurotransmitter molecules first. As you can see, neurons do not behave like your local grocer; they do not rotate their stock. This means that the freshest products (the most recently produced acetylcholine

molecules) are released first, thus guaranteeing that the communication between neurons is successful.

Many health food stores throughout America sell choline powder to gullible customers, claiming that consuming more choline will somehow enable their brains to make more acetylcholine. Given the vital role of acetylcholine in learning and memory, this is an appealing claim. Regrettably, it has no basis in fact. For adults, the brain responds only to deficits, not surpluses, in the diet. It has a ready source of choline in the diet or stored in the liver and, in fact, never develops a deficit in choline, even in patients with Alzheimer's disease. Thus, consuming extra choline does not induce your brain to make more acetylcholine. Instead, it only results in a gaseous by-product that you exhale and that smells like rotting fish. Rather than enhancing your cognitive abilities, choline supplements merely generate a terrible case of bad breath.

Once released, the action of acetylcholine within the synapse is terminated or inactivated by an enzyme called acetylcholinesterase at the rate of approximately 25,000 molecules per second. Thus, even the partial inhibition of this enzyme's activity has a profound effect on synaptic levels of acetylcholine. Many different drugs are capable of inhibiting this enzyme, including some nerve gases that cause synaptic levels of acetylcholine to rise too high and that are therefore highly poisonous, as well as some drugs that cause the level to rise just enough (but not too much) to be clinically beneficial. Physostigmine, obtained from the Calabar bean *Physostigma venenosum*, is highly

toxic but has been given to patients with Alzheimer's disease in order to improve their ability to pay attention or remember the day's events. Unfortunately, its benefits were very limited, and the treatment did not alter the ultimate course of the disease. Huperzine A, from *Huperzia serrata*, is another plant-derived inhibitor of acetylcholinesterase that can easily be purchased commercially. The claims that it has neuroprotective properties or that it will produce cognitive benefits for people with or without dementia are completely false. Huperzine A is as toxic and clinically ineffective as physostigmine—do not waste your money or risk your life.

It is worth considering what would happen if a neuron could not release acetylcholine at all. The botulinum toxin from the *Clostridium botulinum* bacteria that sometimes forms in the foods we eat can inhibit the release of acetylcholine from nerve terminals. Fortunately for your brain, this toxin cannot cross the blood–brain barrier. However, there is more to you than just your brain. Botulinum toxin can significantly impair the ability of your vagus nerve to control your breathing. Your vagus nerve is responsible for causing the contraction of your diaphragm muscle to pull air into your lungs (Figure 3.2). However, if your brain cannot communicate with your diaphragm via the release of acetylcholine from the vagus nerve, then you will stop breathing and die. The botulinum toxin is exceptionally potent: 1 g is sufficient to kill approximately 350,000 people!

Once released into the synapse, the neurotransmitter acetylcholine can act on two quite different protein receptors that

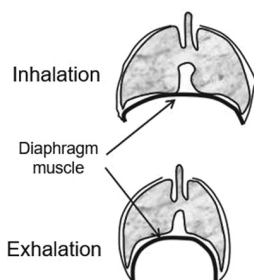


Figure 3.2 The release of acetylcholine onto the diaphragm muscle causes it to contract and pull air into the lungs (inspiration). The relaxation of this muscle allows air to leave the lungs (exhalation).

have been designated, as have most receptors, according to the compounds that were originally used to study them—in this case, muscarine and nicotine. Most of the acetylcholine (or “cholinergic”) receptors in the brain are the muscarinic subtype, whereas less than 10% are nicotinic. Both types of receptors have been found in peanut worms (whose fossils date back a half-billion years), spoon worms, leeches, and earthworms. There is no evidence that these two receptors are related or share a common evolutionary history: They differ in size, structure, and mechanism of action, yet they both respond to acetylcholine. Moreover, their response to different drugs tells us something important about the role that these two different acetylcholine receptors play in the brain and the body. Some drugs block, or antagonize, these receptors, whereas other drugs enhance, or stimulate (i.e., act as agonists of), them. Let’s now examine several types of drugs to identify what their actions reveal about the function of these receptors.

ANTAGONIZING ACETYLCHOLINE

Curare, found in a resinous extract of the plants *Chondrodendron tomentosum* and *Strychnos toxifera*, from the Orinoco and Amazon basins in South America, is an antagonist at nicotinic acetylcholine receptors. Curare does not cross the blood–brain barrier; therefore, its actions are expressed only outside of the brain at the neuromuscular junction where neurons control muscles. Curare is extremely lethal for one simple reason: It blocks the nicotinic receptors located on the diaphragm; therefore, death from curare results from asphyxiation. Imagine that you were just shot by a curare-tipped arrow: You are awake, fully aware of having been shot, yet unable to move, speak, or, ultimately, breathe.

The naturally occurring drugs atropine and scopolamine have a different sort of antagonistic effect: They block the muscarinic subtype of acetylcholine receptors. As a result, they impair our ability to form new memories, and they produce considerable mental confusion and drowsiness. At high doses, atropine and scopolamine can be lethal.

Several plants contain atropine and scopolamine, including henbane (*Hyoscyamus niger*), jimson weed (*Datura stramonium*), and mandrake (*Mandragora officinarum*). The “bane” part of henbane refers to an archaic Old English word for death; according to legend, local farmers noticed that their hens and roosters did not live long after eating this plant. Another plant, the “deadly nightshade,” or *Atropa belladonna*, was given its name by botanist

Carl von Linné in the 18th century to signify its deadly nature. He derived the genus name from one of the Greek fates, Atropos, who cut the thread of life at the appointed time—she was death. Poets and writers have long been aware of the lethal effects of these plants and have often incorporated them into their stories. For example, consider Shakespeare’s tragedy *Hamlet*. King Hamlet of Denmark dies suddenly, ostensibly from snake-bite, and a few weeks later, his brother Claudius marries the king’s widow, Queen Gertrude. The ghost of the king appears before his son, Prince Hamlet, and reveals that Claudius killed him by pouring into his ear the contents of an ampoule of henbane. In Act I, Scene 5, the ghost speaks to Hamlet:

Sleeping within mine orchard,
My custom always in the afternoon,
Upon my secure hour thy uncle stole
With juice of cursed hebona [henbane] in a vial,
And in the porches of mine ears did pour
The leperous distilment, whose effect
Holds such as enmity with blood of man.

Enmity indeed! How did scopolamine and atropine, both components of henbane, kill King Hamlet? To answer this question, let us return to the ANS. Recall the functions of the ANS that I mentioned previously. For example, it controls heart and breathing rate, intestinal motility, pupil dilation, salivation, and perspiration. The two major components of the ANS, the

parasympathetic and sympathetic nervous systems (Figure 3.3), essentially function in competition with each other to maintain a balance so that your heart does not beat too fast or too slowly, you do not breathe too quickly or slowly, the contents of your gut do not move too fast or too slowly, and so forth. When the parasympathetic nervous system is in control, it slows your heart rate, slows your breathing, constricts the pupils of your eyes, increases the production of saliva in your mouth, and so forth. When the sympathetic nervous system is in control, it increases your heart rate, increases your respiration rate, dilates the pupils of your eyes, reduces salivation (leaving you with a dry, metallic taste in your mouth), and so forth. This careful dance between

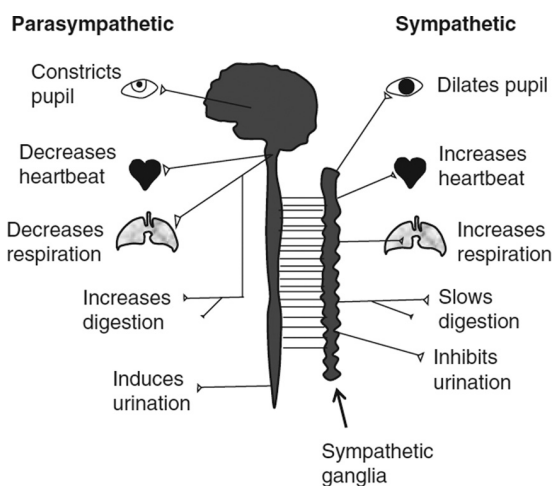


Figure 3.3 The two major components of the autonomic nervous system. The parasympathetic neurons release acetylcholine; the sympathetic neurons release norepinephrine. These two systems provide a balance of control of the function of the organs and structures shown.

these two competing neural systems is choreographed by your brain, but you are usually not aware of it. However, when something disturbs this balance, such as scopolamine, you become very aware that something is wrong.

Recall that scopolamine, an ingredient in henbane, blocks muscarinic acetylcholine receptors. This blockade essentially removes the influence of the parasympathetic nervous system on the body. In the absence of this influence, the balance of forces is upset and the sympathetic nervous system gains the upper hand. Thus, your heart rate increases, your pupils dilate, salivation stops, your ability to urinate is impaired, and you become constipated; overall, things get very uncomfortable. But none of this is directly lethal (unless the constipation makes one commit suicide). If you do die from an overdose of henbane, it is believed to result from either a complex series of events in your brain that lead to the loss of control of your diaphragm, causing death from asphyxiation, or from cardiac arrest. This is why the deadly nightshade is so deadly and why Shakespeare chose to kill King Hamlet with henbane.

An even earlier literary reference to the toxic effects of extracts from these types of plants appeared in Homer's *Odyssey*. Odysseus, the legendary king of Ithaca and hero of the poem, was advised to defend himself against the sorcerer Circe's poison by eating a "moly," which historians think refers to an extract of *Galanthus nivalis*, or snowdrop, a plant similar to henbane. Among the first bulbs to bloom in spring, the snowdrop contains galanthamine, which can inhibit the enzyme

acetylcholinesterase, much like physostigmine. By inhibiting acetylcholinesterase, the moly would increase the amount of acetylcholine in the synapse. The additional acetylcholine would be able to compete successfully with the poison for the acetylcholine receptor and prevent death. During Homer's time, a moly might have been a common antidote against poisonous plants containing scopolamine-like drugs. Ironically, extracts from scopolamine-containing plants, such as the *Datura*, may also have been used as antidotes to poisoning from eating the snowdrop plant, proving correct once again the words of the Roman poet Lucretius: "One man's poison is another man's antidote."

Simply stated, it is just as dangerous to have too much acetylcholine in the synapse as it is to have too little. During World War II, German chemical companies produced nerve gases that were based on the action of the snowdrop plant and thus were very potent inhibitors of the acetylcholinesterase enzyme. During battle, these gases were designed to be sprayed into the air and then inhaled by soldiers, who would quickly become unable to walk or breathe and would ultimately die. Just as the Greeks seem to have discovered two millennia earlier, the soldiers could defend themselves against this poison by injecting themselves with extracts from the *D. stramonium* plant. But timing was everything: The soldiers could safely inject the extracts only if they suspected imminent exposure to a nerve gas. Otherwise, the use of this antidote could backfire if no gas attack occurred. Imagine an entire brigade of soldiers infused

with scopolamine: They would be fully amnesic, unable to urinate, and mentally confused—not exactly the characteristics of an effective combat unit. Indeed, this is exactly what may have led to the defeat of Marc Antony’s army by the Parthians in 36 BCE.

Many of the most effective insecticides available today are based on the same biochemical mechanism of the nerve gases—that is, the potent inhibition of the enzyme acetylcholinesterase. These chemicals are effective as insecticides because insects, which share our evolutionary history on Earth, are also vulnerable to having too much acetylcholine in their synapses.

VOODOO DOLLS, HALLUCINATIONS, AND BEAUTY

This seems as good a place as any to touch on the truly weird to highlight other details relating to antagonists of muscarinic acetylcholine receptors. Voodoo death and the creation of zombies, although not completely well understood as phenomena, are an excellent illustration of the workings of the ANS. Voodoo itself is a complex religion derived from West African polytheism and is practiced primarily in Haiti. I focus on that famous effigy of vengeance that most people associate with the term: the voodoo doll, into which one person sticks spikes or pins as part of a curse on another person. For people who truly believe in the power of the voodoo doll, the fear that this curse generates in the victim is usually quite powerful. The physiological expressions of this fear result from the extreme

activation of the sympathetic nervous system. The unfortunate victim begins to experience uncomfortable heart palpitations, sweating, dry mouth, and heavy breathing that leads to a loss of carbon dioxide and, as a consequence, lightheadedness. This physical condition plays into the person's fear and expectations of what should be happening as a result of this curse; these thoughts produce more fear and more sympathetic ANS activation.

Unless the person suffers a heart attack resulting from some underlying, undiagnosed heart condition, this extremely fearful experience is not usually lethal. Instead, the excessive activation of the sympathetic nervous system triggers a compensatory reflex called the baroreceptor reflex, which results in an abrupt drop in heart rate called reflex bradycardia (meaning slow heart). Therefore, the cursed victim is not frightened to death; rather, a deathlike state comes when the sympathetic ANS ultimately turns off, and there is a rebound of equal and opposite magnitude by the parasympathetic ANS. As the parasympathetic system controls increasingly more of the victim's bodily functions, the heart rate slows dramatically, and the person will slowly lose consciousness. In this state, the unlucky victim of the voodoo curse might appear to be dead. According to legend, some victims have even been buried while still alive, leading to fairly common myths about the dead rising from their graves, not looking too well and certainly annoyed by the ugliness that was just perpetrated upon them—obviously, the makings of a great horror movie and everlasting legend.

Fortunately, there is some fascinating pharmacology to take from the voodoo death legends. Most legends talk about a potion containing extracts from jimson weed, *D. stramonium* (also called the zombie cucumber), which contains scopolamine. How would scopolamine help the victim of a zombie curse? Scopolamine would reduce the influence of the parasympathetic nervous system and prevent the victim from slipping into a zombie-like state.

The actions of scopolamine in the brain are rather complex. For example, low doses produce amnesia and activation of the sympathetic nervous system. They also can produce an array of peripheral side effects that are exemplified by the following story, published in 1980. Police in New York City were finding men wandering around the Central Park area without their pants and their wallets and with no idea of what had happened to them during the previous few hours. The men could see and hear normally and safely avoid objects such as moving cars, dogs, and puzzled tourists. Their mouths were quite dry, and they had dilated pupils and very full bladders that they could not empty. These are all the symptoms of scopolamine ingestion. Ultimately, it was discovered that the men had recently visited prostitutes in the area and had been given a drink containing scopolamine, which had been stolen from a local pharmacy.

Higher doses of scopolamine, on the other hand, can produce visual and auditory hallucinations. The original witches' flying ointment, so called because of its reputed use by medieval witches, was probably an herbal recipe that contained extracts

from the *Datura* and *Mandragora* plants, as well as poplar leaves and fireplace soot, all of which were held together with animal fat or clove oil. In a ritual performed in the nude, the witches would rub the ointment on their foreheads, wrists, hands, or feet. According to Abramelin the Mage (1362–1460), a Jew from Wurzburg, Germany, who wrote a series of books on magic and the occult, the women would also “anoint a staff and ride on it . . . or anoint themselves under the arms and in other hairy places.” Their experiences may underlie the origination of stories about witches flying on broomsticks. By anointing “a staff” with the ointment and then riding on it naked, they would inevitably rub the ointment into the mucous membrane of their labia, which would ensure a speedy absorption of the lipid-soluble active ingredients of the plants in the ointment. The sensation produced by sufficient doses of these plant extracts would include both visual hallucinations and a floating, light-headed feeling. It is not difficult to appreciate why these women might have reported an experience similar to flying through the sky while straddling their broomsticks.

These women likely had one thing in common with the Central Park men: They were effectively high on scopolamine. Although it is not known how scopolamine produces its complex psychoactive effects, these effects are clearly influenced by the dose of scopolamine consumed and by the number and location of muscarinic receptors within the brain that are antagonized. Ophthalmologists use scopolamine for clinical purposes—as an antagonist to block the muscarinic receptors

expressed on the smooth muscles that encircle the iris of the eye and to allow the pupils to dilate, thus enabling these doctors to examine the interior of patients' eyes. There may be another benefit as well, if patients could see well enough to take advantage of it upon leaving the examination room: Those dilated pupils, unconsciously interpreted to indicate excitement, can be a real turn-on to other people. Indeed, people tend to rate others with dilated pupils as being more attractive and interesting. Von Linné knew this when he gave the species name of "belladonna," or beautiful woman, to one of the plants that produce scopolamine. Even today, products containing extracts of the *A. belladonna* plant are sold to women who want to be seen as beautiful and who use these extracts to dilate their eyes. Unfortunately, pupil dilation impairs vision and makes the user quite photophobic; it can also cause profound amnesia. Taken together, however, these multiple conditions might be seen as advantageous by a less attractive suitor.

ENHANCING ACETYLCHOLINE WITH A NUT AND A MUSHROOM

Let us now turn away from the actions of drugs that are antagonists at the muscarinic acetylcholine receptors to consider drugs that are agonists (i.e., stimulants) at these receptors. Arecoline is one such agonist, found in the nut of the areca palm tree (*Areca catechu*) of Asia. The nut is used as a mild euphoriant and antitussive (cough suppressant) throughout Southeast Asia. These effects indicate that arecoline is probably, at the

very least, effectively stimulating the muscarinic acetylcholine receptors within the limbic (emotional) system and coughing centers of the brain.

The nut is often eaten wrapped in a leaf from the betel pepper tree (*Piper betle*), together with a piece of limestone; the presence of this bicarbonate-releasing stone increases the pH in the mouth and accelerates the absorption of arecoline and guvacoline from the nut. Some component of the nut is also converted into a bright red pigment that makes saliva become red and stains the teeth. After a person eats this nut, his or her body converts some of it into a drug called guvacine, which is a potent enhancer of the neurotransmitter γ -aminobutyric acid (GABA), the brain's principal inhibitory transmitter molecule. Therefore, the twofold effect of consuming the betel nut is an enhancement of the inhibitory action of GABA throughout the brain similar to that produced by a barbiturate or alcohol and stimulation of the acetylcholine receptor. For reasons that are not well understood, these combined effects produce feelings of happiness and well-being. These pleasurable feelings are probably the basis for the nut's popularity in Southeast Asia.

Feelings of happiness and well-being can be produced by another drug, muscarine, which also acts by stimulating acetylcholine receptors in the brain and body. Muscarine is present in the mushroom *Amanita muscaria*, which is very brightly colored and appears to be dotted with cottage cheese on its surface (Figure 3.4). Eating this mushroom can also produce hallucinations, although its actual hallucinogenic constituent has not yet been



Figure 3.4 The *Amanita muscaria* mushroom.

conclusively determined. A typical hallucinogenic dose is approximately one to three dried mushrooms, depending on their size and growing conditions. The hallucinations are quite interesting. People report that normal objects appear bigger or smaller than they truly are; this is called macropsia or micropsia, respectively. The author Lewis Carroll was clearly aware of the perceptual changes produced by eating this mushroom, having incorporated them into his book, *Alice in Wonderland*. Carroll may have become familiar with these mushrooms through his close

friendship with the famous mycologist (someone who studies fungi), Mordecai Cooke.

The mushrooms also cause sleepiness and then delirium, so at the very least, they probably interfere with the function of acetylcholine neurons within the cortex. Upon waking, people claim to feel very excited and aggressive for 3 or 4 hours and able to perform extraordinary physical feats. These symptoms are consistent with an overactive sympathetic nervous system: Reduced in activity while the contents of the mushroom are in the body, the sympathetic nervous system rebounds in activity after the drug is excreted.

Petroglyphs found in 1968 in North Africa suggest the existence of a 12,000-year-old cult that is thought to have used the *A. muscaria* mushroom in religious rituals. The *Amanita* mushroom was also a popular recreational and ritualistic drug among people living in northern Europe. However, perhaps its most memorable use was by the Vikings, whose rather unpleasant behaviors during their invasion of Ireland in the eighth-century CE were described as “berserksgang” in the Irish poem “Fury of the Norsemen.” From this poem, which includes the phrase “O Lord Deliver Us,” you can get a clear idea of what happens when the brain is exposed to the contents of the *A. muscaria* mushroom. Its psychoactive ingredients must be quite stable in the body and quite resistant to digestive enzymes because they can be isolated from urine and reused. They will “last” through approximately four consecutive users, as long as those users do

not mind drinking someone else's urine. Evidently, the Vikings did not mind.

The mushroom was also known as "fly agaric" because of its ability to attract and kill flies. Flies also have muscarinic acetylcholine receptors on their neurons; after they ingest parts of the mushroom, the overstimulation of these receptors is apparently sufficient to kill them. But even if they somehow survive that fate, they are likely still doomed because of the actions of the mushroom on their retinas, which contain muscarinic acetylcholine receptors as well. After dining on mushroom pieces, the flies may become so visually impaired as to be vulnerable to a carefully aimed boot.

NICOTINE

What about substances that act as agonists at the nicotinic acetylcholine receptor? At least two may be found in a fruit in your local grocery store. The chemicals punicalin and punicalagin are contained in the rind of the pomegranate, *Punica granatum*; the level of these chemicals is quite high and toxic, although pomegranate seeds are, of course, safe to eat. Another nicotinic agonist, cytosine, is from a more obscure source. It is contained in the seeds of the mescal bean, *Sophora secundiflora*, which was discovered in Central America in archaeological sites dating to 8,000 years ago. The seeds are roasted over a fire and chewed to produce stimulation. The Mescalero Indians also added the beans to beer, whereas the Kickapoo Indians mixed it with tobacco leaves; this mixture was then used to treat earaches.

However, by far one of the best studied agonists of the nicotinic acetylcholine receptor is nicotine. It occurs in more than 64 species of plants throughout the world, including the well-known tobacco plant, which likely uses nicotine as a defense against insects that express nicotine receptors in their bodies and are therefore vulnerable to its toxicity.

Tobacco was first used to treat persistent headaches, colds, and abscesses or sores on the head. Tobacco enemas were used to treat flatulence, and even more surprising, the smoke was once inhaled deeply to lessen bad coughs. In 1560, Jean Nicot (then the French ambassador to Portugal) sent some tobacco to Catherine de Medici, who was then queen to Henry II of France; she reported that it helped treat her migraines. The plant initially was given the title of “herbe sainte,” or holy plant, and then later was dubbed “Herba Regina,” the queen’s herb. Nicot got the credit for the discovery, and Von Linné named the genus *Nicotiana* in his honor. Despite all this royal glory, in the 1890s the US pharmacopeia dropped nicotine from its list of useful therapeutic agents.

A cigarette made from tobacco contains approximately 1 or 2 mg of nicotine. Because nicotine is quite volatile and heat labile, only approximately 20% of it is actually inhaled into the body. However, because of its exceptional lipid solubility, at least 90% of the inhaled nicotine is absorbed into the body. Nicotine can also be rapidly absorbed by the mouth or intact skin. Once the smoke is inhaled, absorption by the lungs and transport to the brain occurs within 2–7 seconds.

This makes smoking tobacco as efficient as an intravenous injection in getting nicotine to its site of action within the brain. This speed of entry into the body may also explain why nicotine is so toxic. Sixty milligrams is considered a lethal dose for a human; death takes only a few minutes to occur and results from a loss of control of the nicotinic receptors on the diaphragm muscles.

Nicotine affects cortical function in a complex dose-dependent manner. Low doses tend to activate the left hemisphere and produce mental stimulation and a feeling of arousal, whereas high doses tend to activate the right hemisphere more strongly and are associated with the sedative effects of nicotine. Therefore, when doing boring tasks, you could take a low dose of nicotine by, for example, smoking one cigarette and could increase your subjective feelings of arousal and attention. In contrast, during anxious or stressful situations, you could take a high dose of nicotine by chain-smoking and may actually reduce your stress by activating the right hemisphere and producing a bit of sedation. These findings demonstrate the competing roles of nicotine receptors in the two hemispheres and tell us something profound about how the two halves of the brain normally function to produce a balance of emotions, attention, and arousal. Moreover, 60% of adults diagnosed with attention-deficit/hyperactivity disorder smoke cigarettes compared to less than 30% of the rest of the population, another interesting finding indicating that acetylcholine nicotinic receptors play an important role in paying attention.

Why is smoking so difficult to give up? Smoking produces a powerful rewarding feeling in the brain. Nicotine is the most addictive drug currently used by humans. It produces a dose-related euphoria that is most pronounced following overnight abstinence. Essentially, it provides its greatest pleasure with its first use of each day and re-addicts the user every morning. This may explain why heavy smokers enjoy lighting up as soon as they awaken in the morning. This is a common response of the brain to the absence of various chemicals that we consume; the reintroduction of a drug or nutrient after a prolonged delay produces a larger effect. For example, food tastes better when we are hungry. The sensitivity of the sensory neurons in our taste buds on the tongue is increased by hunger. Thus, if you are not a good cook, make your dinner guests wait a long time before serving the meal—your cooking will taste better to them. However, if you are a dreadful cook, encourage your guests to smoke—this will tend to deaden their tastes buds.

A recent study identified a way to make nicotine even more rewarding to the brain. The addition of menthol to cigarettes significantly enhances the rewarding impact of nicotine by potentiating its actions at nicotine receptors. Adding menthol actually increases the number of nicotine receptors in the brain, thus making smoking even more rewarding. More than 30 years ago, tobacco companies discovered that adding menthol would increase the addictive properties of tobacco; they just never bothered to share that knowledge. Today, the bestselling cigarettes all contain menthol—now you can appreciate why.

After their initial morning smoke and throughout the rest of the day, smokers carefully, and probably unconsciously, control the amount of nicotine that reaches their brain by altering the number of cigarettes they use per hour, the rate at which they take a puff, and the volume of their inhalation. This careful regulation may optimize the amount of stimulation to the acetylcholine nicotinic receptor and the balance of right versus left cortical activation to balance the level of stimulation and sedation. Apparently, activation of the right hemisphere is greater in men than in women, which might explain why men find smoking more rewarding, and why they are also more likely to smoke, than women.

People with serious mental illness often are heavy smokers. They may be using nicotine to balance the activity between their two hemispheres and thereby lessen the severity of their symptoms. This potentially positive aspect of smoking may explain why, in 1948, the *Journal of the American Medical Association* stated that “from a psychological point of view, in all probability more can be said in behalf of smoking as a form of escape from tension than against it.”

Smoking also influences how your brain experiences food. As if there were not enough to be concerned about for a smoker, two recent studies have identified some interesting risks and benefits of combining smoking with the consumption of certain foods, including cheese, beer, wine (due to the presence of resveratrol), turmeric, fava beans, and pickles. Many decades ago, when tricyclic antidepressant drugs were introduced to the

market, they presented some nasty side effects, including death, when patients consumed any of these foods. The side effect became known as the “cheese effect.” The “cheese effect” is due to the ability of these antidepressant drugs to block the enzyme monoamine oxidase (MAO) and the fact that cheese, beer, wine, and the other foods contain high levels of the amino acid tyramine. Ordinarily, tyramine is easily metabolized and inactivated in the body and brain by MAO. Unfortunately, when MAO is inhibited, the consequences of consuming these foods include wild fluctuations in blood pressure, nausea, headache, rash, dizziness, heart palpitations, and vomiting.

Smoking inhibits MAO. The more a person smokes, the greater the inhibition of this critical enzyme throughout the body. You can easily see the potential problems that might arise if you are a smoker and decide to have a glass of wine or beer with your cheese and crackers. Suddenly, you become very nauseous, and your heart feels as though it is going to pop out of your chest. Your first thought, of course, is that there is something wrong with the food and you begin to question the culinary skills of your host. The interesting and rather complex interaction between smoking and eating cheese does not end with these sickly feelings. In contrast to its effects on MAO, smoking activates an enzyme in the brain that is responsible for converting tyramine into the neurotransmitter dopamine. The simplest way to explain the purpose of dopamine is to say that it is responsible for people being able to feel pleasure. Indeed, neuroscientists

have believed for many years that virtually everything humans enjoy somehow involves triggering the release of dopamine in the brain's pleasure centers. Nicotine has also been found to trigger the release of dopamine.

Taken together, these discoveries suggest that smokers can expect some quite interesting chemical reactions to develop in their bodies at the next wine and cheese party they attend. Nicotine and tobacco smoke (both of which seem to play different roles in this process) would act together to produce additional dopamine from the contents of the diet and also to induce the brain to release that surplus dopamine within the brain's pleasure center. A double whammy of pleasure! Smoking and eating cheese at the same time is therefore simultaneously more rewarding and more dangerous.

Today, our perception of nicotine has been altered principally by the consequences of using the "vehicle" for nicotine administration, the tobacco plant. In the United States alone, tobacco use causes almost one death every minute, or the equivalent of four major airline crashes daily, similar to what occurred on September 11, 2001. If we had to witness that tragedy every day, just imagine the public outcry for greater federal control of tobacco. Unfortunately, because of politics and the fact that tobacco sales (and their taxes) are such a boon to the US economy, this is not likely to ever occur to the degree of banning these sales completely. Meanwhile, people will continue to die from tobacco use and will do so one at a time, at home or in a hospital room, not in large groups on the evening news.

CHAPTER 4

EUPHORIA, DEPRESSION, AND MADNESS

Can the function of just one small group of chemicals really determine whether you are happy or sad? The two neurotransmitters that are considered in this chapter, dopamine and norepinephrine, are chemicals called catecholamines which may do exactly that and much more. Catecholamines occur extensively throughout nature and have been identified in insects, crustaceans, arachnids (spiders), and primates. We know a lot about these neurotransmitters in the human brain primarily because so many drugs and nutrients have been discovered that can modify their function. This chapter discusses some of these substances and examines what their actions tell us about the function of these neurotransmitters. A consistent pattern of effects emerges: Norepinephrine underlies the major components of

arousal and behaviors that arise in association with increased arousal; dopamine is intimately related to the experience of reward and reward-seeking behaviors. Interestingly, it is also linked to the treatment of—if not directly implicated in the cause of—psychosis.

BASIC NEUROSCIENCE OF NOREPINEPHRINE AND DOPAMINE

In humans, almost all of the norepinephrine neurons are located within a region called the locus coeruleus (Latin for “blue area”) at the base of the brain. The name of this region is related to the fact that these neurons concentrate copper. Although copper is required for the synthesis of norepinephrine, the concentration of the copper far exceeds what is necessary for neurotransmitter synthesis. Unfortunately, the presence of this metal makes these neurons vulnerable to oxygen, which poses a particular risk for the brain. I discuss this point later in the chapter, but suffice it to say here that the act of breathing oxygen is a mixed blessing for those of us on the planet who have to do it for a living.

The norepinephrine neurons living in your locus coeruleus project throughout your brain. This broad access allows them to influence your level of arousal and thus almost every aspect of your thinking and behavior. Consistent with this role, it has recently been discovered that schizophrenic patients who display a chronic state of hyperarousal have significantly more norepinephrine neurons in their brains.

Although five times more in number than norepinephrine neurons, dopamine neurons do not project as widely throughout the brain. Instead, these neurons, which originate in a region called the midbrain, send projections forward primarily into basal ganglia and frontal lobes. One major dopamine pathway originates within the substantia nigra, or dark substance, so called because this region concentrates the metal iron into a pigmented substance known as melanin. As with the copper in the locus coeruleus, the oxidation of iron (you know this process as rusting) contributes a significant degree of neuronal vulnerability to oxygen. Indeed, many parts of your brain are actually rusting as you breathe. Dopamine-containing neurons may be vulnerable to the presence of oxygen due to its role in plants as an antioxidant; it may sacrifice its molecular integrity during oxidative stress. Recent evidence suggests that exposure to common pesticides and insecticides may also accelerate the process of dopamine-containing cell death in the substantia nigra. The degeneration of the dopamine neurons in the substantia nigra underlies the progression and symptoms of Parkinson's disease, a disorder characterized by tremors, spasticity, and akinesia, or the absence of movement. These symptoms provide insight into at least one major function of dopamine within your brain. The constant supply of dopamine is necessary to allow you to initiate or inhibit a movement. As you might expect, drugs that interfere with dopamine's normal function (e.g., some antipsychotic medications) produce side

effects that resemble those seen in people with Parkinson's disease.

Two other dopamine pathways originate in a region of the midbrain near the substantia nigra and ascend upward into the brain. One pathway projects to brain regions that are associated with the control of emotion. The other dopamine pathway projects to the frontal lobes. For more than 50 years, scientists have speculated that excessive activity in these two pathways may underlie some of the symptoms associated with psychosis. I return to the potential role of dopamine in psychosis later.

The production of dopamine and norepinephrine in the brain begins with the amino acid tyrosine, which is obtained from one's diet. Tyrosine is converted to the amino acid levodopa (L-DOPA) by the enzyme tyrosine hydroxylase. One very important co-factor in this process is iron. Without iron, tyrosine hydroxylase fails to function normally. People with anemia have reduced body levels of iron and consequently may have reduced tyrosine hydroxylase activity and thus reduced production of norepinephrine and dopamine. The decreased brain levels of these important neurotransmitters may lead to a slight depression, although most likely only in people with severe anemia. Generally, in a normal healthy person, the production of these two neurotransmitters is not easily affected by the contents of the diet.

Tyrosine can also be acted on by the enzyme tyrosinase and converted into a dark pigment. This enzyme is quite interesting to study because it is vulnerable to a genetic mutation

that makes it heat labile (i.e., it only works correctly in the cooler areas of the body). The consequence of this mutation is a lack of pigmentation in humans (albinism) and, conversely, the characteristic pattern of dark pigmentation at the ends of the nose, tail, ears, and paws of Siamese cats (i.e., those parts of the cat that are most distant from the warmer body core). Apparently, this enzyme is critical for the normal decussation, or crossing, of visual tracts, which also underlies the cross-eyed visual problems experienced by Siamese cats. I suggest that the consequences of this mutation underlie this breed's peculiar personality as well.

The second critical enzymatic step in this pathway is the conversion of L-DOPA into dopamine. This conversion process is extremely efficient, which may explain why brain levels of L-DOPA tend to be very low and why providing exogenous L-DOPA to patients who lack sufficient dopamine—that is, those with Parkinson's disease—leads to a dramatic increase in the production of dopamine. The surviving dopamine neurons in these patients' brains will quickly convert L-DOPA into additional dopamine, which is then released.

There is a third enzyme expressed in norepinephrine neurons that converts dopamine into more norepinephrine; therefore, this enzyme is not expressed by dopamine neurons. The enzyme is stored within the synaptic vesicles and lies in wait for the entry of dopamine molecules once they have been synthesized in the cytoplasm of the neuron. In addition to this third enzyme, the vesicles contain copper and the antioxidant

ascorbic acid, also known as vitamin C. Copper is required for the enzyme to function appropriately. Vitamin C maintains the integrity of norepinephrine within the vesicle in the same way that ascorbic acid added to processed meats, such as hotdogs, lengthens the shelf life of these products. Neurons require antioxidants such as vitamin C because they are continually exposed to oxygen from the blood. Without vitamin C, many different neurotransmitters oxidize and become inactive while in storage in the vesicles.

All of these energy-demanding enzymatic steps are conducted for the single purpose of ensuring that vesicles contain an adequate number of biologically active neurotransmitter molecules (usually approximately 10,000) when they release their contents into the synaptic space between neurons. This is the principal mechanism by which one neuron communicates with the next neuron. What would happen if the vesicles contained no neurotransmitter?

Consider the effects of reserpine, a drug found in the snakeroot plant (*Rauwolfia serpentina*), which is indigenous to India, Pakistan, Sri Lanka, and Thailand. It prevents the transport of neurotransmitters into the vesicles for storage. If neurotransmitters cannot be stored safely in vesicles, then they are trapped in the cytoplasm, where they will be destroyed. When too many of the vesicles in nerve terminals are empty, it becomes much more difficult for neurons to communicate with each other, and nervous activity slows down. Therefore, at low doses, reserpine has a tranquilizing effect. At higher doses, because of

the greatly reduced availability of these neurotransmitters, reserpine causes severe depression and mood shifts of the sort that might clarify why the snakeroot plant is called the insanity herb, or “pagla-kadawa,” by local Sherpas. The behavioral symptoms are caused by the deficiency of dopamine and norepinephrine, as well as of the neurotransmitter serotonin, and thus offer insight into the role that these neurotransmitters play in the control of arousal and mood. Given this insight, the effects of drugs that enhance the function of dopamine and norepinephrine in the brain should be easy to predict—that is, increased arousal and enhanced mood associated with euphoria. Let’s now examine a few of these drugs.

AMPHETAMINES AND ECSTASY

The stimulant drug amphetamine dramatically and rapidly induces the release of norepinephrine and dopamine (and serotonin) into the synapse and greatly slows their inactivation by blocking reuptake back into the neuron. The increased and prolonged presence of these neurotransmitters within the synapse produces heightened alertness, euphoria, lowered fatigue, decreased boredom, depressed appetite, and insomnia. Once amphetamine leaves the brain, the rebound symptoms are extreme fatigue and depression.

During World War II, soldiers and airmen on both sides of the battle lines used amphetamine to combat boredom, fear, and fatigue and to increase endurance. Historians suggest that at end of the war, Adolf Hitler’s increasingly paranoid

behaviors may have resulted from his excessive use of amphetamine. Indeed, excessive and prolonged use of amphetamine can produce a condition similar to paranoid schizophrenia, and scientists once believed that studying the consequences of high doses of amphetamine would shed light on the causes of, and potential treatment for, psychosis.

More than half a century later, amphetamine is still popular throughout the world. However, because of our improved understanding of brain function and advances in medicinal chemistry, faster acting and more potent versions of amphetamine have been invented. How? By making amphetamine more fat-soluble. One of the basic principles of neuropharmacology is that lipid (fat) solubility is directly correlated with the speed of uptake of a drug into the brain. Furthermore, the faster a drug enters the brain and somehow alters its physiology, the greater the euphoria the drug is likely to induce. This principle has been known to drug designers for many years. Morphine, for example, became far more fat-soluble and far more euphorigenic (i.e., pleasure-inducing) at the turn of the 19th century when scientists added two acetyl groups to it to produce heroin. Much later, amphetamine was similarly modified to make it more euphorigenic and, therefore, more addicting. The simplest manipulation was the addition of a methyl group to make methamphetamine, a very potent relative of amphetamine that is far more fat-soluble. Not surprisingly, its street name became “speed” because of its speedy entry into the brain.

Over time, attempts to make amphetamine ever more fat-soluble by the addition of carbon atoms (e.g., in the form of methyl or ethyl groups) have produced drugs that are more euphorogenic and hallucinogenic than amphetamine. The most famous of these is 3,4-methylene-dioxymethamphetamine, widely known as Ecstasy. The action of Ecstasy in the brain is very similar to that of amphetamine: It blocks the reuptake of dopamine, norepinephrine, and serotonin and enhances the release of these neurotransmitters. It also produces a dramatic rise in body temperature, or hyperthermia. Indeed, if you were to overdose on Ecstasy, hyperthermia would be the cause of your death. How does this happen? Ecstasy has the ability to uncouple the energy-producing capacity of all of the mitochondria in your body. Uncoupling means that mitochondria lose their ability to generate ATP, which is your body's principal energy currency. When they cannot generate ATP, they start wasting their energy as heat. At typical doses of Ecstasy, this uncoupling effect is seen most dramatically in the muscles. Because males have more muscle mass compared to females, on average, males are more sensitive to the acute toxic effects of the hyperthermia.

I have been amazed at the continued popularity of this drug among my students, who seem to believe that because they are young, they are also immortal and thus immune to danger. I attribute the feelings of immortality to the fact that their frontal lobes are not fully working because they have not yet completed the process of neuronal myelination. Without myelination, electrical signals from neurons fail to reach their destination. The

parts of our brains that myelinate last are also the parts that evolved most recently. These parts include our frontal lobes, which contribute most to our unique personalities and allow us to anticipate the consequences of our actions. Essentially, your frontal lobes tell you that it is a bad idea to drink alcohol and drive or to ignore the consequences of taking Ecstasy. When your frontal lobes finally complete their process of myelination, they begin to work properly, and you stop doing stupid things. Most important, you stop feeling immortal. Apparently, women finish this process by age 25 years and men finish by age 30 years. Thus, a 20-year-old female, although her brain is still myelinating, is closer to maturity than her 20-year-old boyfriend, who still has another 10 years before he can really hear the sense of warnings such as those against drinking and driving or against taking any drug that comes his way. This delay in brain maturation among males may explain the behavior of many members of college fraternities. But women are not immune. A 19-year-old female student told the following story in class one morning: She said that she had met a “nurse” the night before at a bar who offered to give her some pills that she was told would be fun to experience; she only had to return with the “nurse” to her apartment. The characteristics of her experience clearly indicated that the pill contained Ecstasy. This young woman did not seem at all disturbed by the fact that she had willingly allowed a total stranger to place her health at risk as a prank. She told us that when she woke in the morning, she got dressed and came to class.

MOTHER NATURE'S STIMULANTS

Amphetamine does not occur naturally, but some substances found in nature are chemically related to amphetamine and have similar effects on the brain. Ephedrine can be found in *Ephedra sinica*, which has been used in traditional Chinese medicine and is known as *ma huang*. Its effects on the sympathetic nervous system are due to its ability to enhance the release of norepinephrine and prevent its reuptake; ephedrine has very little effect on dopamine and therefore produces less euphoria or craving than amphetamine. However, this extract never achieved complete success as a psychoactive stimulant, primarily because it does not cross the blood–brain barrier as effectively as amphetamine.

Khat

Khat is found in an African plant *Catha edulis*, which contains cathinone and cathine (also known as *d*-norisoephedrine). The habit of chewing khat to produce a mild arousal probably predates coffee drinking by centuries. Decoctions, obtained by boiling in hot water, of the khat plant were once known as Abyssinian tea. As is true for most plant-derived biologically active drugs, the relative concentration of khat's active ingredients depends on where the plant is grown, its age, and the time elapsed after it was harvested. Cathinone is quite unstable, a property that makes storage for widespread distribution of the khat plant nearly impossible. You can, of course, purchase dried leaves from this plant in health food

stores, but they do not contain any active ingredients. Other compounds in this plant, as in so many others, include chemicals called flavonoids that have anti-inflammatory properties. A few of the 40 different biologically active components of the khat plant also produce the unwanted side effects of green teeth and constipation. Because of the prevalence of this last side effect, the sale of laxatives is quite profitable in countries where khat is widely used.

Peyote

Another naturally occurring drug that is similar to amphetamine can be found in the cactus *Lophophora williamsii*. Extracts are used to prepare a drink called peyote that contains 3,4,5-trimethoxyphenylethylamine (the “meth” and “phenyl” point to a molecule that is quite fat-soluble). Known as mescaline, this compound is structurally similar to the catecholamine dopamine; indeed, in plants, dopamine is an important intermediate precursor to the production of mescaline and morphine from the amino acid tyrosine. Indeed, the ability of these drugs to influence brain function is entirely related to their structural similarity to tyrosine. Mescaline acts more directly on serotonin receptors because of the presence of the methoxy groups on the molecule; this feature of the compound’s structure makes it more fat-soluble and therefore better able to enter the brain quickly. These chemical similarities and differences explain why mescaline produces an amphetamine-like euphoria at low doses and hallucinations at higher doses. Indeed,

this euphoria-to-hallucination transition is a common dose-dependent characteristic of many psychoactive plant extracts.

Mescaline

Mescaline is the least potent of all of the known hallucinogens; it is 2,000 times less potent than lysergic acid diethylamide (LSD). This is likely related to the fact that mescaline does not cross the blood–brain barrier as easily as LSD. Furthermore, mescaline is either poorly metabolized or not metabolized at all by humans. This means that a large percentage of mescaline is excreted unchanged, and thus still fully psychoactive, in the urine. For these reasons, rather rigid cultural rituals included a “recycling” program for the experience of ingesting it. Often, persons of highest social or religious rank would consume mescaline in large quantities, eventually excreting it in their urine, which was then consumed by those of lesser social status. Sometimes, because of the gradual loss of potency, the urine from a few people needed to be combined to achieve the greatly anticipated experience. The Vikings were thus not the only group of ancient peoples willing to drink someone else’s urine for a good time.

This reminds me of one of my students, a young woman, who claimed that her boyfriend liked to cook sections of peyote cactus into a lasagna-like preparation that he layered with ricotta cheese and tomatoes. She was curious whether the mescaline in his urine would remain active if she saved the urine for later use. Once you get past the obvious concerns about

the sterility and purity of the collected urine (and the disturbing mental imagery), the active ingredient would probably be quite stable if stored frozen in orange or grapefruit juice to lower the pH of the urine. This approach would, as she observed, avoid the nasty gastrointestinal side effects that usually accompany eating this cactus because of the presence of nonpsychoactive compounds that affect the gut's dopamine and serotonin neurons. One of my inventive marketing students suggested that she consider selling these frozen delights online as "pea-pops."

Asarone

The drug asarone, which derives from the plant *Acorus calamus* (found in Asia, Europe, and North America), is chemically very similar to mescaline, but its pharmacological actions in the brain are much more complex. The roots of this plant are chewed to produce a dose-dependent effect; approximately 2 inches of the root produces a mild euphoria, whereas nearly 10 inches produces hallucinations. In some cultures, wives will chew on the roots and collect their saliva throughout the day for their husbands to enjoy later. Nothing says "welcome home" at the end of a hard day like a nice warm bowl of spit.

Nutmeg and Other Spices

Various psychoactive spices have also been discovered that alter the function of the brain's dopamine, norepinephrine,

and serotonin neurons. For example, the spice nutmeg derives from the nutmeg tree, *Myristica fragrans*, and contains myristicin, which is also chemically quite similar to mescaline. (Myristicin is also found in parsley and carrots but at very low concentrations.) Typically, one must consume approximately 30 g of nutmeg powder—or roughly the contents of an entire container of the product you could purchase at your local grocery store—to experience its psychoactive effects. Reactions vary considerably, from nothing at all to euphoria at low doses and marijuana- and LSD-like experiences at higher doses, with hallucinations that can last up to 48 hours. Chronic use of high doses of nutmeg can produce a reaction similar to psychosis. One other unpleasant side effect of nutmeg is extreme diarrhea caused by the stimulation of dopamine and serotonin neurons within the gut. It has been claimed to be an aphrodisiac. Perhaps for that reason, one of my students consumed an entire canister of nutmeg that he had dissolved in some applesauce; the weekend he spent in the bathroom demonstrated why most people never try nutmeg more than once.

Spices such as saffron, fennel, dill, cinnamon, and anise also contain psychoactive substances that are chemically similar to myristicin. Generally, the level of psychoactive agents in these spices is far too low to produce any noticeable consequences in people using them for cooking, but their role, regardless of how subtle, in enhancing the culinary experience should not be ignored.

Kava Kava

Similar amphetamine-like substances have been found in kava kava, a drink with a truly disgusting taste that is prepared from roots of a pepper tree, *Piper methysticum*, which grows in the South Pacific islands. *Piper* is Latin for “pepper”; *methysticum* is Greek for “intoxicating.” The drink contains various potentially psychoactive resins that include kawain and methysticin. As is true for the complex ingredients of most plants, the psychoactive efficacy of the kava extract does not arise from any one of these compounds but, rather, from a blending of their effects in the brain. These resins are capable of stimulating dopamine and γ -aminobutyric acid receptors, and so their actions are similar to the effects of amphetamine and to those of some popular anti-anxiety drugs. The resins from this plant are quite fat-soluble and thus will enter the brain relatively easily and quickly to produce a relaxed euphoria and sometimes, at high doses, hallucinations.

Half a coconut shell (the typical vessel for its presentation) will contain approximately 150 ml of a foul-tasting, muddy liquid. Sometimes the kava kava preparation is strong enough to put a drinker into a deep, dreamless sleep within 30 minutes. One of my students tried it and reported the hallucination as follows: “The top of my head just blew off!” Not an appealing mental image. Fresh kava kava rootstock yields a greenish milky solution that is considerably stronger than the gray mixture obtained from dry roots.

It is possible to purchase extracts of kava kava plants in many upscale grocery stores, but their ingredients are no longer active. Real kava kava tends to be unstable, particularly with the liquid storage that is commonly used for these products. Given the unstable nature of the ingredients of this plant, the presumed anti-anxiety actions of kava kava extracts obtained in US stores result entirely from the placebo effect. The actions of the psychoactive drug discussed next are most certainly not due to the placebo effect.

Cocaine

The comedian Robin Williams once quipped that cocaine is God's way of telling you that you are making too much money. The United States must indeed be a wealthy country, considering that 3 million of our fellow citizens abuse this drug; this is six times the number of heroin addicts in the country. It is estimated that 50% of Americans between the ages of 25 and 30 years have tried cocaine.

What does cocaine do in the brain? First, it binds to sodium ion channels and blocks them from functioning. This stops the flow of action potentials and prevents neurons from communicating with each other. Cocaine also blocks the conduction of pain signals, which explains why, after it was isolated from the coca plant (*Erythroxylon coca*) in 1855, it was used as a local anesthetic, including for the eyes and for toothaches. But ultimately, its anesthetic actions would be discovered to have

nothing to do with the reason for its later illegal street use: its ability to produce euphoria.

Cocaine acts similarly to amphetamine with regard to its ability to enhance the effects of dopamine and serotonin at the synapse. The actions of cocaine on the brain lead to increased alertness, reduced hunger, increased physical and mental endurance, increased motor activity, and an intensification of most normal pleasures. This last feature may explain why so many claim that cocaine enhances emotional and sexual feelings. Cocaine abusers usually co-administer other drugs that are brain depressants (e.g., alcohol, heroin, or marijuana) to decrease the unpleasant hyperstimulant aspects of cocaine.

Approximately 16–32 mg of cocaine is an effective street dosage that is usually without immediate negative side effects. An increase in heart rate usually occurs within approximately 8 minutes after administration and dissipates 30–40 minutes later. The half-life, or the time it takes for half of the drug to exit the blood and body, is approximately 40–50 minutes. Cocaine will actually degrade spontaneously in the body to produce an inactive compound with a tongue-twister name, benzoylecgonine. The physiological effects of cocaine therefore last for a much shorter period of time than those of amphetamine. Partly for this reason, most users claim that it does not “wear out” the body in the same way that amphetamine does.

Getting cocaine to its site of action within the brain first requires getting adequate amounts of the drug into the blood. Snuffing cocaine by applying it to mucous membranes inside

the nose is much more effective than either oral administration or intravenous use because the drug enters the blood and brain more quickly and is therefore more immediately euphorogenic. Unfortunately, there is a problem with this approach to getting cocaine into the blood. Cocaine constricts the blood vessels feeding the cartilage in the bridge of the nose and, with repeated nasal application, leads to the ischemic (lack of blood) death of the tissues supporting the end of the nose. Initially, the irritation to the tissue causes a runny nose; ultimately, the irritation leads to a true necrosis, or cell death, and the end of the nose either collapses or becomes quite distorted. Why risk the integrity of your nose?

Orally administered cocaine is not well absorbed from the gastrointestinal tract, and its effects on the brain thus tend to be far less reinforcing when taken in this manner. But oral administration does have a long history. Many years before cocaine extracts were applied to mucous membranes, ancient peoples simply ate the leaves of the coca plant. Indeed, although cocaine use peaked in the 1880s and the 1980s, chewing coca leaves for their psychoactive effects—they contain up to 1% cocaine by weight—was a popular practice long before these eras. The leaves have been found in 5,000-year-old graves.

Approximately 800 years ago in South America, people started chewing the leaves wrapped around a piece of limestone to increase the pH in their mouths and to augment the release of cocaine from the leaves. By improving the extraction of cocaine from the leaves, the experience became far more pleasurable.

The Incas introduced religious ritual to its use and invented the word “cocata” to describe the distance a person could walk on one chew of coca leaf before the beneficial effects wore off. The tribal chiefs gave coca leaves to runners in the Andes Mountains to help them tolerate the altitude and to increase their endurance; the runners were also paid in coca leaves, thus maintaining their addiction and continued service until they died of exhaustion and malnutrition. The conquering Spanish subsequently recognized the cost-saving wisdom in this approach and paid their Incan servants with coca leaves, enabling them to work harder and eat less food. Amerigo Vespucci, who gave his name to the newly “discovered” land, wrote about the use of coca leaves by the local tribes.

Fast-forward a number of centuries, and we see the oral use of coca plant extracts taking a new form. In 1862, Angelo Mariani, a Corsican chemist, combined a Bordeaux wine with coca plant extracts to produce and sell “Vin Mariani.” The labels displayed testimonials from Pope Leo XIII, who gave it the Vatican’s gold medal of appreciation, as well as from President Ulysses S. Grant and from Thomas Edison, who claimed that it helped him stay awake longer to complete his experiments. Vin Mariani was such a commercial success that many other alcohol-based tonics containing coca leaf extracts were introduced in the late 1880s. One quite successful tonic was introduced by John S. Pemberton in 1884. Pemberton called his drink “a French wine of coca, ideal tonic.” Later, in 1886, he removed the alcohol, replaced cocaine with an extract from

the kola nut, and called it Coca-Cola. But why combine coca leaf extracts with wine in the first place? The reason is that the combined effect of these two drugs on the brain is far more euphorogenic, and therefore more addicting, than either compound alone. When combined with alcohol, as in Vin Mariani, the mixture forms a powerful psychoactive compound called cocaethylene, which is more fat-soluble than cocaine and thus enters the brain faster; by now you know what that implies in terms of the enhanced pleasure it will produce.

Drug designers are never far behind chemists in discovering new ways to make drugs enter the brain faster. After all, greater addiction of one's customers leads to higher profits. Thus, in the 1960s, free-base cocaine was produced, and people discovered that it very quickly entered the blood and brain and produced an ever greater euphoria. The natural product that had been obtained from the coca leaf for so many centuries exists as cocaine hydrochloride; this is an acidic compound that can be volatilized—that is, turned into a vapor. However, at a high temperature, the cocaine is destroyed. This is why naturally occurring cocaine was never smoked; the active ingredient is completely lost. I predict that someone somewhere at some time must have tried smoking coca leaves and found that it was a disappointing failure. To be effective when smoked, cocaine must be reconverted chemically to its alkaloid, or base, form. The process of converting and then isolating the product is called free-basing. The conversion process requires the use of highly flammable solvents that, when not properly handled, can

set celebrities (e.g., the comedian Richard Pryor), pop singers, and other people on fire.

More recently, modifications in the process of making the basic form of the drug have produced cocaine crystals that spontaneously generate small chunks; this product is called crack—related to the sound the crystals make when heated. It can be smoked and, therefore, will deliver cocaine into the brain as fast as an intravenous injection but without the inconvenient and potentially unhealthy process of using a needle.

Cocaine is so rewarding that its users prefer it to sex, food, and water, thus overriding basic survival drives. In experiments, laboratory animals self-administer cocaine to the point of severe toxicity, physical exhaustion, and even death. Many human users support their habit by selling cocaine or by stealing from friends and co-workers. Even Sigmund Freud, who wrote a scholarly and quite accurate treatise on cocaine's effects, *Über Coca* (1884), got carried away and claimed his use of the drug cured his morphine addiction. Unfortunately, it simply became a second addiction for him.

The compelling and overwhelming nature of cocaine addiction is impressive and tells us something profound about how the brain is built. It is apparently composed of critically important internal neural systems that can produce a powerful rewarding experience usually connected to activities that are the basis for the survival of our species: eating and reproduction. Drugs such as cocaine can hijack these neural processes and stimulate the brain's reward centers so excessively and unnaturally that users

will crave more stimulation, as they would normally crave food and sex. From the brain's perspective, there is no real difference between these cravings. Thus, the familiar moral fiber argument of "just say no" is unbelievably naive and its application cruel. It ignores the complexities of the brain and the influence of culture and evolution on how the brain responds to drugs.

How precisely does cocaine achieve these effects in the brain? As described in Chapter 1, once a neurotransmitter is released from its neuronal terminal, its actions within the synapse are ended principally by reuptake into the presynaptic terminal. Cocaine primarily blocks the reuptake of dopamine but also acts similarly on norepinephrine and serotonin reuptake. If your neuronal terminals can be seen as acting like little vacuum cleaners, then cocaine essentially clogs the vacuum nozzle. As a consequence of this blockade, the concentrations of dopamine, norepinephrine, and serotonin within the synaptic cleft between two neurons increase dramatically. Within millions of synapses in the brain, these neurotransmitters are now free to continue to stimulate their receptors over and over, again and again. There are neuronal terminals for dopamine, norepinephrine, and serotonin scattered throughout the entire brain, and thus the consequences of cocaine on brain function are also widespread.

As we have seen before, what happens after a drug exits the brain tells us something about what parts of the brain were affected under the influence of that drug. With regard to cocaine, these include the arousal systems within the brainstem, the

feeding centers within the hypothalamus, and the reward centers within the frontal lobes and limbic system. Thus, cocaine reduces the need for sleep, and its absence produces extreme sleepiness; it reduces the desire to eat, and its absence is associated with increased food consumption; it produces extreme euphoria, and its absence leads to a severe depression (it is thought that the emotional highs and lows that cocaine abuse produces over time may explain the origin of the novella, *The Strange Case of Dr. Jekyll and Mr. Hyde*, by Robert Louis Stevenson). Excessive, long-term, intravenous use of cocaine tends to produce especially severe rebound phenomena, including psychotic behaviors together with delusions of grandeur and hallucinations. For many drugs that affect the brain, including cocaine, the degree of rebound symptoms is typically related to how many times a person has used the drug. Moreover, the effects of cocaine on brain chemistry and physiology may be long term. Even after withdrawal from the drug, most chronic users report visual disturbances such as “snow lights” and other sensory disturbances such as formication, or the feeling of bugs crawling on the skin; these symptoms usually only occur after prolonged use of cocaine. These delayed effects might be viewed as echoes of neural activity reverberating within the circuits of the brain following the powerful stimulation produced by cocaine.

Lidocaine is chemically similar to cocaine; it is also a sodium channel-blocking drug, which is why it is an effective topical pain reliever commonly sold over-the-counter in drug stores. However, in contrast to cocaine, it has no reinforcing,

euphoric effect at all, and animals, including humans, will not self-administer it. This confirms the validity of the finding that the anesthetic actions of cocaine do not contribute to its ability to produce euphoria.

But what explains why we experience euphoria from cocaine, amphetamine, or Ecstasy? Euphoria is the brain's unfailing response to the fast entry of drugs that increase the level of the neurotransmitter dopamine in the synapse between neurons. Again, increasing the fat solubility of these drugs speeds their entry into the brain and makes them more pleasurable. The brain behaves as though it likes drugs that quickly change its level of activity. Just how does dopamine facilitate this experience?

DOPAMINE: THE GAS PEDAL OF PLEASURE

Much of the current evidence provides only indirect confirmation of dopamine's role in experiencing pleasure. First, every drug of abuse somehow enhances the function of dopamine neurons. Probably everything we choose to do for pleasure—including eating, having sex, or listening to beautiful music—somehow affects our dopamine neurons. Second, drugs that antagonize the function of dopamine, such as the antipsychotic drugs discussed in the next section, greatly reduce our ability to experience pleasure. Third, dopamine sets the pace at which the frontal lobes process information, akin to setting the ticking rate of a clock. The faster your clock ticks, the faster your brain processes information. Drugs that increase the release

of dopamine often speed up your thinking process. They also produce increased motor activity, such as pacing and fidgeting. These side effects occur in children treated with drugs, all of which are chemically modified molecules of amphetamine, for attention-deficit/hyperactivity disorder; their performance in school improves, but they are more hyperactive. Drugs such as amphetamine and cocaine speed up the clock, whereas drugs that impair the function of dopamine, such as the antipsychotics, tend to slow mental processing speed. With normal aging, the slow decline in the release of dopamine in the frontal lobes gradually slows one's ability to process information as quickly as one could when younger. Patients with Parkinson's disease, caused by the degeneration of dopamine neurons, suffer from the slowing of their higher cognitive abilities and from emotional depression, including the inability to experience pleasure. The drugs that patients with Parkinson's take to lessen their symptoms enhance the function of dopamine and tend to produce a slight euphoria and, occasionally, an increase in the incidence of compulsive behaviors such as gambling.

Considered together, the effects of a diverse array of drugs all signify that your brain is a race car and that dopamine is the gas pedal. Your brain "feels" euphoria when the gas pedal is pushed quickly (by ever-increasing fat solubility), and your thoughts are allowed to fly as fast as possible around your mental track. The forces of evolution have shaped your brain to truly enjoy working fast—the faster the better because fast brains are more likely to exist within creatures who survive and who will

therefore pass on this trait to the next generation. Thus, classic Darwinism underlies why we enjoy what we enjoy so much—be it having sex, eating chocolate, or ingesting drugs of abuse such as amphetamine, Ecstasy, and cocaine.

TREATING PSYCHOSIS

What happens when the gas pedal is stuck full on? Is this the basis of psychosis? What can be done to fix it? Whatever the causes of psychosis may be, almost universally, the treatment is to block the ability of dopamine to access its receptors. Most of the catecholamine-enhancing drugs that I have discussed thus far interfere with the ability of the brain's presynaptic neurons to produce, store, and release or inactivate the neurotransmitters dopamine and norepinephrine. Antipsychotic drugs, however, work at the other side of the synapse, achieving considerable therapeutic efficacy in many psychotic patients by blocking the function of their dopamine receptors in postsynaptic neurons. Let's examine what this action can teach us about the function of dopamine in the brain and the neurological mechanisms underlying psychosis.

Psychosis is essentially a generic term for a mental condition associated with a loss of contact with reality. Individuals who are psychotic report hallucinations, delusions, and highly disorganized thinking. As a result, they tend to have great difficulty functioning in their daily lives and have trouble sustaining normal social interactions with others. Drugs that block dopamine receptors are capable of reducing some of the symptoms

associated with psychosis. But herein lies a complexity: In no way do the antipsychotic effects of these drugs prove that psychosis is caused by a dysfunction of dopamine neurons, any more than reducing depressive symptoms in some people through medications that selectively block reuptake of dopamine, norepinephrine, or serotonin proves that a dysfunction of these neurotransmitters underlies depression. This is a very important general point to consider when examining drug action as a way of understanding brain function.

In fact, an alteration in dopamine function probably does not cause psychosis; rather, it is most likely a secondary consequence of a complex array of alterations of one (particularly glutamate) or more different neural systems in the brain. This may explain why the blockade of some dopamine receptors within certain brain regions reduces the severity of a few bothersome psychotic symptoms but not others. The antagonism of dopamine receptors may simply compensate for the presence of an error of chemistry that exists somewhere in the brain. Whatever the reason for their efficacy, all we know for certain is that antipsychotics that block dopamine receptors provide significant benefits for some, but not all, patients.

Unfortunately, these drugs—especially the “first generation” of antipsychotics introduced in the 1950s—produce side effects similar to those seen in patients with Parkinson’s disease: tremors when at rest, reduction of voluntary movement, muscle spasticity and dystonia, and sustained muscle contractions. These symptoms confirm the role of dopamine neurons

in the initiation and control of movement. Antipsychotic drugs also block dopamine receptors within a region of the brain that controls the release of the hormone prolactin. The result is an increase in the release of prolactin and thus an increase in breast tissue growth. Increased breast development can be very disturbing to male patients who may already be paranoid about the medications they are given.

Newer, “second-generation” antipsychotics have side effects as well—for example, they may cause significant weight gain that many patients find frustrating. Recent evidence suggests that the weight gain is related to the blockade of histamine receptors in the brain. Interestingly, the original clinical use of the first commercially successful antipsychotic drug, chlorpromazine (sold as Thorazine in the United States), was for its ability to block histamine receptors and reduce symptoms of the common cold; only later was it recognized that this drug could also reduce psychotic symptoms. Recently, the connection between histamine and dopamine in the brain has become even more interesting. Apparently, many of the newer over-the-counter antihistamine medications are capable of blocking the reuptake of dopamine in a manner reminiscent of cocaine. Suddenly, treating one’s sniffles has become a far more euphorigenic experience.

In a manner similar to that observed following treatment with antidepressant drugs, the side effects of dopamine receptor blockade occur rather quickly, but the clinical benefits require 2 or 3 weeks, or more, to fully develop. This also implies that compensatory changes in brain function are required for

these drugs to produce clinical benefits in psychotic patients. These changes most likely require the activation or inactivation of genes in a specific population of neurons within selected brain regions.

By now, you have a sense of the interwoven roles of dopamine, norepinephrine, and acetylcholine in the control of movement, reward, mood, arousal, and learning and attention. By considering how various drugs manipulate these neurotransmitter systems within the brain, scientists have discovered some consistent patterns that allow us to make predictions about what to expect when specific types of drugs are taken. The same holds true for the neurotransmitter system mentioned several times in this chapter: serotonin. What are the consequences of its manipulation in the brain? Read on.

YOUR BRAIN'S ANCHOR TO REALITY

How does the brain filter incoming sensory information so that sights and sounds do not become mixed together? What happens when the brain loses this filtering ability as a result of, for example, taking a hallucinogenic drug? What have we learned about depression and anxiety from the drugs that we administer to treat these disorders? The answers to these questions are slowly being revealed as more becomes known about the actions of serotonin in the brain.

Serotonin is a very ancient neurotransmitter that has been found in the venom of amphibians, wasps, and scorpions and within the nematocysts of the sea anemone as well as in the nervous system of parasitic flatworms, crickets, and lobsters. Within the human body, 90% of the total serotonin is contained

within the neurons of the gut and is released from the intestines to determine bone growth or shrinkage. Another 8% of the body's serotonin is found in the blood and is localized inside platelets and mast cells; in fact, it was initially discovered in *serum* and determined to have *tonic* (or constricting) effects on the vascular system—hence its name. The remaining few percent is found in the brain, in roughly the same location as in every other vertebrate brain.

Neurons that produce and release serotonin in the brain are organized into a series of nuclei that lie in a chain along the midline, or seam, of the brainstem; these are called the raphe nuclei (*raphe* means “seam” in Latin). These neurons project their axons to every part of the brain, and some of these axons make contact with blood vessels; the neurons also project downward into the spinal cord. If you were able to insert a recording device into the major raphe nuclei and “listen” to the activity of your serotonin neurons, you would discover that they have a regular, slow spontaneous level of activity that varies little while you are awake. When you fall asleep, the activity of these neurons slows. When you start to dream—or if, as discussed later, you ingest a hallucinogen—these neurons temporarily cease their activity.

Despite the relative scarcity of serotonin neurons in your brain, drugs that alter serotonin function can produce profound changes in how you feel and how you experience the world around you. For example, such drugs often indirectly stimulate the sympathetic autonomic nervous system and produce increased heart rate, increased respiration, dilated pupils, and

other unpleasant side effects. On the other hand, the effects of serotonin on blood vessel dilation may underlie the ability of an entire class of drugs, known as the triptans, to attenuate the pain associated with a migraine headache.

Other drugs can also help alleviate symptoms that often accompany migraines and that involve serotonin—that is, depression and sleep problems. The diverse and continual actions of serotonin throughout the human brain require a constant supply of nutrients from the diet. The production of serotonin requires the absorption of the amino acid tryptophan from one's food. Transport of this amino acid is influenced by the level of other amino acids in one's blood; that level, in turn, is also influenced by what one eats.

Within the neurons of your brain, tryptophan is converted to 5-hydroxy-tryptophan by tryptophan hydroxylase. This enzyme is never completely inundated with tryptophan—mainly because it is so challenging for tryptophan to be transported across the blood–brain barrier. Therefore, if you eat less tryptophan, your brain generally produces less serotonin. Studies have shown that consuming a diet low in tryptophan can negatively, and also very quickly (usually within a few hours), influence serotonin-controlled brain processes that affect emotion and sleep.

TRYPTOPHAN SUPPLEMENTS

A lack of tryptophan uptake into the brain can produce profound effects on its function. This fact raises an important

question: Can oral tryptophan supplements increase brain tryptophan levels and improve mood? The answer is no. There is no evidence for improving mood through dietary enhancement of tryptophan levels in the blood, primarily because it is very difficult to change brain tryptophan levels through diet alone. Tryptophan supplementation and depletion studies suggest that altering tryptophan levels only benefits people who have a personal or family history of depression. Therefore, unless you have an underlying psychiatric condition, it is unlikely that tryptophan supplementation will provide any positive benefits to your mental health. Popular media articles often recommend diets and foods to increase blood tryptophan levels and raise brain serotonin levels. Such recommendations, although superficially appealing, are misleading and not supported by any current scientific studies. If you become drowsy after taking a tryptophan supplement, you have just experienced the placebo effect.

A variety of products claim to induce sleep by supplying large doses of 5-hydroxy-tryptophan, the immediate precursor to serotonin production. Again, the claim seems reasonable. The problem is that 5-hydroxy-tryptophan cannot cross the blood–brain barrier into the brain. Thus, any benefits these products might offer are entirely due to the placebo effect or some other ingredient hidden in them.

Moreover, the activity of serotonin neurons in the brain can be disabled; this inactivation is correlated with the initiation of hallucinations. This is not to say that we can manipulate our

diet to undermine serotonin release so as to experience a hallucination. We cannot. But certain drugs that will initiate this effect, and their action, as well as the experiences they produce, can tell us something about the normal function of serotonin in the brain.

HALLUCINOGENS

How do hallucinogens work? Hallucinogens do not produce perceptions of things that are not actually present; generally, they distort the ability of the brain to represent the perception of objects that are present. For example, hallucinations induced by chemicals that manipulate the neurochemistry of the visual cortex will distort proportion, form, movement, and the color of objects, but the objects will likely remain recognizable. Hallucinogens induce mental states that are typically only experienced in dreams or, for some people, during extreme religious jubilation. Thus, for the same reason that no one has ever seen an actual alien from another planet in their dreams, no one has ever seen an actual alien from another planet in their hallucinations. This explains why aliens in the movies are always upright, symmetrically organized bipeds, with their brains located at the front end of their feeding tube, just like us.

Thus, in order to understand how your brain produces an altered sensory experience (a hallucination), you need to understand how your brain produces a normal sensory experience—that is, the normal waking world that you experience each moment. Let's begin by recognizing a large globular brain

region called the thalamus. The thalamus lies deep in the center of the brain and is highly interconnected with the overlying cortex. All of your sensory information is received, processed, and distributed to reciprocally connected regions of cortex; the continual cross-talk between these two brain regions is thought to underlie your experience of normal waking consciousness. When the cross-talk between the thalamus and overlying neo-cortex is disturbed or imbalanced in its rhythm, you experience this as a hallucination. This explanation raises the question of how hallucinogens produce the disturbance in the communication between thalamus and cortex. In order to answer that question, you need to learn about a couple of serotonin receptors.

All of the known hallucinogens, except one, bind to a series of G protein-coupled serotonin receptors. Currently, there are 14 different serotonin receptors in the brain and body. The best studied hallucinogenic drug, D-lysergic acid diethylamide (LSD), binds to a variety of different serotonin-sensitive receptors on the surface of neurons. At doses typically achieved in the brain, LSD interacts with at least 6 different serotonin receptors. In contrast, LSD's affinity for most of the dopamine, norepinephrine, and histamine receptors is simply too low for it to influence their function at levels typically achieved in the brain. Thus, the psychoactive actions of LSD are most likely due to its ability to stimulate two serotonin receptors, one (5HT-2A) that is excitatory and one (5HT-1A) that is inhibitory. Initially, LSD slows the activity of serotonin neurons in the raphe nuclei. The left side of Figure 5.1 shows graphically what the activity

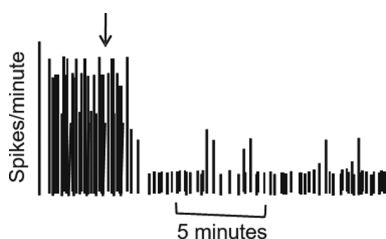


Figure 5.1 The activity of serotonin would look like this if you placed an electrode into one of the raphe nuclei in the brainstem. If LSD is administered at the arrow, then the activity of these cells slows down.

of serotonin would look like if an electrode was placed into one of the raphe nuclei in the brainstem and then LSD was administered to it. At first, the firing is quite regular. The arrow in the figure indicates the point at which LSD is injected into the brain. Only a few minutes later, the activity of the serotonin neurons slows significantly, similar to that seen when one enters dream sleep. However, that similarity is only a neat coincidence; the half-life of LSD is approximately 3 hours, at which time the hallucinatory effects reach their peak. The psychoactive effect of LSD far outlasts the slowing of serotonin neural activity; therefore, the slowed activity of serotonin neurons in the raphe nuclei does not explain why we hallucinate on this drug and why the hallucinations are so similar to dreaming. The effects of LSD on serotonin neurons may only be the initial trigger that sets in motion a cascade of complex processes throughout the brain that is experienced as a hallucination.

A naturally occurring version of LSD is D-lysergic acid monoethylamide. It is slightly less fat-soluble (one less ethyl

group) than LSD, but it too can produce hallucinations. *Claviceps purpurea*, the ergot fungus that produces this compound, also generates a toxin that mimics the action of serotonin, particularly its ability to constrict blood vessels. Consumption of bread made from grain or corn that is contaminated with this fungus causes a burning in the extremities resulting from extreme constriction of blood vessels and leads to limb death. One outbreak of ergotism, as this condition came to be known, may have caused the death of nearly 40,000 people in Europe in 944 CE; at that time, it was called *ignis sacer*, or “Saint Anthony’s holy fire,” after the monks of the Order of Hospitallers of St. Anthony near Grenoble, France. Consumption of ergot-contaminated grains may also have been responsible for a number of mystical experiences reported in the past, including those that took place annually during the ancient Greek ceremonies known as the Eleusinian Mysteries. Some historians believe that ergot-contaminated rye may have caused the behaviors that eventually led to the Salem witchcraft trials that began in December 1691. According to available records, eight girls suffered from “distempers” that included, according to witnesses, “disorderly speech, odd postures and gestures, and convulsive fits.” Although ergotism was quite familiar to medical science and to historians by the 17th century, the New England Puritans chose to view these symptoms as the work of Satan brought about by the practice of witchcraft. By September 1692, 20 men and women had been tried and executed for “their part” in the practice, and 2 died in prison.

Psilocybin, a chemically similar naturally occurring molecule, is much less potent than LSD but likely shares aspects of its actions on serotonin neurons once the body converts it into psilocin. Our ancestors probably discovered its sources—*Psilocybe mexicana*, *Psilocybe semilanceata*, and *Psilocybe cyanescens*—by accident when foraging for edible mushrooms. Just imagine how horrific and unexpected the experience must have been for the first person who inadvertently prepared one of these mushrooms for consumption, bringing new meaning to the phrase “dinner and a show.” Sixteenth-century Central American Indians, according to the naturalist Francisco Hernandez, called these mushrooms “Teonanácatl,” possibly translated as “God’s flesh” or, simply, “sacred mushroom.” Albert Hofmann, the scientist credited with the inadvertent discovery of LSD when investigating its effects, is also credited with isolating the active ingredient of this mushroom in 1958. He claimed to have ingested 32 dried mushrooms, probably 10 times the usual dose taken today, to determine their effects. He wrote that the effects were similar to those he had experienced with LSD. It is worth stating the obvious at this point: Please do not ever experiment with unknown plant extracts on yourself, especially if there is any risk that they might affect your brain. I know this warning seems self-evident, but too many students have brought empty vials to my class and asked me, “I took this last night and I was wondering if you could tell me what it was?” These

questions might actually seem appropriate when one is 19 years old and feels immortal.

Psilocybin is made by more than 75 different species of mushrooms. It is also chemically similar to bufotenine, an interesting hallucinogenic molecule that is chemically very similar in structure to serotonin. Bufotenine has been discovered in a truly diverse set of locations: the skin and glands of a South American toad, seed pods from the South American tree *Piptadenia peregrina*, and the leaves and bark of the Central American mimosa *Acacia niopo*. The seeds from *P. peregrina* are ground with limestone to increase the extraction of the bufotenine, much as tobacco companies today add ammonia to raise the pH and increase the absorption of nicotine in the mouth. The grounded blend of bean pod and limestone is used as a snuff called “yopo.” Young boys blow the snuff into each other’s nostrils through a forked tube made from hollow chicken bones. Interestingly, bufotenine may also be present in the *Amanita muscaria* mushroom, which may be responsible for some of the psychoactive effects described in Chapter 4. The actions of bufotenine on the brain are still speculative because no one has yet demonstrated that it can actually cross the blood–brain barrier. Bufotenine’s reputation may be more directly related to its toxic effects outside of the brain.

In fact, no one is certain how LSD or any of the hallucinogens actually work or just how serotonin factors into their hallucinatory effects. Confounding this uncertainty is the fact that some hallucinogens have no apparent effect on serotonin at all. For

example, salvinorin A, from the Mexican plant *Salvia divinorum*, is a very potent naturally occurring hallucinogenic compound that is similar to morphine in its actions but has no identified action at serotonin receptors.

WE MAY BE BORN HALLUCINATING

The complex sensory experiences known as hallucinations can occur from other sources besides drugs such as LSD or psilocybin, and this fact may shed some light on the nature of the hallucinatory experience, drug-induced or otherwise, and its connection to serotonin. Consider, for example, a hypothetical scenario.

Imagine yourself as a newborn lying in a crib. Your brain's serotonin neurons at this age, and during the first couple years of your life, are not working completely because the neurons and glia that support them have not fully developed. In addition, the makeup of serotonin receptors at this age has not yet converted to the adult balance of excitatory and inhibitory subtypes of receptors. Your sensory systems—visual, auditory, and olfactory abilities in particular—are working, but your serotonergic system is not adequately installed to assist them with the processing of the incoming sensory information to the brain. Suddenly, you sense something looming over your crib—a large green, distorted face with a screeching voice and reeking of a yellow odor—and you scream in fear. You have just had your first hallucination. You have also just experienced synesthesia, or the merging and mixing of sensory

processes—for example, sights that produce sounds or smells that have color.

Now imagine yourself 20 years later, with your serotonergic system fully developed. Let us assume that you are not actually a “synesthete”—that rare person who has this condition that mixes data from the different senses as an inherited part of his or her life. However, take a hallucinogenic drug at age 20 years (or any adult age) and you could have a temporary synesthetic experience similar to what you had in your crib as an infant. Why? The inhibited function of your serotonergic system that is induced by a hallucinogen may reproduce the condition of synesthesia that was simply “normal” when you were a newborn. As a newborn, you would find this condition to be frightening. However, as an adult who has taken a hallucinogen, you might, in the right setting, come to believe that the condition is a transcendently mystical experience.

HALLUCINOGENS AND RELIGIOSITY

Timothy Leary, the famous LSD guru of the 1960s counter-culture movement, commented in 1964, “A psychedelic experience is a journey to new realms of consciousness. The scope and content of the experience is limitless, but its characteristic features are the transcendence of verbal concepts, of space time dimensions, and of the ego and identity.” His description has a spiritual flavor that might be very familiar to people who are skillful at tantric yoga or transcendental meditation. Mind-altering or mind-expanding drugs, usually referring to

hallucinogens, alter your consciousness, your sense of personal space and time, and your perception of the real world around you. In reality, the actions of hallucinogens in the brain that lead to an “expanding of the mind” probably result from relatively subtle alterations in normal serotonin neuronal function. These changes, as mentioned previously, set in motion a cascade of poorly understood neural processes that impair aspects of normal consciousness.

One function of consciousness, and a role probably influenced by serotonin, is its ability to filter out the overwhelming and confusing mass of sensory input that your brain receives while you are awake. If you lost the ability to filter incoming sensory stimuli, you would probably become very disoriented and confused. Drug-induced mind expansion can therefore only be experienced safely—that is, so as to avoid completely freaking out—in a highly structured and protected setting. It should come as no surprise, then, that many cultures have developed strict religious and social rules around the use of plants that produce hallucinations. Extracts from the classical entheogenic psychoactive plants, or symbolic representations of them such as the burning of incense, have often played a significant role in religious ceremonies. Indeed, the near-universal co-occurrence of religion and the use of natural hallucinatory agents may point to the crossroads that connect various hypotheses on why religiosity is so common across diverse primitive societies. Specific plants sometimes gave birth to specific deities. For example, the Poppy Goddess of Crete

was represented standing in a trance-like state wearing a crown of poppies; the plant henbane (*Hyoscamus niger*) was, in different cultures and at different times, associated with the Norse God Thor, the Celtic God Bel, and the Roman God Jupiter; and cannabis (*Cannabis sativa*) was associated with the goddess of love known as Freya. Odin, the father of Thor who was worshiped for his control over healing and death, was, quite naturally, allied with opium, the deadly nightshade (*Atropa belladonna*), and a deadly mushroom (*A. muscaria*). The Egyptians considered their goddess Osiris to be the personification of *Psilocybe cubensis*.

What I am suggesting is that the appearance of small mystical societies in ancient times that ultimately evolved into more familiar modern-day organized religions was assisted by the universal presence of hallucinogenic plants that were able to alter how the brain functioned and to facilitate each culture's communication with their gods and goddesses via the trance-like state they induced. Given the ubiquity of hallucinogen-inducing plants throughout the world, it should also come as no surprise that in recorded history, humans have worshiped more than 2,500 major deities; the actual number is probably far greater. You, or someone you know, probably worships one of these deities. The similarities between a hallucinatory experience and, for some, an intense religious experience are consistent with the hypothesis that religion has a biological basis that was shaped by our shared evolution with, and constant exposure to, the hallucinatory plants around us. The pervasive use of hallucinogenic plants by our ancestors

may underlie some of the fantastic stories that have become associated with various religions. For example, some people believe that the first chapter of the Book of Ezekiel describes this prophet's encounter with beings from outer space during the 6th century BCE; a more reasonable explanation might be that the experience was initiated by the consumption of a hallucinogenic plant targeting the brain's serotonergic system. The visions described are very similar to the colorful, sparkling images and pulsating wheels spinning within row of outer wheels reported by modern users of hallucinogenic drugs. Therefore, because serotonin neurons play a role in how hallucinogens interact with the brain, it is also possible that serotonin plays a role in the individual expressions of religiosity across cultures.

In addition, there may be a correlation between religiosity, specific genetic markers underlying the function of serotonin, and other mental experiences besides hallucinations. Genetically altered mice and positron emission tomography studies on humans have been very useful in demonstrating the potential role of specific serotonin receptors in the regulation of mood and anxiety. For example, mice lacking a particular serotonin receptor, known as type 5HT-1A, show more anxiety-like behavior. Some recently discovered drugs target this receptor to reduce the symptoms of depression and anxiety in humans. The overall effectiveness of these drugs suggests that this receptor in particular may play an important role in the normal control of anxiety or mood.

So what is the connection to one's personal degree of religiosity? The number of type 5HT-1A serotonin receptors in the brain is inversely correlated with self-ratings of religiosity and spirituality. People who respond negatively (e.g., with excessive anxiety or depression) to the challenges of everyday life have fewer 5HT-1A receptors and are more likely to find comfort in religious faith and practice. Moreover, a series of studies demonstrated that people with certain serotonin receptor profiles suffer more often with social anxiety disorder, which is characterized by an extreme fear that other people are thinking bad things about them. Fortunately, compared to people who do not have these types of serotonin receptors in their brains, these people tend to respond more positively to placebos or affirmative suggestions from people whom they respect or admire. Taken together, these findings suggest that people who yearn for more religious leadership in their lives may have inherited fewer serotonin receptors compared to those who never express such yearnings.

Before drawing too close of a correlation between religiosity and the number of type 1A serotonin receptors, it must be recognized that other features of the brain also correlate with the tendency to rate oneself as religious. A recent investigation discovered that the tendency to display extravagant religious behaviors correlated significantly with atrophy (i.e., shrinkage) of the right hippocampus in patients with untreatable epilepsy. In fact, the medical literature is replete with reports of epilepsy patients with religious delusions. Decreased brain

activity in the hippocampus has also been correlated with the feeling of a “sensed presence” or the eerie feeling of an unseen person nearby. Recent studies using sophisticated brain imaging techniques also suggest that the prefrontal cortex is more likely involved in controlling our religious, moral, and paranormal beliefs.

To understand why the brain generates religious sensations under these unusual conditions, it is necessary to appreciate what it does under normal circumstances. Usually, your brain receives sensory inputs from your body and produces a sense of where you are in the world, what you are doing at this moment, and what is happening all around you. This incoming information is constantly updated and provides you with a sense of “self.” If your senses are impaired or your brain’s ability to interpret sensory information is altered because of a hallucinogenic drug or a disorder such as epilepsy, your brain is forced to do the best it can with what it has working. Thus, under these conditions, you might have some very unusual sensory experiences, such as feelings of floating in space, a connection to everything in the universe, or a communication with your god; however you might see him or her.

It is clear that for lack of any more precise way to quantify these experiences, neuroscientists often describe religious phenomena in terms of neurobiological processes whose activity or inactivity they can observe with their brain scanners. Indeed, there might not be anything more to a religious experience than the activation of the right dorsal region of the hippocampus or

the inactivation of the top part of the parietal lobe, to name but two currently appealing hypotheses.

MIXING HALLUCINOGENS

My students definitely enjoy mixing their drugs in creative ways similar to what bartenders have done for alcoholic drinks. And to continue the parallel, they give their concoctions amusing names: “Candy-flipping” is a combination of MDMA (Ecstasy) followed by LSD; “hippy flipping” pairs two different psychedelic mushrooms; “kitty flipping” combines ketamine with MDMA; and “candy flipping on a string” is the trifecta combination of cocaine, LSD, and MDMA. I have no doubt that this list is not exhaustive. One of my students, an intelligent and devout young Muslim woman, admitted during class that she had been candy-flipping every weekend for the previous 2 years. She was convinced that the combination of these two hallucinogens was superior and more pleasant than either drug taken alone. I have heard this claim for many years, and I find it difficult to reconcile it with how scientists currently view the actions of hallucinogens in the brain. Why should taking a drug that kills serotonergic neurons—MDMA—actually enhance the actions of another drug—LSD—that requires the presence of serotonergic neurons? These anecdotal reports are fascinating and confirm my previous statement: We do not currently understand how any hallucinogen works within the brain.

CHAPTER 6

MARIJUANA IN THE BRAIN

What drug produces euphoria and, under some circumstances, might actually be good for your brain? Can smoking marijuana prevent age-related memory loss, for example? To answer these and similar questions, I turn now to a neurotransmitter system in the brain that was discovered through the use of one of the most common drugs in history. This system may not have the most familiar name—endogenous cannabinoid neurotransmitter—but the drug that tells us most about its function is certainly a household word: marijuana. Indeed, few drugs have the kind of colorful history that marijuana has achieved. Thus, before examining the neurotransmitter that it affects, a brief story of the drug is presented.

DOPE AND A ROPE

Among species of marijuana plants, *Cannabis indica* is the one grown principally for its psychoactive resins. It is likely a shorter, bushier version of *Cannabis sativa*, which is used primarily for its fibers to make rope. Both plants, like catnip, contain active ingredients belonging to a family of compounds called terpenes, of which the primary psychoactive terpene is thought to be concentrated in the plants' resin as delta-9-tetrahydrocannabinol (THC). Cannabis plants are herbaceous plants that exist as either males or females and have a 4- to 8-month life cycle. In the wild, the plants are wind pollinated, with the male plants dying soon after releasing their pollen. Archeological records in the form of imprints on pottery suggest that the plant was being utilized for cloth and rope making at the beginning of the Holocene era approximately 11,000 years ago. Probably the oldest reference to the cannabis plant, in a pharmacy book from 2737 BCE, is related to its use as a medicine. The first Chinese emperor Shennong ("the Divine Farmer"; a legend claims that his body was transparent so that he could monitor the effects of the many different herbs and plants he tested on himself) referred to it as the "liberator of sin" and recommended it for the treatment of "female weakness," gout, rheumatism, malaria, constipation, and absent-mindedness. By 1000 BCE, its medicinal use, as indicated by available writings, had spread to India. By 500 BCE, it was familiar to the ancient Greeks.

Initially investigated more than 100 years ago by two chemists, the Smith brothers (William and Andrew) of later cough-drop fame, the plants contain at least 60 cannabinoid-based compounds, with 4 major cannabinoids: *trans*-delta-9-THC and delta-8-THC; cannabidiol (CBD; the second most abundant psychoactive ingredient after THC); and cannabinol, which is a decomposition product of THC that accumulates as cannabis samples age. After ingestion, *trans*-delta-9-THC is converted in the liver to 11-hydroxy-THC, which is equally potent and psychoactive. Depending on the concentration of various cannabinoids and other plant components, users may be exposed to a variety of active ingredients with quite different pharmacological effects. Increasingly, marijuana plants are being bred to express very high concentrations of THC, the primary psychoactive compound. By contrast, CBD, a non-psychoactive cannabinoid that dampens down the effects (including the psychoactive effects) of THC and that was present in significant amounts in cannabis used centuries ago, has been bred out of modern plants. However, some growers are breeding marijuana plants with significantly higher levels of CBD. Does this affect the experience of smoking? Yes, it does. If the ratio of THC to CBD is 1:1, the level of THC in the brain and blood is roughly doubled within just 30 minutes because CBD slows the metabolism of THC within the liver. If the CBD:THC ratio approaches 8:1, the antagonistic properties of CBD become more prominent, reducing the euphoria produced by THC.

Due to its lipid solubility, THC is preferentially absorbed into body fat; with daily administration, it reaches a peak concentration in approximately 4 or 5 days. It is then slowly released back into the blood, where it can be taken up by the brain. Due to accumulation in body fat, the half-life for the elimination of THC from body may be approximately 7 days; the complete elimination of a single dose of THC may require up to 30 days.

Both CBD and THC are capable of interacting with the brain; however, they do not do so with the same degree of effectiveness. First, CBD does not cross the blood–brain barrier as easily as does THC. Furthermore, scientists have shown that THC is 1,000 times more potent than CBD. This means that the dose of THC the brain requires in order to experience a typical “high” is 1,000 times lower than the required dose of CBD. This chemical property of CBD has led to the accurate claim that CBD does not make one feel “high.” A person would need to consume 1,000 “joints” of the genetically modified CBD marijuana plant to get high. The effectiveness of CBD at its receptor is so low that it behaves as though it is blocking the effects of THC. It has become quite apparent that no single component of the plant is entirely good or bad, therapeutic or harmful, or deserving of our complete attention. To date, all of the positive evidence supporting the use of medical marijuana in humans has come from studies of the entire plant or experimental investigations of THC. CBD acts on a number of targets that are linked to neurological therapeutics, but its actions are not

consistent with modulation of such targets that would derive a therapeutically beneficial outcome. In addition, although more than 65 discrete molecular targets have been reported in the literature for CBD, a relatively limited number represent plausible targets for the drug's action in neurological disorders. The molecular targets of CBD reported in the literature are unlikely to be of relevance due to effects being observed only at extremely high concentrations. Therefore, due to its poor bioavailability, CBD does not reach an adequate concentration at relevant sites of action within the brain.

Does the balance of THC and CBD matter? A recent study suggested that both compounds working together reduced brain inflammation far more effectively than did either THC or CBD working alone. Essentially, CBD, the second most abundant cannabinoid in the plant, may primarily serve to mitigate many of the more negative, unpleasant actions of THC.

One potential way to achieve an optimal balance between THC and CBD is to consume the plant without heating it. When humans were given an ethanol extract of marijuana that was not heated, the blood levels of the acidic forms of CBD and THC were much higher than the levels of the active (i.e., non-acidic) forms. Overall, heating marijuana achieved a significantly lower level of both THC and CBD in the blood. The study concluded that consuming the unheated extracts from marijuana might induce a combination of chemicals that would be more tolerable and have fewer negative side effects. Heating the plant or exposing it to light and air leads to the production

of a series of molecules that may contribute to the overall psychoactive experience.

The earliest reference to the use of cannabis as an inebriant comes from stonework from the 23rd century BCE in the Egyptian Old Kingdom. In 430 BCE, the Greek historian Herodotus of Halicarnassus wrote that the Scythians burned the seeds and inhaled the smoke to induce intoxication during funerals. The plant is also mentioned several times (as “*kaneh-bosem*,” כֶּנֶב־בֹּסֶם) in the Old Testament (as per Yahweh’s instruction to Moses in Exodus 30:23) as a bartering material, incense, and an ingredient in holy anointing oil; it was likely used by the high priests of the temple as well as by Jesus. At that time in history, the word *messiah* simply meant “the anointed one.” Use of the plant as an inebriant spread to the Muslim world and North Africa by 1000 CE and became an epidemic by the 12th century. The exploring Spaniards likely brought *kaneh-bos*, by now probably pronounced as *cannabis*, to the New World in approximately 1545.

Meanwhile, let’s not forget that other, more humdrum role that cannabis has played in history. English settlers brought it, as well as tobacco, to Jamestown, Virginia, by 1611 and used its fibers to make rope. In the 1700s, George Washington grew cannabis on his farm and, according to entries in his diary, maintained a keen interest in cultivating better strains of the plant, evidently for the purpose of producing a better quality of rope. In 1942, the US government made a number of movie-shorts aimed at encouraging farmers to plant hemp, or cannabis,

for wartime use as rope. Other rather famous historical uses of cannabis fiber are said to include Chinese paper, the ropes and sails on Christopher Columbus's ships, the Declaration of Independence, World War II parachutes, and the first Levi jeans.

Today, when most people hear the term marijuana, they think of the leafy material from *C. indica* that is generally smoked. It contains 2%–5% THC. Sinsemilla or ganja, made from the unpollinated female cannabis plant, may contain up to 15% THC. Hashish, which is actually the Arabic word for grass (which might explain the slang term for this plant), is made from a dried concentrate of the resin of cannabis flowers and contains approximately 8%–14% THC; hashish oil typically has 15%–60% THC. Bhang, a drink popular in India that is made of cannabis leaves, milk, sugar, and spices, has 2%–5% THC. Kief (from the Arabic *kaif* كيف meaning “pleasure, well-being”) is made from the dried resin of *C. indica* and usually has very high THC levels. Budder is a processed and concentrated form of hashish oil that is reported to contain between 82% and 99% THC by weight. Given its potency and effectiveness, it probably takes a lot of bread to buy this budder.

Whatever its form, marijuana is today often categorized, incorrectly, as a gateway drug for its role in leading users to try other illegal drugs. Overall, statistics show that very few young people use other illegal drugs without first trying marijuana. However, the majority of marijuana users (approximately 60%) do not go on to use any other illicit drugs. By contrast, according to some statistics, most users report having tried legal

substances—cigarettes or beer—before trying marijuana. Thus, using the same definition as applied to marijuana, tobacco and alcohol products should be considered the actual gateway drugs. It is worth noting that alcohol is now considered as addictive as heroin, and tobacco is considered as addictive as crack cocaine. Obviously, the addiction properties of a drug do not determine whether it is legal or illegal. The legal standing of marijuana in most states demonstrates that fear and myth almost always trump science.

What does marijuana do in the brain? It produces some excitatory behavioral changes, including euphoria, but it is not generally regarded as a stimulant. It can also produce some sedative effects, but not to the extent of a barbiturate or alcohol. It produces mild analgesic effects (pain relief) as well, but this action is not related pharmacologically to the pain-relieving effects of opiates or aspirin. Finally, marijuana produces hallucinations at high doses, but its structure does not resemble lysergic acid diethylamide (LSD) or any other drug formally categorized as a hallucinogen. Thus, marijuana's effects on the body and brain are complex. Just how does it achieve these effects?

THE BRAIN'S OWN MARIJUANA-LIKE NEUROTRANSMITTER

The very high potency and structure of the cannabinoids contained within the marijuana plant enable them to cross the blood–brain barrier and bind to a receptor for the brain's very own endogenous cannabinoid neurotransmitter system.

If this were not the case, then the marijuana plant would be popular only for its use in making rope, paper, and cloth. The two currently identified neurotransmitter compounds (and there are probably more) in this system are anandamide, from the Sanskrit word *ananda* meaning “bliss,” and 2-AG (2-arachidonoyl-glycerol), which occurs at much higher levels in the brain than anandamide and binds most readily to the CB₁ receptor; this receptor is most likely responsible for marijuana’s psychoactive effects. Unlike the other neurotransmitters that I have discussed, these two “endocannabinoids” are not stored in synaptic vesicles. Rather, they are both produced within neurons and released to flow backward across the synapse to find their receptors, designated as CB₁ and CB₂. There are more of these CB receptors in the human brain than for many of the other known neurotransmitters that have been discussed. The great abundance of these receptors and their widespread location indicate the importance of the endocannabinoid system in the regulation of the brain’s normal functioning.

THE FUNCTION OF ENDOGENOUS CANNABIS-LIKE CHEMICALS

To gain insight into the consequences of smoking (or eating) marijuana, let’s discuss what endocannabinoids do in the brain. For example, anandamide inhibits the release of glutamate and acetylcholine within the cortex and hippocampus, an action that may underlie the ability of marijuana to impair

one's capacity to form new memories when using the drug. Anandamide also inhibits the release of dopamine; the presence of endocannabinoid receptors in the parts of the brain that control movement may explain the stumbling behavior that some marijuana users experience.

Anandamide has also been shown to prevent the release of the inhibitory neurotransmitter γ -aminobutyric acid (GABA), thus altering the balance of excitation and inhibition throughout the brain, particularly within the brain's reward center. There is still conflicting evidence from human and animal studies concerning the effects of THC on dopamine. Acute THC administration increases the activity of dopamine neurons, leading to the increased release of dopamine; this action likely plays a critical role in the ability of marijuana to produce euphoria. The mechanism underlying this effect is indirect because the dopamine neurons do not express CB receptors. By preventing the release of GABA onto these dopamine neurons, their activity increases and dopamine is released into the brain's reward center. The fact that THC's actions are indirect may explain why marijuana is far less addicting than drugs that act directly on dopamine neurons. In contrast, long-term use of THC is associated with blunting of activity in the dopamine reward system even though long-term users continue to report feelings of euphoria when using marijuana. This surprising discovery raises the question about the role dopamine release plays in the psychoactive effects of marijuana.

THE MUNCHIES AND DEPRESSION

Stimulation of cannabinoid receptors in the feeding centers of the hypothalamus may underlie the classic marijuana side effect known as the “munchies.” This effect coincidentally drew the attention of scientists who conducted a series of clinical trials using a drug that blocks the brain’s cannabinoid receptors. Their hope was that this drug’s blocking action would produce an “anti-munchies” effect, thereby reducing food consumption and providing help to overweight patients. At first, the drug worked fairly well. People reported being less attracted to eating. Unfortunately, they also became severely depressed. This discovery indicates that the endogenous cannabinoid system is normally involved, either directly or indirectly, in elevating or controlling mood and that antagonizing the cannabinoid receptors in the brain, as occurred with this novel drug, can produce some dangerous consequences.

PROTECTION FROM INJURY AND AGING

In contrast, stimulating the brain’s cannabinoid receptors may offer protection from the consequences of stroke, chronic pain, and neuroinflammation. Surprisingly, it may also protect against some aspects of age-associated memory loss. Ordinarily, we do not view marijuana as being good for our brains and certainly not for making memories. How could a drug that clearly impairs memory while people are under its sway protect their brains from the consequences of aging?

The answer likely has everything to do with the way that young and old brains function and the age-related changes in the actions of the neurotransmitters acetylcholine and glutamate. These two neurotransmitters are involved in making new memories and destroying old or unnecessary ones. Early in life, this process of creation and destruction is in balance, and so interfering with it—which occurs when using marijuana—might impair memory. However, later in life, the roles of these neurotransmitters change in significant ways. In addition, the aged brain displays increasing evidence of inflammation and a dramatic decline in the production of new neurons, called neurogenesis. Marijuana may offer protection in at least three different ways: by preventing the damaging actions of glutamate, by reducing brain inflammation, and by restoring neurogenesis. Thus, later in life, marijuana might actually help one's brain rather than harm it. Research in my laboratory by Dr. Yannick Marchalant suggests that it takes very little marijuana to produce benefits in the older brain; his motto is “a puff is enough.” The challenge for pharmacologists in the future will be to isolate the beneficial aspects of marijuana from its psychoactive effects, which themselves can be an additional burden to those suffering from the consequences of an aging brain.

Considerable evidence from animal studies supports the use of marijuana as a preventative for the development of dementia. In contrast, no evidence suggests that using marijuana is beneficial to patients who are currently suffering symptoms of dementia associated with Alzheimer's disease. Indeed, marijuana

should never be administered to someone with a mild or major cognitive impairment; the psychoactive “high” would likely be quite frightening to an elderly patient experiencing the symptoms of dementia.

MARIJUANA FOR MIGRAINES

Migraine sufferers have few options for reducing their headache pain, and most of the medications available have unpleasant side effects that limit their long-term usefulness. Approximately 20 years ago, a new class of drugs, the triptans, was introduced as an effective and safe alternative treatment. This class of drug works effectively for most patients but must be taken at the first sign of a headache. These drugs have their own unwanted side effects, such as feeling hot or cold, weak, or “strange” in some way. The strange feelings are often given the term serotonin syndrome and also include changes in mental status. These changes in mental status can be quite significant in individuals who carry a genetic vulnerability, such as people with bipolar illness or schizophrenia. The assumption has been that these drugs work by acting upon serotonin receptors, which leads to a constriction of cerebral blood vessels. This assumption may be incorrect.

One potentially important mechanism that was initially published in 1987 described how migraine headaches developed in some people soon after they abruptly discontinued their long-term marijuana use. The implication was that marijuana was preventing the onset of migraines in vulnerable individuals.

In addition, marijuana has long been known to possess analgesic properties. Possibly, the marijuana was somehow masking the pain of the migraines.

A recent study from the University of California, San Francisco, offers a fascinating explanation for why the use of both triptans and marijuana prevents migraine headaches. The brain's own endogenous marijuana-like chemicals produce analgesia by modulating the entry of pain signals into the brain at the level of the spinal cord. Future generations of pain relievers will likely be developed on the basis of this action of marijuana in the body. The advantage of targeting the endogenous marijuana system is that only noxious or painful signals are blocked; normal touch sensation remains normal. This study made two significant advances: It confirmed the role of the endogenous marijuana neurotransmitter system as a potential target for treating migraines, and the results suggest that triptans may produce their migraine relief by activating the brain's own endogenous marijuana-like chemicals. This study may lead to the development of more effective migraine prevention and treatment. The challenge will be to identify a dose of marijuana that produces pain relief without disturbing normal cognitive function.

MARIJUANA AT BREAKFAST

Two of America's favorite psychoactive herbals, marijuana and coffee, are now available together in a K-cup and ready for brewing. It is inevitable that these two popular, rather inexpensive

and legal (in many states) herbals would be combined in a ready-to-use form. What will the combined effects of a hot water extract (decoction in pharmacological terms) of these two plants do to the brain? What will it feel like? Concerning coffee, the effects are entirely predictable. Most people know what it feels like to self-administer caffeine. Concerning marijuana, the answer is not at all predictable. The problem is that no one knows what components of the plant—that is, the balance of active and inactive compounds—will be extracted by the hot water.

Most of us have heard about the methods that humans utilize to self-administer the active ingredients of marijuana. For more than 6 millennia, humans have inhaled the smoke from the burning plant or its extracted oils or consumed parts of the plant in cooked food. Why have we never heard about preparing marijuana in the same way that we prepare tea or coffee—that is, by hot water extraction? The answer is likely because the cognitive effects produced by drinking a marijuana-like tea were simply not as pleasurable to our ancestors. During the past few millennia, someone somewhere must have already tried this. It is just too easy to prepare a warm drink and much less irritating to the throat than inhaling the smoke. Whatever the reason, this method of marijuana administration never became popular.

Our ancestors tried many different approaches to obtaining psychoactive effects from the plants that grew around them. Someone must have tried chewing on tobacco leaves and coca leaves and discovered that doing the latter produced a much better feeling than doing the former. Sucking on coca leaves has

a long history; inhaling the smoke of a burning coca plant has no history. Why? Because the cocaine in coca leaves is unstable when burned; thus, inhaling the smoke would not produce euphoria. Not until this century did scientists discover that cocaine could be converted from its acid form found naturally in the plant into its basic form (today called free-base cocaine) that would tolerate the high temperatures produced by burning without being destroyed. That is why people today smoke free-base cocaine.

Caffeine and marijuana have vastly different effects within the brain; this makes predicting how the combination might affect mood or thinking exceptionally difficult. Caffeine is considered a brain stimulant; marijuana is not a stimulant, nor is it a depressant. The brain's response to marijuana is far more complex than its response to caffeine. The brain contains far more receptors for marijuana to act upon than it does for caffeine. Compounding this problem is the influence of drug tolerance. Long-term coffee drinkers who never smoked marijuana in the past will respond quite differently to the combination of marijuana and coffee compared to people who rarely drank coffee but regularly used marijuana. Genetics, age, and gender will also play a role in each person's response to this drink. Some people are born more vulnerable to the euphoric properties of drugs and thus more likely become addicted; males typically experience a greater euphoria in response to drugs of abuse, and the aging brain slowly changes how it responds to marijuana over time.

I have heard numerous testimonials from my students claiming that the combination made the experience both better and worse than using either herbal alone. Scientists have known for many decades that combining psychoactive drugs can produce highly variable effects on brain function. Today, due to a total lack of knowledge, combining marijuana and coffee is still pharmacological roulette.

MARIJUANA FOR THE TREATMENT OF PSYCHIC PAIN

The loss of someone you love hurts. Losing your job is painful. No one wants to be ignored because it brings on heartache and depression and possibly increases one's chances of developing cancer or dementia. The field of psychoneuroimmunology has evolved to study the link between social and physical pain. Obviously, to anyone who has experienced any of these events in life, the link between psychic and physical is quite real, and the symptoms are very difficult to treat.

During the evolution of the human brain, those areas that were once only responsible for experiencing the sensory component of pain slowly evolved to provide the sensations associated with the emotional components of pain and its experience. We now respond with a psychic aching to social isolation that is often accompanied by a headache, nausea, depression, loss of appetite and many other essential body functions. Recently, scientists speculated that because these two systems overlap functionally and anatomically in the brain, it might be possible

to reduce social pain by targeting physical pain with common over-the-counter drugs.

Two different types of common analgesics, acetaminophen and ibuprofen (i.e., Tylenol and Advil), are capable of producing this combined benefit by enhancing the action of the brain's endogenous marijuana neurotransmitters. A recent study demonstrated that regular marijuana use reduced the experience of low self-worth and the incidence of major depressive episodes in lonely people. This research supports the hypothesis that treating physical pain with simple over-the-counter drugs might lessen the psychic pain as well.

How are these simple over-the-counter drugs able to provide relief of psychic pain? They enhance the action of anandamide. Anandamide and the other marijuana-like chemicals in the brain are well known to control happiness and euphoria. Once anandamide is released inside the brain, specific enzymes rather quickly inactivate it. One of these enzymes is cyclooxygenase (COX). Ibuprofen and acetaminophen inhibit the function of COX. Thus, taking these drugs may enhance the actions of anandamide and thereby mimic the effects of marijuana in the brain. Obviously, their action in the brain must be rather subtle; otherwise, these products would no longer be legally available. Ultimately, targeting the biological mechanisms underlying the symptoms of loneliness might only require a trip to the local drugstore.

Again, the distribution of a neurotransmitter provides clues to its function in the brain. For example, our brains'

endogenous cannabinoid neurons are in the hypothalamus feeding centers; when these receptors are stimulated, we feel hungry, and when they are blocked, we become less interested in eating. Cannabinoid neurons also influence the function of our cortex and various limbic (emotion-controlling) regions; when we stimulate these receptors, we impair higher cognitive functions as we experience euphoria, and when they are blocked, we feel depression. Because our brains appear to have a large number of different types of neurons that are affected by marijuana, a complete explanation of this drug's effects remains nearly impossible. What seems clear, however, is that the endogenous cannabinoid neurotransmitters that our brains produce do not appear to transmit information *per se* but appear to modulate how other neurotransmitter systems function. In this way, they act quite differently from the manner in which most other neurotransmitters behave.

CHAPTER 7

SIMPLE MOLECULES THAT TURN YOU ON AND OFF

Why is a drug such as phencyclidine (PCP) potentially lethal? Why does drinking alcohol make you drowsy? How do anti-anxiety drugs work, and why is it so dangerous to take them and alcohol at the same time? The answers to these questions have everything to do with the most abundant neurotransmitters in your brain—simple amino acids that are used for two simple functions: to turn on or turn off individual neurons. When used for communication, neurons usually respond to amino acid neurotransmitters—principally glutamate and γ -aminobutyric acid (GABA)—with either excitation or inhibition. Glutamate is the principal excitatory amino acid neurotransmitter, whereas GABA is the principal inhibitory amino acid neurotransmitter.

GLUTAMATE: THE NEUROTRANSMITTER THAT TURNS YOU ON

What is so important about glutamate? It makes and breaks connections between neurons, and it turns on other neurons to stimulate them into action. Glutamate neurotransmission is mediated through receptors that allow the passage of sodium or calcium ions into neurons; the receptors were named according to the chemical tools that were historically used to study them. For example, the subtype of glutamate receptors known as *N*-methyl-D-aspartate (NMDA) allows the entry of calcium ions into neurons. Following the entry of calcium ions, some truly interesting things begin to happen inside the neuron that lead to the production of what one might call a “memory.” Calcium ions activate a complex cascade of biochemical changes that ultimately involve the genes of the neuron and that may actually change how the neuron behaves for the rest of one’s life. These biochemical changes may also alter how one neuron communicates with hundreds of other neurons.

Think of this neural process as a symphony of musicians playing together for the first time. Initially, everyone is playing his or her own song. Then the conductor arrives and hands out a musical score; all of the musicians begin to play in a complex pattern of rhythms that conveys information. Like the conductor, calcium ions entering via NMDA channels initiate the process of forming an ensemble of neuronal activity. Your neurons are the musicians, and when they become linked to each

other according to some common pattern of activity, they form an ensemble that plays a particular song, or memory, which can recur only when the neurons of that particular ensemble play the same pattern together. In this analogy, memories can be viewed as symphonies of activity in our brains, and just as we enjoy playing the same tunes over and over again, we also enjoy replaying pleasant memories. Unfortunately, glutamate's actions can prime us to play unpleasant or traumatic memories over and over again as well when they are triggered by innocent events in our daily lives.

In addition, the entry of calcium ions into neurons may sometimes become excessive as a result of aging, disease, or stroke and may initiate some harmful processes that may contribute to the removal of synapses or even the death of neurons. This information tells us quite a lot about the role of glutamate: When it works correctly, memories can be formed; when it does not work correctly, such as when it induces too much calcium to enter the neuron, then death and destruction follow and memory is lost. Thus, maintaining a good balance of function related to the entry of calcium ions is a challenging but critical requirement for neurons, and the amino acid neurotransmitter glutamate plays a critical role in this process.

Glutamate also has a unique function in brain development. When you were very young, the neurons in your brain developed many connections, or synapses, with other neurons to optimize your ability to learn a great deal of information quickly, such as how to move your hands and feet, what your mother's

voice sounds like, or what the color red looks like. But as you grew older (during adolescence), your brain became a bit like an overwired computer—for it to work better and faster, with less likelihood of failing, it became advantageous for it to remove unnecessary “wires,” or connections. This is where glutamate’s other unique abilities come into play. Your brain uses glutamate to prune synapses that have become unnecessary, which in turn allows the remaining neural circuits to function more efficiently. Later, when you are an adult, glutamate is critical for allowing your brain to be “plastic,” to mold your responses to the environment so that you increase your chances of survival. Thus, like the Roman God Janus, the neurotransmitter glutamate has two faces: One is important for the early brain development and function in our past; the other is important for brain pruning and subsequent function in our future. Meanwhile, its staying power can sometimes be a mixed blessing. For example, as mentioned previously, traumatic memories formed through glutamate’s actions can continue to haunt a person long after the event that created those memories has occurred. The best example of this is called post-traumatic stress disorder; the unpleasant memories that characterize this disorder are very difficult to treat because of the amazing efficacy of glutamate to form lasting changes in the brain.

Currently, very few safe drugs are used clinically to target glutamate receptors. However, two drugs of abuse, phencyclidine (aka PCP or angel dust) and ketamine, can antagonize the NMDA type of glutamate receptor. Because these drugs

block this principal excitatory neurotransmitter, they depress the brain's general level of activity. Your brain's information processing simply slows further and further until it can no longer keep you conscious. Phencyclidine was once used as an anesthetic, with some unfortunate consequences. Patients lost the ability to breathe, they became delirious and disoriented, and their heart rate decreased so much that they sometimes slipped into a coma and died.

Because phencyclidine is so potent, scientists believe that the brain makes its own endogenous PCP-like molecule, now called angeldustin, should it one day be isolated. Recent studies suggest that the reduced function of angeldustin may actually contribute to certain psychiatric syndromes, such as mania, and cause too much activity of the glutamate receptors in the brains of manic patients. Others have suggested that whatever the cause, increased function of the brain's principal excitatory neurotransmitter drives the symptoms of mania, such as racing thoughts, insomnia, and impulsiveness. However, the medical treatment of mania, usually with the use of a salt called lithium chloride, does not involve reducing neuronal functioning of glutamate but instead slows the manic brain by very different mechanisms. One of these mechanisms may be related to lithium's ability to induce the birth of new GABA-releasing neurons, of which the brains of manic patients have a reduced number. This possibility would make sense given the particular nature of that neurotransmitter. In any case, too much inhibition of glutamate would severely impair the brain's ability to

process information. Our brains need to have glutamate's excitatory actions working appropriately for us to learn and pay attention. Rather than reduce an overactive brain by using drugs that inhibit glutamate, humans have discovered many different drugs that force our brains to slow down by stimulating the function of GABA neurons.

GABA: THE NEUROTRANSMITTER THAT TURNS YOU OFF

In contrast to glutamate, the amino acid neurotransmitter GABA turns neurons off. After being released into the synaptic space, it binds to a protein receptor. The best studied of these is the GABA_A receptor, and drugs that bind to it enhance the ability of GABA to stabilize the activity of the neuron. In so doing, these drugs have produced dramatic therapeutic benefits for a wide range of disorders, particularly for the treatment of anxiety and insomnia. Why should this be the case? There are two simple reasons: GABA receptors are widely distributed throughout all brain regions, and GABA is virtually always inhibitory. So any drug that enhances GABA receptor function produces an overall decrease in the activity of neurons everywhere in the brain. Contrary to the claims made in popular magazines, you cannot accomplish this effect simply by eating GABA-containing substances to increase the amount of GABA in your brain. While floating in the bloodstream, ingested GABA becomes electrically charged, preventing it from passing across the blood-brain barrier. Therefore, taking a few hundred

milligrams of GABA every day will not reduce your anxiety or help you sleep. Instead, your treatments of choice should be drugs that turn on your existing GABA receptors so they can turn off your brain—either a little to reduce your anxiety or a lot to make you sleep.

Although recent evidence suggests that anxiety, like depression and migraine headaches, may be related more to the dysfunction of serotonin receptors than to GABA, medical science prefers to treat anxiety with prescription, GABA-enhancing drugs, which do work to reduce this symptom. What do the actions of these drugs tell us about the causes of anxiety in the brain? Not much. Again, simply because it is possible to treat the symptoms of a disorder by manipulating a particular neurotransmitter system in the brain does not tell us anything about the actual cause of the disorder. All we can say with certainty is that if you are feeling anxious, taking one of these drugs will make you feel less so.

ENHANCING THE ACTION OF GABA WITH FOOD AND DRUGS

Among the earliest anti-anxiety treatments were drugs that simply made one sleepy—these drugs essentially depressed activity in the brain and made it difficult to feel anything at all. Various salts made from the common element bromine were used to reduce brain activity associated with epilepsy, anxiety, or stress. Fans of old movies set in a bygone era may remember the occasional actress holding her forehead and stating that she

needed to “take a Bromo” to treat a headache. Although these salts were effective at reducing the neural activity in the brain that is required to experience pain, or to even maintain wakefulness, they were extremely toxic to the kidneys and ultimately removed from the commercial market. They were replaced by opiates, which were available without restriction during the 18th and 19th centuries. So was a more popular and socially acceptable drug that in many cultures, including our own, still has almost iconic status today—alcohol.

ALCOHOL

Alcohol (ethyl, not methyl) may have been the first anxiety-reducing agent. There is evidence that distillation of grains to make alcohol-containing beverages, what today we refer to as beer, may have begun in the Fertile Crescent (between present-day Iran, Iraq, Syria, and Israel) by approximately 10,000 BCE. The ancient Egyptians also produced alcoholic beverages, referring in some passages within their texts to the social problems associated with drunkenness. Other Egyptian texts, written in approximately 1600 BCE, contained 100 different medical prescriptions calling for the use of alcohol. Over subsequent centuries, several types of alcohol, distilled and fermented, were developed, and they all had their calming effects.

Alcohol has at least two principal actions in the brain. First, it enhances the widespread inhibitory effects of the neurotransmitter GABA and acts as a depressant on the entire central nervous system. For this reason, in the 19th century, alcohol was

widely used as a general anesthetic. Unfortunately, the duration of its depressant action on the brain was too long and could not be controlled easily or safely. The effective dose for surgical analgesia using alcohol is very close to its lethal dose. Therefore, it was possible to induce sufficient anesthesia in a cowboy for a surgeon to remove an arrow from a leg, but it was unlikely that the unfortunate cowboy would survive the operation. Thus, if the arrow did not kill him, the operation certainly might. Of course, prior to the 20th century, this was generally true of most medicines. Now you understand why Hippocrates requested in his oath that physicians, at the very least, do no harm. Drug therapies in ancient times often produced more harm than benefit to the patient.

In addition to its actions on GABA receptors, alcohol inhibits the brain's principal excitatory neurotransmitter system, glutamate. Given glutamate's critical role in making memories, this inhibitory effect may underlie the amnesia that is often associated with intoxication—that is, the classic blackout. It may also explain the inappropriate behavior that often occurs when people drink. The consumption of only modest amounts of alcohol produces an apparent stimulation of the brain that may result in unrestrained activity of various brain regions caused by the lessening of their inhibitory controls. Which behaviors are released from control first? Usually, alcohol consumption initially releases what are called “punished behaviors,” such as “not” drinking and driving, “not” dancing on picnic tables naked in the park at midnight, and so on. You get the

idea: These are behaviors that we are warned against undertaking by our parents, the police, or our personal deity.

As with most drugs that affect your brain, the rate at which your blood alcohol levels rise also affects your behavior—that is, faster changes in blood alcohol levels produce more dramatic effects on your behavior. As alcohol levels increase, increasingly more of your brain is turned off by alcohol's enhancement of GABA. Ultimately, when blood alcohol levels become too high, neurons critical to controlling your breathing and heart rate are inactivated because of overstimulation of their GABA receptors. Therefore, death resulting from alcohol intoxication occurs because you stop breathing. Usually, before that happens, your brain's vomiting control center will become activated at blood alcohol levels of approximately 0.12%. However, if you drink slowly and steadily, you can sneak up on these protective neurons and inactivate them with alcohol. Once this happens, your body makes no effort to rid itself of alcohol in the stomach by vomiting, and the levels of alcohol in your blood can continue to rise to lethal levels. Thus, vomiting at the end of a party is a good thing, really. Your body is trying to protect you.

There is ample evidence that alcohol was tested in ancient times for its potential benefits beyond being a source of nutrition. Unfortunately, the side effects usually greatly outweighed the benefits. Alcohol alters the activity of neurons that project into the cerebellum, a structure that is critical for the timing and execution of smooth movements. This leads to the incoordination that is seen in people after drinking alcoholic beverages.

Finally, our drinking behavior is greatly influenced by our environment. The people who make a profit on the sale of alcoholic beverages are well aware of this fact and clearly take advantage of that knowledge in designing their environments.

MUSIC AND HEARTBEATS

When studies of the behavior of people in bars were performed, time was found to be a major predictor of alcohol abuse; for example, the shorter the stay in the bar, the faster the rate of consumption. People drinking alone stayed the shortest time and drank the most; thus, there are usually plenty of single (usually uncomfortable) barstools available. One study compared drinking behavior in two different settings, a rock and roll bar and a country and western bar. The study found a correlation between the sipping rate and the beats per minute of the music. Fast-paced music was associated with the slowest drinking rate. Music that was closest to a person's resting heart rate produced the fastest drinking. Lyrics of slow songs also contributed to drinking behavior. Tear-jerk lonesome country and western lyrics involving losing, hurting, and cheating, or working, dying, and drinking, or wailing and self-pitying were associated with increased drinking—who's not surprised? Live bands and action photography flashing on the walls also increased drinking rates. Next time you find yourself in such an environment, take notice of how carefully and subtly your behavior is being controlled so that you will spend the most amount of money in the shortest period of time.

BARBITURATES

At the end of the 19th century, it was obvious that an alternative drug for anxiety was necessary that would be safer than the popular and highly available alcohol and opium. In 1904, the first barbiturate, barbital, was introduced and sold as Veronal. It was a nontoxic sedative, and because of its anti-convulsant properties, it also appeared to be ideal for treating and preventing the symptoms of epilepsy. As you might have guessed already, barbiturates reduce neural activity in the brain by enhancing the function of GABA receptors and producing widespread synaptic inhibition, just like alcohol.

The safety of barbiturates is subject to much debate. In high doses, they are lethal, which is the reason why for many years barbiturate overdose was a common way by which people committed suicide. In addition, the rebound produced by withdrawal from barbiturates is characterized by increased neural activity throughout the brain, leading to symptoms that are often the motivation for taking these drugs in the first place, such as anxiety, disorientation, hallucinations, convulsions, insomnia, tachycardia, or nightmares. The fact that alcohol can prevent the withdrawal symptoms of barbiturates shows the commonality of their action at the GABA receptor. This commonality underlies the reason why alcohol and barbiturates produce a synergistic toxicity in the brain. This means that these drugs should never be taken together because their effects will be compounded, or even multiplied, and can induce a dramatic

and possibly permanent loss of higher brain function, leading to a vegetative state or coma. This array of potentially life-threatening risks associated with barbiturates led to the introduction of an entirely new class of anti-anxiety medications to the market—benzodiazepines.

BENZODIAZEPINES

The first benzodiazepine, chlordiazepoxide, was initially synthesized in 1947 and first sold commercially in 1960 as Librium (because it produced an emotional equilibrium). Soon thereafter, diazepam was sold as Valium (Latin for “be strong and well”) and quickly became the most prescribed anti-anxiety drug in the Western world. Both of these drugs are converted into other psychoactive agents within the brain and body. Some of these metabolites were isolated from the urine of people taking Valium and Librium and were discovered to be quite effective new drugs that could reduce anxiety and produce sleepiness. Because of changes in fat solubility, these newer drugs acted on the brain faster and, as typically follows, had a shorter duration of action. They are generally safe to use in controlled doses, but again, withdrawal from them produces abrupt increases in widespread neural activity that is often expressed as insomnia and anxiety. Recently, an even newer class of drugs called non-benzodiazepines was introduced to consumers, and these drugs reduce anxiety and induce sleepiness.

All of these drugs, benzodiazepine and non-benzodiazepine alike, exert their effects only in the presence of GABA, enhancing

the action of GABA at its receptor. The highest concentration of these receptors is found in the neocortex, hippocampus, cerebellum, and throughout the limbic system (which is involved in producing both pleasant and unpleasant emotional responses). The presence of these receptors within the hippocampus may explain why benzodiazepines can produce amnesia. They may inactivate the neural circuits in this structure that are critical for the consolidation of memories.

Recent studies suggest that the brain may contain its own family of valium-like compounds, the β -carbolines. Some of these antagonize GABA function and others enhance it, but all may share a similar ability to inhibit the destruction of the neurotransmitters dopamine, norepinephrine, and serotonin. Taken together, these effects would tend to produce a mild, relaxed euphoria. The balance of action of these endogenous antianxiety compounds is determined by the genes we inherit from our parents, which control the carbolines produced and probably predispose us to being anxious or laid back throughout our lives. It is now thought that anxiety disorders may be related to a dysfunction of GABA receptors and the balance of function of these carbolines.

Indeed, scientists have speculated that the brains of people who suffer from generalized anxiety disorder may produce too many of these chemicals from their diet. It is true that some carbolines can be formed spontaneously from the constituents of our diet. For example, coffee produces β -carbolines, and alcohol can be converted by bacterium in the gut, *Helicobacter*

pylori, to form a β -carboline. Whether these exogenous β -carbolines are produced in sufficient quantities to produce functional consequences in the brain remains to be determined. It is known, however, that the carbolines produced in the brain are similar to those found in plants. For example, extracts of the vine *Banisteriopsis caapi* contain the β -carboline harmaline. Harmaline and dimethyltryptamine (DMT) are the key ingredients in the mildly psychoactive sacramental beverage Ayahuasca from the Amazon. The harmaline inhibits monoamine oxidase, thus prolonging the action of DMT in the brain. Because the ingredients in these vines resemble molecules used by the brain, their consumption can influence how one thinks and feels. It perhaps stands to reason then, if not yet confirmed in fact, that consuming exogenous β -carbolines to correct an endogenous imbalance of these molecules would have a similar influence on the brain.

ABSINTHE, VERMOUTH, AND BÉNÉDICTINE

What would it feel like if you ingested a drug that blocked the brain's most important inhibitory neurotransmitter? Would you become excited? Thujone is such a drug; it blocks the action of GABA at one of its principal receptors in the brain. Thujone can be found in many different plants, but it is most often associated with wormwood (*Artemisia absinthium*), the extract of which, when mixed with alcohol, produces a bright green drink called absinthe. During the mid-1800s, this drink

became very popular in Europe, especially among such artists as Manet, Degas, Toulouse-Lautrec, and Van Gogh. The ritual was to pour the emerald-green liquid slowly over sugar held in a perforated spoon and then dilute it with water. The taste was very bitter, and the drink was said to produce a “lucid drunkenness.” Then, during the late 1800s, studies by the French psychiatrist Valentin Magnan discovered that wormwood oil produced inappropriately increased brain activity—that is, an epileptic reaction. Thus, it was thought that the effects of chronic use of absinthe—such as contractions of the face muscles and extremities, anxiety, paranoia, energy loss, numbness, headaches, delirium, paralysis, and death—resulted from the existence of thujone in the wormwood extract used in this drink. One author wrote in the *American Journal of Pharmacy* in 1868 that “it’s an ignoble poison, destroying life not until it has more or less brutalized its votaries, and made driveling idiots of them.” A campaign against thujone ensued and resulted, by the early 20th century, in the banning of absinthe in many countries, including the United States.

Today, however, it is known that the manner in which absinthe was once prepared would have produced only very low levels of thujone in a typical serving. Therefore, the symptoms noted among chronic users of absinthe more likely resulted from the excessive consumption of improperly distilled spirits rather than from the effects of thujone. To be sure, thujone is a GABA antagonist and can produce excitatory effects in small doses, but these effects are mild. It can be found in very low

amounts in drinks such as vermouth (from the German *Wermuth* for “wormwood”), chartreuse, and Bénédictine. Of course, it remains in similarly small amounts in absinthe, the legal sale of which has now resumed in most countries.

ENHANCING GABA

What would it feel like if you ingested a plant that stimulated your brain’s most important inhibitory neurotransmitter? Would you become relaxed and sleepy? The complex extracts of the valerian plant. The actual constituents of any valerian preparation depend on the valerian species used (there are at least 350 of them) and the method of extraction (aqueous vs. oil). Indeed, these two features are critical in determining the actual constituents of any plant extract.

Pharmacopoeias from throughout the world often include the use of an extract from this plant for its proclivity as a sedative, anxiolytic, or sleep aid. The pharmacological actions of the extract are likely due to the action of two terpenes, either valerenic acid or valtrate, depending on the species utilized. The roots of the plant contain high levels of GABA. GABA cannot cross the blood–brain barrier; therefore, the presence of GABA in the extract plays no role in the actions of the valerian preparation on the brain. The terpenes are capable of crossing the blood–brain barrier and have been shown to stimulate GABA receptors and inhibit the inactivation of GABA by preventing reuptake. Unfortunately, studies in humans have not been able to reliably confirm the

effectiveness of valerian extracts in the production of sleep or reduction in anxiety.

THE STUFF OF NIGHTMARES

Many drugs that induce sleep also cause nightmares. One way to understand how and why some drugs produce nightmares is to consider the conditions that induce them. Children with cerebral palsy frequently complain about nightmares. War veterans, with or without brain injury, frequently report combat-related nightmares as a major component of what is now called post-traumatic stress disorder (PTSD). Marijuana has been shown to reliably reduce insomnia and nightmares in patients suffering from PTSD. Prazosin is also an effective option for combat-related PTSD nightmares. The beneficial actions of these two drugs, marijuana and prazosin, provide some insight into the mechanisms that underlie the appearance of nightmares. Prazosin blocks a specific type of norepinephrine receptor. It is most often used to improve urinary flow in elderly men with enlarged prostates. Veterans Administration hospitals have found that prazosin treatment alleviates two common symptoms of elderly male war veterans—impaired urinary flow associated with an enlarged prostate and nightmares. The role of norepinephrine in nightmares is also supported by the discovery that yohimbine, a drug that increases the activity of norepinephrine neurons in the brain, increases the number of PTSD-related nightmares.

Obviously, nightmares occur while people sleep. Scientists have divided sleep into two general phases: rapid eye movement (REM) and non-rapid eye movement (non-REM) sleep. These two phases alternate throughout the night, with non-REM sleep predominating during the first few hours after falling asleep. Most, but certainly not all, dreaming occurs during REM sleep. Any medication that reduces the amount of time the brain spends in REM sleep can induce the brain to respond with REM rebound. For example, alcohol reduces REM sleep. Thus, if you fall asleep drunk, the alcohol in your blood prevents your brain from dreaming until the alcohol is metabolized and no longer influences brain function. Once this happens, the brain spends a larger percentage of time in REM sleep—that is, REM rebound. Dreams that occur during REM rebound tend to be nightmares. The withdrawal from drugs that share alcohol's agonist actions at the GABA receptor, such as most of the benzodiazepines, also induces nightmares even though they do not always produce REM suppression. This suggests an important role for GABA, and the medications that influence it, in the control of nightmares.

The duration of each REM sleep period that a person experiences each night is tightly controlled by the actions of the neurotransmitter acetylcholine. Drugs that antagonize the action of acetylcholine, directly or indirectly, tend to produce nightmares. Unfortunately, as mentioned in previous chapters, many medications inadvertently antagonize acetylcholine, including antihistamines, some of the tricyclic antidepressants

and cardiovascular medications commonly prescribed to reduce blood pressure, the popular anti-ulcer drug ranitidine and some common anti-psychotic medications, as well as drugs to prevent motion sickness. The newer antidepressant paroxetine has the highest incidence of nightmare production; it acts by preventing the reuptake of serotonin, thus implicating a role for this neurotransmitter system as well. Because so many people take one of these common medications daily, the probability of experiencing recurring drug-induced nightmares is quite high.

Why do some nightmares involve the terrifying feeling of being buried alive or the feeling that it is difficult to breathe? These dreams of suffocation usually occur during non-REM sleep when one's respiration and heart rate are significantly slowed down. If you are dreaming while experiencing these physiological conditions, your brain incorporates their sensory qualities into your dream narrative. Sometimes, just being tightly wrapped up in your bed sheets provides a sufficient sensory stimulus, due to reduced respiration, to induce the dream experience of suffocation.

In summary, drugs that enhance the function of norepinephrine or serotonin (and probably dopamine) neurons, drugs that impair the function of acetylcholine neurons, highly unpleasant memories, alcohol and most of the drugs that are used to reduce anxiety or induce drowsiness, or even overly tight bed sheets can all induce nightmares. Given how widespread the use of many of these drugs has become, it is amazing that most of us do not experience a nightmare every night.

REMNANTS OF AN ANCIENT PAST

Very primitive multicellular organisms, such as the Cnidarian hydra (e.g., *Chlorohydra viridissima*, the ultimate simple feeding tube with the most ancient nervous system), have nervous systems that extensively use simple amino acids, such as γ -aminobutyric acid and glutamate, and simple proteins as neurotransmitters, suggesting that these proteins were the first signaling molecules used by primordial nervous systems. If we extract a few of these proteins from the “brain” of a typical hydra and inject them in human neurons, they will produce similar signaling responses from those neurons.

In fact, the proteins used by hydra in their nervous systems are identical to some of the proteins that our brains use to help us think and feel. These ancient proteins are called neuropeptides.

A neuropeptide looks like a string of beads, with each bead representing an amino acid. Neuropeptides may be assembled from only a few or from hundreds of different amino acids. Your body contains many different types of neuropeptides that are assembled from the amino acids found in your diet. Neurons that produce and release these neuropeptides are found throughout the body and brain and influence a diverse array of body functions, including the release of hormones and the absorption of nutrients from the blood.

The evolutionary history of our neuropeptides is quite interesting and tells us a great deal about their current role and why they are found in certain places in the body and not others. One very important neuropeptide is insulin, which is produced by the pancreas. Some neuroscientists have speculated that an insulin-like peptide might have been the principal ancestor to many of our other neuropeptides that are still structurally related to each other. For example, growth hormone and prolactin—peptides that control breast development and milk production, respectively—may have diverged from a common ancestor approximately 350 million years ago. Therefore, it is not surprising that growth and nursing are also closely related to each other. As studies of mammals and hydra have demonstrated, evolution does not tinker with some molecules. If something works well, it tends to stay around and continue to be used across eons of time.

Alternatively, some neuropeptides have been modified only slightly but often for related purposes. For example,

most animal venoms are derived from neuropeptide-related precursors, and some may have originated from brain peptides that initially appeared at least 100 million years ago and have since been undergoing modification and mutation. Yet, some venoms still retain the ability to perform functions that their evolutionary parent molecule still performs, such as an insulin-like ability to control blood glucose levels. Because of this shared evolutionary history, venoms extracted from species that range from very simple single-celled organisms to very complex animals and plants have become popular tools for scientists studying how human neuropeptide neurons function. During the past 30 years, these studies have demonstrated that there are more than 100 different neuropeptide neurotransmitters in the human brain and body. These neuropeptides are found at very low concentrations and are very potent.

This chapter focuses on neuropeptide neurotransmitters whose actions in the brain were discovered through the euphoric and pain-relieving effects of one of the most powerful and addicting classes of drugs ever known. By way of contrast, it also discusses the pain-relieving effects of a few drugs that do not work through these neuropeptides but, rather, through a very different mechanism. The contrast is interesting in what it tells us about these neuropeptides in the context of the full arsenal of mechanisms that the body uses to protect itself from pain and other distress.

OPIATES AND OPIATE-LIKE NEUROTRANSMITTERS

The euphoric and sleep-producing effects of opiates, which are derived from the poppy plant, were well known to ancient civilizations. Approximately 4000 BCE, for example, the Sumerians (Babylonians) carved pictures of the poppy plant into tablets inscribed with the words *bul* (“joy”) and *gil* (“plant”). In the classical literature of Virgil (1st century BCE), Somnus, the Roman God of sleep (a translation of the Greek Hypnos), was sometimes described as carrying poppies and an opium container from which he poured juice into the eyes of the sleeper. Chinese legend has the poppy plant springing up from the earth where the Buddha’s eyelids had fallen after he cut them off to prevent sleep.

The first specific medical use of opium was described in the Ebers papyrus of ancient Egypt (approximately 1500 BCE), in which it is presented as a remedy for excessive crying in children. The substance was important for Greek medicine as well. According to Galen, the last of the great Greek physicians from ancient times (2nd century CE), opium was an antidote to poison and venoms and cured headaches, vertigo, deafness, blindness, muteness, coughs, colic, and jaundice. He also noted its recreational use at the time, commenting on the widespread sale of opium cakes and candies.

Various opium preparations, usually as extractions into some type of alcoholic beverage, were later developed, including

Dr. Thomas Sydenham's version of laudanum during the 17th century, which contained 2 ounces of strained opium, 1 ounce of saffron, and a dram of cinnamon and cloves dissolved in a pint of Canary wine. The 19th-century author Thomas De Quincey purchased laudanum for a toothache and then spent the rest of his life taking the drug and writing about his experiences with it (*Confessions of an English Opium-Eater*, 1821). Another preparation was paregoric, a combination of opium, camphor, and anise oil that was developed in the mid-20th century for the treatment of diarrhea in infants.

In approximately 1806, when working as a pharmacist's apprentice in Paderborn, Germany, Friedrich Sertürner isolated the primary active ingredient in opium and called it morphium after Morpheus, the Greek God of dreams and the son of Hypnos. Later investigations discovered an additional active ingredient called codeine, the Greek word for "poppy head." In 1874, chemists attached two acetyl groups to morphine and produced heroin, which Bayer Labs marketed in 1898 as a supposedly non-addicting substitute for codeine. The two additional acetyl groups made heroin more potent than morphine because they increased its fat solubility and allowed more of the drug to enter the brain very rapidly. Heroin is, in short, just a chemical trick to get morphine into the brain faster. However, once inside the brain, heroin can do nothing on its own. First, it must be converted into morphine by enzymes that remove those two additional acetyl groups. Then, as the molecule originally

found in the poppy seed, it can act to produce pain relief or euphoria.

The effects of morphine, codeine, and heroin in the brain are dose related. Small doses produce drowsiness, decreased anxiety and inhibition, reduced concentration, muscle relaxation, pain relief, depressed respiration, constricted pupils, nausea, and a decreased cough reflex, which is why codeine was used in cough suppressants. At slightly higher doses, morphine and heroin can produce a state of intense elation or euphoria. Their euphorigenic property is related to their speed of entry into the brain, which again is directly related to their fat solubility. The euphoric effect is most enhanced by injecting these drugs into a vein, thus greatly accelerating their entry into the brain, and results in the “kick, bang, or rush” that addicts describe as an abdominal orgasm—a sudden flush of warmth localized in the pit of the stomach. Interestingly, the user does not experience this rush if the drug is smoked, sniffed, or swallowed because of the much slower absorption and entry into the brain via these methods of administration.

As always, the law of initial value determines how a person responds to a drug. For example, in well-adjusted, emotionally stable, pain-free people, morphine may produce restlessness and anxiety. In contrast, elation most often occurs in users who are either abnormally depressed or highly excited. At very high doses of morphine, the profound depression of brain activity deepens into a state of unconsciousness that can be fatal. Respiratory

depression caused by inhibition of the brain's breathing centers is the ultimate cause of death.

The effects of morphine eventually led many scientists to predict that the brain possesses its own endogenous opiate-like neurotransmitters and its own complement of endogenous opiate receptors in the brain. In the mid-1970s, research confirmed that the brain and body do indeed contain some endogenous morphine-like peptides, which were christened "endorphins." These peptides control our experience of pain by stopping the flow of pain signals into our brains, and this action is enhanced by the taking of opiate drugs such as morphine, as well as by engaging in activities (e.g., jogging) that can produce an "endorphin high."

Our ancestors were intimately aware of the beneficial effects of other plant extracts for the treatment of pain. For example, myrrh—isolated from the dried resin in the bark of *Commiphora myrrha*, a shrub found in Somalia and throughout the Middle East—was historically used in liniments, including in Chinese medicine, to treat the symptoms of arthritis and as an antiseptic ointment. It may be slightly more potent than morphine and may act via central endogenous opiate receptors to produce pain relief. Another resin, frankincense, can be extracted from the *Boswellia sacra* tree and exhibits a mild anti-inflammatory action similar to that of aspirin. In ancient times, frankincense and myrrh were commonly used together as a salve to relieve postpartum pain and to reduce bleeding after delivery. They were

also burned as incense and, as immortalized in the Christmas story of the three wise men, were highly valued as a gift.

Our ancestors were, of course, ignorant of the neurobiology of opiates or how pain was produced in the human body. In the distant past, when a person felt pain—particularly in the absence of evidence of injury—spiritual healers or medicine men developed fanciful myths to explain the cause of the pain, treated it with a decoction from the willow tree or myrrh shrub, and were often rewarded with elevated positions in their communities when their treatments seemed to magically make the pain go away and produced an intense feeling of joy at the same time. With the advent of modern science, we know more about the mechanisms of pain and about the reasons why some drugs are better at treating pain than others.

Morphine-like proteins, as well as many other psychoactive chemicals capable of acting on the brain's neurotransmitter receptors, may also originate from many commonly consumed foods, including milk; eggs; cheese; grains such as rice, wheat, rye, and barley; spinach; mushrooms; pumpkin; meat; and various fish, such as tuna, sardine, herring, and salmon. Dairy products in particular contain a protein known as casein, which enzymes in the intestines can easily convert into β -caseomorphine. When newborns start nursing, the β -caseomorphine can easily pass out of the immature gut and into the brain (both are still lacking viable barriers at this young age) and produce euphoria. The pleasurable feeling produced by this heroin-like compound in newborn mammals after their first taste of mother's milk

is believed to encourage infants to return repeatedly for nourishment. Adults do not experience this euphoria after drinking milk because of the intact blood–gut and blood–brain barriers. Perhaps if we could experience the euphoria of heroin and the pain relief of morphine with each glass of milk, then dairy cows would be sold only on the black market. Finally, each year, many of my students ask whether the opiate-containing poppy seeds consumed as part of a morning muffin or bagel have pain-relieving or other psychoactive effects. The answer is no because the dose is far too low. Nonetheless, it is possible to detect traces of morphine and codeine in the urine within a few hours after consumption. Keep that in mind during your next job interview process.

The gluten in wheat, barley, and rye produces a related compound in the gut called gluteomorphin. Whether gluteomorphin produces any cognitive changes is currently unknown.

GLUTEN IN THE BRAIN

Is eating gluten always bad for everyone? Absolutely not. If you are not gluten sensitive, then avoiding gluten is a bad idea according to the results of a large research study involving more than 15,000 participants who were followed for 30 years. Obesity, which is quickly becoming a health problem in many countries, is a risk factor for developing type 2 diabetes, a condition that induces oxidative stress and brain inflammation that is now known to increase the risk of developing Alzheimer's disease. Eating gluten may be one way to reduce your risk of

developing type 2 diabetes. In 2017, the American College of Cardiology recommended against the adoption of gluten-free diets for people without a medical necessity, noting that many of the health claims regarding gluten-free diets are unsubstantiated. Thus, unless you suffer from celiac disease, going gluten free is not a good dietary decision. Gluten-free diets have been promoted by uninformed nutritional prophets using dietary scare tactics even though there is very little reliable evidence that eliminating gluten from the diet does much to improve long-term health.

CHAPTER 9

SLEEPING VERSUS WAKING

Why do treatments for the symptoms of the common cold make us drowsy? How does coffee work? This chapter touches briefly on neurotransmitters whose actions in the brain affect our sleep–wake cycle and on a few well-known substances that block these effects. One such neurotransmitter is histamine, whose neurons influence our level of arousal throughout the day. Over-the-counter antihistamine medications used to treat allergies and cold symptoms block histamine receptors and interfere with the ability of this neurotransmitter to keep one aroused and awake. The result is drowsiness. Meanwhile, because γ -aminobutyric acid (GABA) neurons induce sleepiness by turning off histamine and acetylcholine neurons, any drug that enhances the action of GABA (e.g., alcohol, barbiturates, or Valium) is going to be synergistic

with the over-the-counter antihistamine drugs. Thus, if taken together, these two kinds of drugs can cause a life-threatening depression in brain activity.

ADENOSINE

This neurotransmitter has diverse functions throughout the brain that are also related to sleep–wake cycles. Much is known about adenosine because of the ready availability of a very safe, highly effective adenosine receptor antagonist that is served hot or cold, with or without cream, throughout the world—caffeinated coffee. Caffeine is also commonly found with theophylline (a molecule that is very similar to caffeine) in tea. Indeed, although caffeine is found in at least 63 plant species, 54% of the world's consumption derives from just two different beans, *Coffea arabica* and *Coffea robusta*, and 43% derives from the tea plant *Camellia sinensis*.

Coffee is rich in biologically active substances such as trigonelline, quinolinic acid, tannic acid, and pyrogalllic acid. The vitamin niacin is formed in large amounts from trigonelline during the coffee bean roasting process. Brewing coffee produces low levels of acrylamide, which is toxic at such high doses that cannot be attained no matter how much coffee one consumes. Acrylamide is more commonly consumed in potatoes and grain products such as French fries and potato chips. Coffee is also a rich source of antioxidants. Various ingredients in coffee beans contribute to aspects of the drink—for example, its bitterness—that people find either appealing or unpleasant.

Recently, some entrepreneurs have found a way to remove the bitterness by “filtering” coffee beans through the gastrointestinal tract of the Asian palm civet, *Paradoxurus hermaphroditus*. The civets, nocturnal omnivores that are approximately the size of a cat, eat the beans, which then pass through the animals’ gastrointestinal system undigested but presumably not unaffected. The beans are then extracted from the animals’ stool, cleaned up, and sold. It is hardly an enticing process, but the claim is that the animals’ digestive enzymes metabolize the proteins that cause the bitter taste of the coffee bean. Although this is certainly possible, the novel flavor of the beans is just as likely a result of the beans’ absorption of some of the less appealing contents of the animals’ gut.

Coffee drinking (or consuming caffeine from non-coffee sources) has been associated with a significantly lower risk of developing Parkinson’s and Alzheimer’s disease. The neuroprotective effect requires approximately five or six cups of coffee per day for many years and appears to be mostly beneficial only to males. Women benefit from coffee drinking in other ways, particularly with regard to a reduced incidence of type 2 diabetes.

Nonfiltered, boiled coffee, in contrast to filtered coffee, increases serum levels of the bad cholesterol, low-density lipoprotein (LDL), without affecting blood levels of the good cholesterol, high-density lipoprotein (HDL). Thus, it appears that the constituents of coffee may alter the way we metabolize and distribute our fat. Does this translate into

removal of fat from around the waist? A group of scientists at the University of Southern Queensland in Toowoomba, Australia, attempted to answer this question. When obese diabetic rats were given caffeine for 30 weeks, their ability to regulate blood sugar and insulin levels improved; unfortunately, the level of cholesterol in their blood increased significantly. Rats placed on cafeteria-style diets high in carbohydrates and fat developed symptoms of the now infamous metabolic syndrome, characterized by obesity, hypertension, impaired glucose tolerance, cardiovascular damage, and fatty liver and elevated blood lipids. Daily coffee intake (equal to approximately five cups of regular brewed coffee per day) significantly benefited these rats by improving the health of their cardiovascular system, lowering blood pressure, and improving liver function and glucose tolerance. The contractility of their heart muscle improved in a way that resembled the hypertrophy often seen in athletes in which the heart actually becomes more efficient. The Australian scientists concluded that coffee drinking has many health benefits; however, reducing belly fat is not one of them.

Overall, people who drink substantial amounts of coffee daily tend to live longer than people who do not. In addition, recent evidence suggests that moderate coffee drinking of approximately two or three cups each day might reduce one's chance of developing Alzheimer's disease. What is the connection between coffee, diabetes, and diseases of the brain? No one is sure, but elevated insulin levels in the blood may be a critical

link because type 2 diabetes makes both men and women more likely to develop both Parkinson's and Alzheimer's disease.

Many people drink coffee to reduce drowsiness. How does caffeine achieve this effect in the brain? The answer begins with a consideration of the function of the acetylcholine neurons that control one's ability to pay attention. Adenosine negatively controls the activity of these neurons, meaning that when adenosine binds to its receptor on acetylcholine neurons, their activity slows. The production and release of adenosine in your brain is linked to metabolic activity while you are awake. Therefore, the concentration of adenosine in the neighborhood of acetylcholine neurons increases constantly while your brain is active during the day. As the levels of adenosine increase, they steadily inhibit your acetylcholine neurons, your brain's activity gradually slows, and you begin to feel drowsy and ultimately fall asleep. Caffeine comes to the rescue because it, like theophylline from tea, is a potent blocker of adenosine receptors and, therefore, of the adenosine-driven drowsiness and sleep. One can take this too far, however. One of my students decided to test these caffeine effects by ingesting a packet of instant coffee right out of the box. He reported that he enjoyed eating it so much that he decided to finish off the entire container of 32 packets! Three days later, he stopped having explosive diarrhea and finally fell asleep completely exhausted.

Given everything that you have read about drugs that produce a rewarding and euphoric feeling, you might suspect that coffee also somehow affects dopamine neurons. You would

be wrong. Recent positron emission tomography studies have demonstrated that caffeine consumption does not activate dopamine neurons.

WHY DOES COFFEE MAKE US FEEL SO GOOD?

We all remember our first cup of coffee; it tasted terrible. It was too hot, too bitter, and maybe too sweet, but it offered the promise of alertness after a night of poor sleep. The wonderful thing about coffee is that it delivers on its promise every time; subsequently, you have likely not been able to walk away from it. If you have ever had to give up caffeinated coffee to lessen the symptoms of fibrocystic breast disease or the tremors associated with Parkinson's disease, you know well the craving that can develop. Why does this happen? Scientists once thought that coffee stimulated the release of the neurotransmitter dopamine. Dopamine produces the euphoria and pleasant feelings that people often associate with their first cup of coffee in the morning. Many drugs that produce euphoria, such as cocaine, amphetamine, and Ecstasy, act upon dopamine in the brain. This action by coffee is no longer an adequate explanation for why caffeine is the most widely consumed psychoactive substance in the world. This lack of stimulation of the brain's principal reward system probably explains why caffeine exhibits such mild reinforcing effects. Despite caffeine's weak ability to induce a powerful euphoria, when combined with other stimulating drugs, such as nicotine, amphetamine, and

cocaine, it significantly increases their reinforcing properties. I speculate that this unusual feature of caffeine explains why so many of my students taking attention-deficit/hyperactivity disorder medications are heavy coffee consumers. The ability of coffee to make other components of our diet more enjoyable may also explain why 80% of all people in North America have measureable levels of caffeine in their brains from embryo to death.

However, do we all really just crave more arousal? Is being more aroused enough to explain why, for some people, coffee is akin to cocaine—they crave it constantly and will work hard to have a supply always at hand? Voltaire, Bach, and Beethoven all wrote about their love of coffee and likely utilized it to enhance their creative abilities. One of my students claimed that he regularly consumed two full pots of coffee (equivalent to approximately 20 cups of coffee!) every morning before coming to class. He indicated that he knew it was time to stop when the tremors in his hands became impossible to control. This student's experience reminds me of the verses of the French novelist Honoré de Balzac:

This coffee plunges into the stomach . . . the mind is aroused, and ideas pour forth like the battalions of the Grand Army on the field of battle. . . . Memories charge at full gallop . . . the light cavalry of comparisons deploys itself magnificently; the artillery of logic hurry in with their train of ammunition; flashes of wit pop up like sharp-shooters.

To me, these behaviors suggest a level of addiction that goes beyond the enhancement of one neurotransmitter system and may explain why he died of caffeine poisoning.

A recent report by a group of scientists from Rome outlined how coffee's addictive properties involve the brain's marijuana-like neurotransmitter system. This is how it all seems to work. When you first started drinking coffee, the arousal was all you wanted and also all that you got. Still, being more attentive and vigilant was all you needed to get through the day. As you continued drinking coffee, your liver compensated for the additional chemicals in your diet by becoming more efficient at metabolizing the caffeine. Your brain also made some adjustments. Ultimately, you needed increasingly more coffee each day to achieve the same level of arousal and vigilance. While all of this was occurring, something else far more mysterious was happening inside your brain: Caffeine had begun stimulating your brain's endogenous marijuana neurotransmitter system. These biochemical adjustments introduced an entirely new level of pleasure to your morning cup of java. In addition, they made avoiding that third or fourth cup of coffee even more difficult to accomplish. However, there is a surprise ending to this tale.

DECAF COFFEE IS JUST AS GOOD FOR YOU

It is the end of the day and you have failed to consume the recommended amount of coffee to prevent Parkinson's and Alzheimer's disease or prostate cancer or diabetes. Maybe it is

time to settle down with a cup of decaffeinated coffee. However, does decaffeinated coffee offer the same health benefits as caffeinated coffee? The answer is a qualified yes. Fortunately, with or without the caffeine, coffee is rich in biologically active substances such as phenols that exhibit both antioxidant and anti-carcinogenic properties. Some studies suggest that certain oils produced when coffee beans are roasted may favorably affect blood sugar control by enhancing the action of insulin to remove sugar from the blood. Trigonelline—a molecule of the vitamin niacin but with a methyl group attached—may help prevent dental caries by preventing the bacteria *Streptococcus mutans* from adhering to teeth. Trigonelline is unstable above 160°F; the methyl group detaches, unleashing the niacin (vitamin B₃). The vitamin niacin is formed in large amounts from trigonelline during the coffee bean roasting process. Two or three espressos can provide half one's recommended daily allowance and may be responsible for lowering blood cholesterol. Chlorogenic acid is an antioxidant whose actions may underlie the presumed ability of coffee to prevent type 2 diabetes mellitus. It can reduce the production of glucose by the liver and lessen the hyperglycemic peak in the blood following the consumption of sugar. The plant is believed to use this chemical to defend itself from viruses, bacteria, and fungi; it may provide the same benefits for humans.

Ferulic acid is an antioxidant that neutralizes free radicals and may prevent oxidative damage to our bodies caused by exposure to ultraviolet light when we unwisely do not use sunscreen. Ferulic acid can also decrease blood glucose levels and reduce

the level of cholesterol and triglyceride; these actions may underlie the potential benefits of coffee drinking, decaffeinated or not. Caffeinated coffee has been shown to increase blood pressure and may pose a health threat to people with cardiovascular disease; fortunately, decaffeinated coffee does not pose this risk.

COFFEE OR TEA: WHICH IS BETTER?

The cognitive decline of a large group of people who regularly consume coffee or tea (approximately five cups of each beverage per week) was monitored for 9 years. Overall, the tea drinkers exhibited a slower rate of cognitive decline compared to the coffee drinkers, but the difference was rather modest. Coffee drinkers are often also smokers; in addition, they consume more calories, eat less fruit, and have a more sedentary lifestyle than people who drink tea. Therefore, the best advice may have been offered by the 19th-century Dutch physician Cornelius Buntekuh, who advised “men and women to drink tea daily, hour by hour if possible; beginning with ten cups a day, and increasing the dose to the utmost the stomach can contain and the kidneys can eliminate.” Well, maybe not that much, but you get the idea.

WHY DO YOU WAKE UP FEELING SO TIRED?

The alarm rings, you awaken, and you are still drowsy: Why? Being sleepy in the morning does not make any sense; after all, you have just been asleep for the past 8 hours. Shouldn't you

wake up refreshed, aroused, and attentive? No, and there are a series of ways to explain why.

During the previous few hours before waking in the morning, you have spent most of your time in REM sleep, dreaming. Your brain was very active during dreaming and quickly consumed large quantities of the energy molecule ATP. The “A” in ATP stands for adenosine. The production and release of adenosine in your brain is linked to metabolic activity while you are sleeping. There is a direct correlation between increasing levels of adenosine in your brain and increasing levels of drowsiness. Why? Adenosine is a neurotransmitter that inhibits (i.e., turns off) the activity of many different neurons that are responsible for making you aroused and attentive, including neurons that release dopamine, serotonin, norepinephrine, and glutamate. You wake up drowsy because the adenosine debris that collected within your brain while you were dreaming is actively turning off all of these critical neural systems scattered throughout your brain.

WHO DID YOU SLEEP WITH LAST NIGHT?

Couples sleeping in pairs were investigated for sleep quality—that is, for the correct balance of non-REM and REM sleep, as well as their own subjective view of how they slept. For women, sharing a bed with a man had a negative effect on sleep quality. However, having sex prior to sleeping mitigated the women’s negative subjective report without changing the

objective results—that is, their balance of non-REM and REM was still abnormal. In contrast, the sleep efficiency of the men was not reduced by the presence of a female partner, regardless of whether or not they had sexual contact. In contrast to the women, the men's subjective assessments of sleep quality were lower when sleeping alone. Thus, men benefit from sleeping with women; women do not benefit from sleeping with men, unless sexual contact precedes sleep—and even then their sleep still suffers for doing so.

DID YOU GO TO BED LATE LAST NIGHT?

People who prefer to stay up late (evening types) wake up at a later time and perform best, both mentally and physically, in the late afternoon or evening. Evening-type individuals are significantly more likely to suffer from poor sleep quality, daytime dysfunction, and sleep-related anxiety compared to morning-type individuals. Even more disconcerting is that late bedtime is associated with decreased hippocampal volume in young healthy subjects. Shrinkage of the hippocampus has been associated with impaired learning and memory abilities. Going to bed late also induces you to consume more calories for the obvious reason that you are spending more time awake.

DID YOU GO TO BED HUNGRY LAST NIGHT?

What you eat before bedtime also might improve your chances of getting a good night's sleep. A recent study suggests that

eating something sweet might help induce drowsiness. Elevated blood sugar levels have been shown to increase the activity of neurons that promote sleep. These neurons live in a region of the brain that lacks a blood–brain barrier; thus, when they sense the presence of sugar in the blood, they make one feel drowsy. This might explain why we feel like taking a nap after eating a large meal. This is just one more bit of evidence demonstrating the brain’s significant requirement for sugar in order to maintain normal function. Getting a good night’s sleep is not always easy for most people. With aging, normal sleep rhythms become increasingly disrupted, leading to daytime sleepiness.

WHAT IF YOU DO NOT GET ENOUGH SLEEP?

Although scientists have not discovered why we sleep, they have discovered that we need between 6 and 8 hours every night. Not getting enough sleep makes us more likely to pick fights and focus on negative memories and feelings. The emotional volatility is possibly due to the impaired ability of the frontal lobes to maintain control over our emotional limbic system. We also become less able to follow conversations and more likely to lose focus during those conversations. Sleep deprivation impairs memory storage and also makes it more likely that we will “remember” events that did not actually occur. Extreme sleep deprivation also may lead to impaired decision-making and possibly to visual hallucinations. Not getting enough sleep on a consistent basis places one at risk of developing autoimmune

disorders, cancer, metabolic syndrome, and depression. Why? Some recent studies have reported that sleep is important for purging the brain of abnormal, and possibly toxic, proteins that can accumulate and increase the probability of developing dementia in old age. Whatever you are doing right now, stop and go take a nap. Preferably alone.

CHAPTER 10

BRAIN ENHANCEMENT AND OTHER MAGICAL BELIEFS

Overall, our knowledge about the human brain remains quite incomplete, and in the gulf of what we have yet to discover lie numerous unanswered questions and unproven theories about various aspects of our experience as emotional, sentient beings. Countless myths have been invented to fill this gulf of ignorance, including myths concerning normal age-related mental decline and the benefits of herbal remedies purported to restore function in the aging brain. Our brains change throughout our lives, and not always for the better. Why do they change? There are many causes of cognitive decline, including drugs that stimulate γ -aminobutyric acid receptors too well, calcium channel blockers such as lamotrigine or lithium, dementia and various diseases of the brain and body, head injury, hormone imbalance,

dietary nutrient deficiency or excess, heavy metal toxicity, sleep deprivation, and prolonged stress. The treatments are as varied as the causes. The good news is that sometimes these treatments are relatively effective at assisting the compensation or recovery of a diseased or injured brain.

No treatments are currently available that can reverse one of the major causes of cognitive decline: normal aging. In other words, it is impossible to enhance the function of a normal brain as it ages, despite recent research that has focused on achieving this goal. This fact has not deterred con artists from placing numerous advertisements on the Internet and elsewhere that claim their products are effective brain boosters or cognition enhancers. In general, these products take advantage of the ability of stimulants to enhance performance. Notice the difference in my terms: Stimulants only enhance performance, not intelligence or cognitive function. The classic brain stimulants previously mentioned—coffee, amphetamine, and nicotine—might improve performance, engaging certain neurotransmitters in the process, but they do not raise one's IQ score and do not stop normal age-related cognitive decline. The continuing myth of cognitive enhancers relies on the tendency of people to confuse faster performance with real intelligence. We sometimes assume that people who speak quickly are smarter than people who speak slowly. Is there some truth to this assumption? Usually not, but sometimes the answer is yes. Let us look at why this might be the case.

One interesting and surprising predictor of intelligence is finger-tapping speed, which is influenced by the level of dopamine in the forebrain. Dopamine plays an important role in controlling the timing of movement. For example, people with Parkinson's disease have reduced levels of dopamine in their forebrain and move slowly. In advanced stages of the disease, these patients also suffer with a slowing of mental function. Research on the brain's timing system, its ticking clock, has often pointed to the important role of dopamine. People who tap their fingers fast usually think fast, and their increased processing speed correlates with their IQ score. So how to explain why coffee drinking does not make us smarter? Processing speed for your brain can be compared to processing speed for your computer. Today, most people use computers that process data at gigabytes per second; a few years ago, you may have used computers that processed at megabytes per second. We do not assume that the computers are smarter today, just faster. Yet, the way that data can be manipulated makes it appear as though the current computers are better somehow. Your brain is much like this, and dopamine seems to be responsible for the clock speed that is tied to your processing speed. More dopamine in the forebrain translates into a faster finger-tapping speed and correlates with a higher IQ than that recorded in people who do not tap as fast.

There are almost certainly many features of the brain other than dopamine release that influence intelligence. Making us faster does not make us smarter. However, drugs that increase

dopamine release tend to be stimulants and tend to speed us up and produce arousal; they are also highly abused. There is a good reason why people do not use heroin or alcohol to make themselves feel smarter: These drugs do not increase dopamine release in the forebrain. They slow you down and make you act and feel fuzzyheaded and stupid. So why not just take a lot of stimulants and increase your brain's processing speed to the point where you appear to be a genius, even if you are not? The answer is that your brain is probably already functioning almost as fast as is safe. Most of us can increase the processing speed slightly without risk. Unfortunately, your neural processing speed in your brain is already just a few extra action potentials per second away from a seizure. Indeed, your brain works so fast that you are always vulnerable to seizures in response to many different stimuli, such as a minor head injury, a stroke, rapidly flashing lights, a tumor, vascular abnormalities, or small hemorrhages. Given the limitations of our brain physiology and chemistry, we are probably as smart as we possibly can be at this time in our development as a species.

Your brain is a product of its complex and multi-million-year history of solving the problems of survival for its host feeding tube in an ever-changing environment. Some of your brain structures evolved to solve one problem at one point in the evolution of our species and then ended up being used for another, often related, problem. By now, you have seen that the same thing can be said of its neurotransmitters. Overall, your brain is fairly fast but not too efficient, which is probably why

stimulants can make us perform some tasks slightly better. The brain shows no evidence of being designed in any intelligent manner; it simply works as best as it needs to work to allow us to survive and thrive in our current environment. If that comfortable environment changes sufficiently or too quickly, there is no guarantee that our species will survive. After all, more than 97% of all species known to have existed on Earth have already become extinct. No species has had a lock on having a perfect body or brain that allowed it to survive in all environments. The Nobel Prize-winning French biologist François Jacob wrote that “evolution is a tinkerer”—it did not intentionally create anything beyond what was needed at the time for survival. This is why we, and every other species on the planet, are always vulnerable to significant changes in our environment. Overall, the indifferent forces of its environment, not any willful intent, organized the brain. Brain scientists working in this area hold out hope that there might be some wiggle room for improved performance. Thus far, however, no one has been able to design a drug therapy that can make a person smarter in any real way, other than increasing processing speed. Therefore, if we examine the so-called memory boosters and cognitive enhancers on the market today, we find that they contain caffeine and sugar and some peculiar amino acids and a few vitamins that together do nothing except make us a little poorer. At this point in time in the 21st century, nothing—let me repeat that—nothing exists that can truly make us smarter; so do not waste your money on anything that promises to do so. However, do not

despair—we can probably age better; some of these solutions are mentioned next.

Interestingly, some substances that we would not typically consider to be healthy can have beneficial effects on how the brain ages. For example, nicotine may be neuroprotective, as may the contents of tobacco smoke, which contains very high levels of chemicals that are efficient chelators of heavy metals. There is, in any case, a reduced incidence of Parkinson's disease among people who smoke. Consumption of large volumes of caffeine-containing drinks is also associated with reduced incidence of Parkinson's disease. The regular consumption of alcohol, primarily beer, has been correlated with a later onset of Alzheimer's disease; this might result from the ability of alcohol to reduce blood levels of cholesterol, which is directly correlated with a greater risk of dementia in later life. Marijuana can be quite beneficial in reducing the onset of age-related diseases that involve brain inflammation, including multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, and a variety of autoimmune diseases. A few recent studies have suggested that people who smoked marijuana in the 1960s are today somewhat less likely to develop Alzheimer's disease.

Can smoking marijuana prevent Alzheimer's disease? Yes, but several guidelines must be followed:

1. Do not use marijuana when the brain is young.
2. Smoke only one puff of marijuana each day between the ages of 30 and 60 years.

3. Use the kind of marijuana that was popular in the 1960s—that is, that has not been genetically altered to enhance the level of one or two ingredients.
4. If signs of dementia have already appeared, it is unlikely that smoking marijuana will be beneficial; doing so might worsen the symptoms of dementia.

An explanation for each of these points follows.

Ordinarily, marijuana is not viewed as being beneficial for the brain. How could a drug that clearly impairs memory while people are under its sway protect brains from the consequences of Alzheimer's disease? The answer is that it does so due to a series of changes in brain chemistry that occur during normal aging that alter how the brain responds to marijuana. Positron emission tomography imaging studies of humans have shown that after age 30 years, the brain gradually displays increasing evidence of inflammation. With advancing age, brain inflammation continues to worsen, leading to a decline in the production of new neurons, called neurogenesis, that are important for making new memories. In contrast, young brains do not display signs of inflammation and are therefore more vulnerable to the negative consequences of marijuana use. Research in my laboratory has demonstrated that stimulating the brain's marijuana receptors offers protection by reducing brain inflammation and by restoring neurogenesis. Thus, later in life, marijuana might actually help the brain rather than harm it. It takes very little marijuana to produce benefits in the older brain. My lab coined

the motto “a puff is enough” because it appears as though only a single puff each day is necessary to produce significant benefit. The evidence available from studies of humans and animal models of Alzheimer’s disease indicates that long-term, low-dose daily exposure, during mid-life, to the complex blend of compounds in the marijuana plant can effectively slow the brain processes underlying Alzheimer’s disease.

This is not an advertisement for you to take up smoking cigarettes and pot or drinking beer and coffee because you think doing so will save you from the ravages of the previously mentioned diseases. I mention the beneficial effects of these substances only to emphasize a point: Scientists know about the correlations between the regular use of these popular herbal-based drugs and the reduced incidence of some age-related brain disorders because millions of people have administered billions of doses of these substances during the past thousand years, but only relatively recently has careful record-keeping allowed us to observe the quite subtle, yet very consistent, benefits provided by these drugs. Thus, it is only because these drugs are so widely abused that their positive effects on the brain have been noticed. There may be wonderful new drugs to be discovered in, for example, cauliflower or haggis, but too few people have been willing to eat them in sufficient numbers and for a sufficient period of time for epidemiologists to take notice of their hidden benefits on the brain, if they exist.

Many plants contain compounds that should be able to enhance the brain’s performance or protect neurons following

injury. For example, potatoes, tomatoes, and eggplants contain solanine and α -chaconine, which can enhance the action of acetylcholine. Yams contain diosgenin, which can protect the brain following brief episodes of reduced blood flow. Yet eating these foods does not improve memory. Your mood should be enhanced slightly by eating fava beans (with or without a fine Chianti) because they contain L-DOPA, a precursor to the production of dopamine, the reward chemical in your brain. The reason why eating fava beans does not make you feel happier is because it is highly unlikely that their ingredients will gain access to the site of action in the brain, at a sufficient concentration, to produce a noticeable effect on brain function. This might explain why no one is hawking potatoes, fava beans, or eggplants as a cure for dementia.

I can assure you that someone is now selling “the cure” for mental decline. I truly wish that a cure did exist; I would be first in line to get it. We would all prefer to defy the aging process by simply taking a pill and to be able to eat with impunity everything we desire rather than following our mothers’ prosaic advice about moderate, healthy eating. But again, and alas, no such cure exists. The fact that science has not yet invented a true brain enhancer has not stopped people from selling drugs, ancient elixirs, unusual therapies with mystical names, and hundreds of books that all boast of the properties of this or that miracle, age-defying brain booster. If someone might gain financially from your gullibility, then what he or she is selling

is probably useless; furthermore, there is no guarantee that it is safe.

Currently, nothing has been discovered that can significantly enhance cognition or prevent brain aging. Despite this, people will always be willing to sell you something, be it a book supporting a peculiar diet or a pill containing a special ingredient, that they claim will do so. Why do so many people fall under the spell of charlatans? How can so many people feel so strongly that these drugs work on them? The answer is quite easy to summarize in three words—*the placebo effect*. This fascinating effect is discussed more fully later. Essentially, we want these drugs to do something—anything—so we fool ourselves into thinking that they do. After all, we have just spent a lot of money on a pill! Read on for an example.

GINKGO BILOBA

The Internet is bursting with claims that pills and drinks containing extracts of the ginkgo biloba plant may neutralize free radicals, dilate the blood vessels in your brain, make you smarter, and slow the aging process. How does ginkgo biloba do all of these wonderful things for you? The claim is that ginkgo biloba increases the function of acetylcholine neurons and thereby enhances memory and arouses and improves attentional ability.

Dozens of clinical trials have examined the cognitive effects of ginkgo plant extracts in humans. A great majority of the studies indicating a positive effect have involved patients who

had a mild to moderate memory impairment, frequently with a diagnosis of early Alzheimer's disease. Most experiments tested learning, memory, and, less often, attention. Most of the subjects were selected and tested long after they began using ginkgo products, typically several months; thus, their cognitive level before using ginkgo is unknown. This fact may have introduced a bias. For example, higher scores on the memory and learning tests may have come from subjects with better cognitive abilities who could read and understand articles suggesting that ginkgo might help them or who were better able to remember to take the drug. These critical factors were never considered by the authors of these studies. Testing any drug that claims to enhance cognitive function will have this kind of potential bias in the choice of subjects. At the very least, researchers need to give cognitive function tests both before and after the patients start taking ginkgo, or else the experimental results showing improved cognitive function from the use of this substance are suspect.

There is another serious problem with clinical trials on plant extracts: determining how much of a given extract a patient should be given and which extract is the effective one. When ancient Chinese herbalists recommended that their patients take ginkgo biloba, or any number of other plant extracts that have been prescribed during the past two millennia, they estimated dosage based on past experience. But plants are complicated organisms that make a large variety of molecules, some of which are active in the brain, some of which are not active in the brain

but are quite nutritious, and some of which are inert. Moreover, the contents of plants change according to growing conditions. How much of any particular extract should therefore be taken by a person who seeks the benefit that ginkgo might offer? No one knows! The studies necessary to establish a truly effective dose have never been performed rigorously.

The little research that exists suggests that the ingredients of these herbals have numerous potential mechanisms of action on a variety of neural systems. Unfortunately, there is a lack of unanimity in the research because of various methodological problems in many of these studies, such as inadequate sample size (the number of subjects in the study) and lack of a double-blind, placebo-controlled paradigm, the gold standard of modern scientific research. This paradigm means that no one involved in a drug trial—including its investigators and its subjects—knows which tested substance, whether an active drug or a placebo (usually an inactive form of the drug under study or a sugar pill), is being administered. The purpose of this approach has to do, again, with bias—to keep investigator and subject bias from influencing the trial's results.

In fact, on the rare occasion that this standard has been applied to studies on alternative medicines such as ginkgo biloba, the results have not been positive. For example, a pair of very large clinical trials that followed the health of more than 3,000 people of various ages for 8 years clearly demonstrated that ginkgo biloba cannot influence the development of age-related memory problems. Another trial indicated that the use of

gingko may actually be harmful by increasing an individual's risk of non-hemorrhagic stroke, which occurs when a blood vessel in the brain becomes blocked and shuts off blood flow.

These are just a handful of studies, however, and much more high-quality research needs to occur before the effectiveness of ginkgo biloba and other herbal products is irrefutably proven or disproven. In the meantime, most manufacturers of these products prefer to err on the side of selling diluted samples to avoid any toxic side effects and potential lawsuits from people who survive the experience. But that is still no guarantee that the samples are safe. Unacceptably high levels of pesticides and carcinogens have, for example, been found in a large percentage of imported samples.

These concerns aside, many people are convinced that they benefit from substances such as ginkgo biloba or the countless other products on the market that promise enhanced cognitive function. Why? Because, in brief, they want these drugs to do something—anything—so they fool themselves into thinking that they do. We all are subject to this faulty logic from time to time. Furthermore, the World Health Organization estimates that due to a lack of adequate medical expertise, more than 80% of the world's population relies on herbal remedies administered for self-diagnosed mental and physical illnesses.

VITAMIN SUPPLEMENTS

Americans spend billions of dollars on multivitamin—mineral supplements, but are they getting a return on their

investment? Not always. Numerous studies involving hundreds of thousands of men and women of all ages and genetic backgrounds have found little or no long-lasting benefits from taking a multivitamin–mineral daily supplement. One large study followed 182,000 men and women; those who took daily multivitamins did not live longer or have less heart disease or cancer, the two primary killers of Americans. In a study that followed 161,000 postmenopausal women for effects of multivitamin use, those who took daily multivitamins were not less likely to develop breast, ovarian, or any other cancer than women who did not take multivitamins. Among 83,000 middle-aged to elderly men who were followed, those who took daily multivitamins were no less likely to die from coronary heart disease or stroke than were men who did not take multivitamins.

So maybe you are still hoping that taking multivitamins, at the very least, might offer some modest benefits for your substantial investment of time and money. Unfortunately, after many decades of research, evidence for even modest health benefits is still lacking. Even when researchers examined the benefits of multivitamins for symptoms associated with the common cold, they could find no significant health benefits.

What about the brain? Surely, multivitamins help the brain; just look at the hundreds of claims on the Internet! Nope.

When healthy older men and women, aged 60–91 years, were given daily multivitamin supplements for 6 months, they demonstrated no significant improvements on memory or other cognitive function tests compared to controls who were given a

sugar pill. Vitamin E supplements are no longer recommended for brain health; indeed, the high doses originally thought to help slow the onset of dementia with aging are now recognized to increase the risk of cerebral hemorrhage.

Despite a total lack of evidence that multivitamins offer any real long-term health benefits, many people are addicted to them. This is why Americans produce the most expensive urine in the world; we merely excrete whatever our bodies do not need immediately.

Concerns about vitamins and the balance of their risks versus their benefits were expressed during the early 1950s when parents learned that powerful chemicals—vitamins and minerals—were being added to their children's favorite breakfast cereals. The solution for some manufacturers was to offer the pills as effigies of popular cartoon characters. As recently as 2004, Denmark outlawed some vitamin-fortified cereals because of concerns that extremely high levels of vitamin B₆, calcium, folic acid, and iron might achieve toxic levels if eaten daily; the risk is particularly high for young children—the principal consumers of many enriched cereals. The Danes might be overreacting; however, it is probably not a good idea to take a daily multivitamin if you are eating a cereal containing 100% of the daily recommended levels.

Overall, most of us are wasting our money because we have been completely sold on the belief that we need these chemicals to be healthy. The epidemiological evidence does not support this belief. Indeed, some things that were once thought to be

critical for good health, such as selenium or vitamin A, are simply not a major health concern; indeed, recent recommendations are to avoid high doses of these two supplements.

However, and this cannot be overstated, some people do need supplements of certain vitamins and minerals because of poor diets, disease states, advanced age, gender, lack of sunshine, and so on. Most people are aware of the scientifically supported recommendations that some should consume more vitamin D (particularly people taking statins to reduce blood lipids), take folic acid during pregnancy, take certain B vitamins to maintain mental and physical health, and consume additional iron (particularly women older than age 50 years).

Supplementation with thiamine (vitamin B₁) may slow the onset of dementia associated with Alzheimer's disease; recent studies also suggest that thiamine supplementation might reduce some of the characteristic pathological changes that underlie the disease. Thiamine deficiency produces many of the same symptoms as those seen in patients with Alzheimer's disease. Unlike most other supplementation claims, numerous scientific studies have provided some insight into why thiamine supplementation might be effective in some patients. Thiamine is critical for metabolism of the brain's major source of energy—sugar. The brains of patients with Alzheimer's disease often show reduced levels of thiamine-dependent enzymes that are associated with reduce utilization of sugar by the brain. Thiamine deficiency might be due to reduced dietary levels, reduced absorption, or the

unintended consequence of some medication. Because thiamine in most dietary sources is water-soluble, most of the dosage is likely to be excreted in the urine before gaining access to the brain. In contrast, a fat-soluble form of thiamine, called benfotiamine, can be found in crushed garlic, onions, leeks, and shallots.

Iron also plays a critical role in brain chemistry; the lack of it, called anemia, is associated with apathy and depression. Iron deficiency has also been found in children with attention-deficit/hyperactivity disorder. One should not consume too many iron supplements because too much iron in the body can be quite harmful. The iron will attract bacteria that want to utilize it for their own purposes. People with elevated levels of iron in their body experience more infections than do people who are iron-deficient. Finally, you should try to get calcium into your diet, no matter who you are.

Moderation is still the best approach for most of us: This includes moderation in the number of calories consumed each day, moderation in one's daily exercise routine, and a good attempt to obtain vitamins and minerals from their natural sources. Forget about expensive supplements and just eat small amounts of many different foods. Finally, aggressively avoid almost anything from a cow or pig. Obviously, suggesting that you should not purchase expensive dietary supplements goes against everything you have heard from the people who sell these products. My mantra: Save your money and save your brain.

PSEUDOSCIENCE

Probably the most ridiculous pseudoscientific therapy that is relevant to this book is homeopathy. This bit of nonsense is based on two ideas: that “like cures like” and that incredibly small amounts of a medicine are stronger than larger quantities. The homeopathic concept is that you dilute these medicines so much that instead of causing the symptom, they cure it. In fact, when you dilute a substance to the degree that is recommended, you end up with nothing at all. Essentially, homeopathic treatments are just water, usually with a little sugar added for a nice flavor.

In addition to drugs and herbals that are marketed using pseudoscientific logic, there are almost as many nondrug interventions for your brain that also lack any shred of scientific proof. These interventions usually invoke the actions of some mystical force that physicists have repeatedly failed to discover. The fact that these interventions lack any scientific support does not deter desperate people, usually encouraged by the willfully ignorant, from seeking them out and, most important, paying for them. Craniosacral therapy, ear candling, magnet therapy, crystal healing, cupping, Rolfing, neurolinguistic programming, psychokinesis, and primal therapy are just a few of the frequently mentioned examples of completely ineffective interventions. In addition, “energy medicines,” such as Reiki, which involve “laying on of the hands” or various types of hand waving above the body, or any of the numerous naturopathic

practices have never been proven to provide any medical relief beyond that produced by the placebo effect.

THE PLACEBO EFFECT

When it comes to alternative medicines and therapies that, like ginkgo biloba, claim to enhance your brain function, never underestimate the power of your own expectations. Not only does your brain influence how you think and feel but also, by the nature of your thoughts and expectations, you can influence how your brain and body function. Thoughts and brain function form a two-way street: You often feel sad when you are ill and can think yourself sick when you are depressed. Just like “The Force” in a Jedi, the placebo effect is strong in some of us, and it can be used for good or evil. A very good example of the dark side of the placebo effect is the results of a recent large study of the effects of prayer by large groups of people on the health of others. When a typical sick person was not aware that someone was praying for him or her to get healthy, the sick person’s health was unchanged during the duration of the study. This discovery was in direct contrast to an older, smaller, and very poorly designed study that widely reported some positive benefits of prayer. The most interesting outcome of the recent investigation was that the people who actually were aware that others were praying for them became significantly sicker. The authors speculated that the peer pressure to become healthy produced so much stress that the afflicted patients became even less healthy. This study made me wonder whether I should stop

sending get-well cards to people while they are in the hospital. Is that too much pressure on them to get well?

When it comes to alternative medicines and therapies that claim to enhance your brain function, never underestimate the power of your own expectations. Therefore, the best approach, and cheapest one by far, is to expect great things of your brain and generate your own placebo effect. Much has been written about the value of the placebo effect in the practice of medicine, but how this effect emerges and whether it can be controlled are issues that are not yet understood. Essentially, scientists have analyzed the effect based on results of placebo-controlled studies of actual drugs on the brain or have compared only the effects of a placebo against the consequences of no treatment at all. Their findings have been intriguing, if still largely inconclusive. However, in one area of study that is not directly related to an actual treatment, the findings are more definitive. Numerous meta-analyses (which are later analyses of other researchers' data) have shown that only the perception of pain can be statistically demonstrated to be influenced by our minds, which scientists refer to as the emergent property of our brains. This influence of our thoughts and expectations on how we experience pain is a true placebo effect.

In one study, published in late 2008, scientists measured pain perception in two groups of people—devout practicing Catholics and professed atheists and agnostics—while they viewed an image of the Virgin Mary or the painting of Lady with an Ermine, by Leonardo da Vinci. The devout Catholics

perceived electrical pulses to their hand as being less painful when they looked at the Virgin Mary than when they looked at the da Vinci work. In contrast, the atheists and agnostics derived no pain relief while viewing either picture. Magnetic resonance imaging scans demonstrated that the Catholics' pain relief was associated with greatly increased brain activity in their right ventrolateral prefrontal cortex. This brain region is believed to be involved in controlling the emotional response to sensory stimuli, such as pain. Perhaps this study has, in fact, shown us the location of the placebo effect.

Other studies using brain imaging techniques to show correlations between brain activity and the extent of reported placebo effects have demonstrated that some people show greater placebo responses than others but that everyone appears to be capable of having such a response. There is also increasing proof that the use of placebos might benefit people with Parkinson's disease, depression, and anxiety. In the future, with better testing measures, scientists will likely demonstrate how the placebo effect influences many aspects of our health. In short, the placebo effect is real; we simply do not understand entirely how it works, but the evidence thus far is truly remarkable, particularly with regard to pain. Some people are able to block incoming pain signals or alter how they are perceived. In addition, without a doubt, your mind can make the experience of pain more or less agonizing depending on how you feel—for example, are you fatigued, anxious, fearful, or bored? Do you expect more painful experiences to be coming soon?

There is growing evidence that an individual's genetic makeup, now referred to as the placeboome, influences clinical outcomes and potentially may allow for identification of placebo responders. The genes for four different neurotransmitters have been implicated to underlie the placebo effect. At least 10 genes that influence both dopamine and serotonin function may underlie the robustly demonstrated placebo effect on mood, particularly the symptoms of depression. In addition, there are specific genes that influence the endogenous opiate and cannabinoid neurotransmitter systems that likely underlie the ability of placebos to produce analgesia, as described previously. Overall, the pain-reducing action of a placebo seems to be responsible for approximately half of the response to pain-reducing medications. This is true regardless of whether the active medication is aspirin or morphine, meaning that placebo morphine is significantly more powerful than placebo aspirin. Why? Because people expect that morphine is more powerful than aspirin.

With regard to depression, the placebo response ranges from approximately 30% to 40% of the response to any standard antidepressant medication. There is one key aspect of the placebo effect that unmasks its presence in any treatment: The placebo effect always occurs faster than "real" drug effects. If you ever see a claim for "immediate benefits," you can be assured that it is all placebo. Also, a recent study discovered that placebo effects do not demonstrate normal extinction. This means that people will continue to claim benefit from a placebo pill even

when the pill no longer produces its original benefits. The true believer refuses to give up false hope.

The placebo effect comes into play sometimes in surprising ways. For example, the color of the pill you take influences your expectation of what it will do to you. Obviously, pills can be made any color, yet most people like their anti-anxiety pills to be blue or pink or some other soft, warm color; they prefer their powerful anti-cancer pills to be red or brightly colored. Americans do not like black or brown pills, in contrast to the preference of people in the United Kingdom or Europe. Thus, the majority of over-the-counter medications that Americans purchase are in the form of small, white, round pills. Yet large pills, or pills with odd shapes, are also assumed to be more powerful, or just simply better, than tiny round pills. Sometimes, a simple change in color or shape restores a drug's ability to produce a placebo effect. In addition, sometimes the effect derives from the pill-taking regimen. For example, you expect that when you are instructed to take a medication only during a full moon, or only every other Thursday, it must be extremely, almost mystically, effective. Herbalists and chiropractors often take advantage of this concept by recommending odd or excessive dosages of peculiar-looking pills or foul-smelling potions. We all want to believe that the pills we take will help us feel and function better; fortunately, due to the phenomenon of the placebo effect, we do sometimes, but only for a while, benefit even from the most bogus of potions and pills. As Tinker Bell said, "You just have to believe!" If all you are getting is a sugar pill,

then does it really matter whether you are fooled into believing the lie? Possibly, it depends on the cost of the sugar pills and the risk one assumes by not taking a medicine of proven effectiveness in a timely manner for a medical condition. The risk of taking substances that merely promise the elusive Holy Grail of enhanced, age-defying brain function may be no less dire, depending on the true nature of the “sugar” that is in them.

It is so easy to be fooled. Our brains are not as perfect as we would like them to be, and so we keep searching for the magic pill or potion that will make us smarter and prevent the inexorable effects of aging. As long as we keep searching, someone will be there to sell it to us, and we will stand in line to buy it, none the wiser or healthier and a lot poorer. Still, that does not mean that there is no hope. You have seen that there is one very simple and money-saving thing that you can do to enhance your brain’s performance and to slow the aging process: Eat a lot less food, because you should never underestimate the power of food on your mind.

CLOSING THOUGHTS

My broad purpose in this book was to demonstrate that we can use our current knowledge of how drugs and nutrients affect the brain to gain a better appreciation of how the brain works. I hope that you have learned that there is a degree of predictability about how your brain responds to the drugs and food you consume. It is not very mysterious. As science continues to advance our understanding of how the

brain works, much of the myth and mystery that have always surrounded its function will vanish. The chemicals we consume either influence the brain's function or do nothing; the former are drugs, whereas the latter are food. How you respond to any particular chemical you consume depends on you—that is, your biology, sex, age, state of health, the genes you inherited from your parents, and your expectation about what the chemical should do. Do not forget that the brain is the organ of the mind; whatever it experiences becomes your reality. Thus, chemicals that alter how your brain functions can change your personal experience of reality. Finally, always interpret how the brain responds to the chemicals you consume in terms of how its function was shaped by evolution. The brain has only two purposes: your survival and the continuation of your genes. As you learn more about the brain, whether from the suggested readings or from other sources, you will become a wiser consumer of both the nutrients and drugs that affect how you think and feel.

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