YOUR BRAIN ON FOOD

How Chemicals Control Your Thoughts and Feelings

Third Edition

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For Jane

CONTENTS

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 1

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* (φαρμακος) 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.

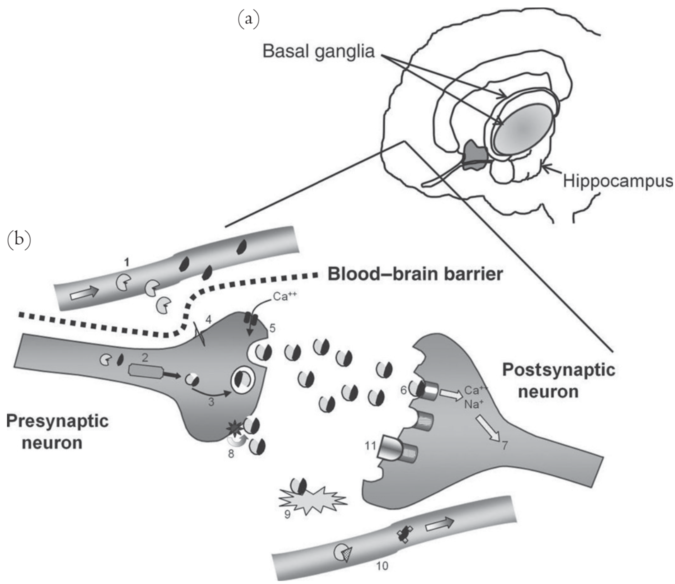

Figure 1.1 The anatomy of a few brain regions that are discussed later in the book (a). How individual neurons communicate with each other (b). See text for details.

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