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CHAPTER 3

How Drugs Work in the Body and on the Mind

After you have completed this chapter, you should have an understanding of

- The ways drugs are administered and later eliminated from the body
- Factors determining the behavioural impact of drugs
- The sympathetic and parasympathetic branches of the autonomic nervous system
- The basic structures of the brain
- How neurons work, and how they communicate with each other
- The functions of seven major neurotransmitters in the brain
- How psychoactive drugs influence neuronal communication
- How receptors respond to neurotransmitters
- The physiological basis for the effect of receptors
- Tolerance effects and psychological dependence
- The placebo effect in drug-taking behaviour

You can think of addiction as a form of "learning gone bad." Drugs can infiltrate into the brain because they can speak the brain's own language.

Neurochemical pathways and synaptic processes have no choice but to respond to drugs as they do to chemicals and signals that occur naturally in the brain, which are far gentler and have served us well for millions of years.

Meanwhile, drugs are hijacking the brain. They ambush, alter, corrupt, infest, curtail. They commandeer brain processes, reshape networks. And their demands escalate over time.

Reflections on substance abuse from the perspective of neuroscience[1]

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You might have heard of this classic public-service announcement, which aired frequently on television in the late 1980s:

> *This is your brain (image of an egg held in hand).*
> *This is drugs (image of a sizzling frying pan).*
> *This is your brain on drugs (image of the egg frying in pan).*
> *Any questions?*[2]

Giving the viewer considerable "food for thought," this message had an immediate impact on the public: Don't do drugs because drugs will fry your brain. The creators of this message were speaking metaphorically, of course. In effect, they were saying that certain classes of drugs have a devastating impact on the human brain. Therefore, stay away from them.

It was (and still is) an important message to convey, though it can be argued that there are better ways to persuade people not to do something than by seeing scary images. Nonetheless, those who felt the impact of watching that egg fry found the experience hard to forget.

At the same time, an equally important message is that there are other classes of drugs that have enormously beneficial effects on the brain. Drugs are used to treat major mental illnesses such as schizophrenia and depression (see Chapter 15) and play a major role in reducing pain and relieving feelings of anxiety (see Chapters 5 and 13). Whether drugs in general have a positive or a negative effect on us depends, at least in part, on how they interact with physiological processes in the body.

As noted in Chapter 1, psychoactive drugs affect our behaviour and experience through their effects on brain functioning. Therefore, our understanding of drugs and their effects is closely connected with the progress we have made in our understanding of the ways drugs work in the brain. This chapter will describe the basic functions of the nervous system and the ways in which drugs alter these functions. It will serve as a foundation for understanding specific classes of drugs covered in the chapters that follow.

A reasonable place to start is to ask the question: How do drugs get into the body in the first place?

by the numbers . . .

100 billion	Estimated number of neurons in the human brain
10–100 trillion	Estimated number of synapses in the human brain
20–25	Approximate wattage of a lightbulb, equivalent to the total electrical power generated by the brain

Sources: Drachman, D. (2005). Do we have brain to spare? *Neurology, 64,* 2004–2005; Kety, S. (1961). Energy metabolism of the brain during sleep. In G. E. W. Wolstenhome & M. O'Connor (Eds.). *CIBA Foundation Symposium on the nature of sleep.* Boston: Little, Brown, pp. 375–381; Thompson, R. F. (1993). *The brain: A neuroscience primer* (2nd ed., pp. 75, 299). New York: Freeman.

How Drugs Enter the Body

There are four principal routes through which drugs can be delivered into the body: *oral administration*, *injection*, *inhalation*, and *absorption through the skin or membranes.* In all four delivery methods, the goal is for the drug to be absorbed into the bloodstream. In the case of psychoactive drugs, a drug effect depends not only on its reaching the bloodstream but on its reaching the brain as well.

Oral Administration

Ingesting a drug by mouth, digesting it, and absorbing it into the bloodstream through the gastrointestinal tract is the most common and most easy way of taking a drug. On the one hand, oral administration and reliance on the digestive process for delivering a drug into the bloodstream provides a degree of safety. Poisons typically taste so vile that we normally spit them out before swallowing; others will cause us to be nauseated, and the drug will be expelled through vomiting. In the case of hazardous substances that are not immediately rejected, we can benefit from the fact that the absorption process for orally administered drugs is relatively slow. Generally speaking, it takes between 5 and 30 minutes after ingestion for most of the absorption process to be completed. Therefore, there is at least a little time after accidental overdoses or suicide attempts to induce vomiting or pump the stomach.

On the other hand, the gastrointestinal tract contains a number of natural barriers that slow down or, in some cases, prevent the absorption of certain drugs that we might actually want to absorb. One such barrier is related to a drug's alkalinity or acidity (defined as its pH value). The interior of the stomach is highly acidic (pH ~ 2.0), and the fate of a particular drug depends on how it reacts with that environment. Weakly acidic drugs such as aspirin are absorbed better in the stomach than highly alkaline drugs such as morphine, heroin, and cocaine. Insulin is destroyed by stomach acid, so it cannot be administered orally, whereas a neutral (neither acidic nor alkalinic)

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© Richard Lord/The Image Works

Alcohol is easily absorbed into the bloodstream and the brain. For other orally consumed drugs, however, absorption is relatively slow, because they must first be processed by the digestive system.

substance such as alcohol is readily absorbed at all points along the gastrointestinal tract. In the case of alcohol, the brain gets the message very quickly.

Why does the pH of a drug alter how it gets absorbed? It all has to do with ionization. If a drug stays in its nonionized form it passes more easily into the bloodstream, whereas an ionized drug will not. Ionization is determined by the pH of the surrounding environment, such that an acidic drug will become ionized in an alkaline environment, and vice versa. The membrane separating the gastrointestinal tract from blood capillaries is made up of two layers of fat molecules, making it necessary for substances to be *lipid-soluble*, or soluble in fats, in order to pass through it and into the bloodstream.

If it survives the stomach, the drug can also proceed from the small intestine into the bloodstream. Even after successful absorption into blood capillaries, however, substances must then pass through the liver for a "screening process" before being released into the general circulation. Enzymes in the liver are capable of breaking down (metabolizing) the molecular structure of certain drugs, thus reducing the amount that eventually enters the bloodstream. This function of the liver, referred to as *first-pass metabolism*, plays an essential role in protecting us from potentially toxic substances that might have been ingested by mouth. A further barrier, which separates the bloodstream (circulatory system) from brain tissue itself, will be discussed in a later section.

As a result of all these natural barriers, orally administered drugs need to be ingested at deliberately elevated dose levels, to allow for the fact that some proportion of the drug will not make it through to the bloodstream. We can try to compensate for the loss of the drug during digestion, but we are often only making an educated guess. The internal state of the gastrointestinal tract changes constantly over time, making it either more or less likely that a drug will reach the circulatory system. The presence or absence of undigested food, whether the undigested food interacts with the chemical nature of the drug, and the activity level of specific liver enzymes that control the absorption of the drug into the bloodstream are examples of factors that make it difficult to make exact predictions about the strength of the drug when it finally enters the bloodstream (see Chapter 14).

Injection

One solution to the problems of oral administration is to bypass the digestive process entirely and deliver the drug more directly into the bloodstream through a hypodermic syringe and needle.

A very fast means of injection is an **intravenous (i.v.)** injection, as the drug is delivered into a vein without any intermediary tissue. An intravenous injection of heroin in the forearm, for example, arrives at the brain in less than 15 seconds. The effects of abused drugs delivered in this way, often called *mainlining*, are not only rapid but also extremely intense. In a medical setting, intravenous injections provide a great deal of control over dosage and the opportunity to administer multiple drugs at the same time. The principal disadvantage, however, is that the effects of intravenous drugs are irreversible.

intravenous (i.v.): Into a vein.

The most common method of administration of heroin is a direct injection into the bloodstream.

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In the event of a mistake or unexpected reaction, there is no turning back unless some other drug (called an *antidote*) is available that can counteract the first one. In addition, repeated injections through a particular vein may cause the vein to collapse or develop a blood clot.

With **intramuscular (i.m.)** injections, the drug is delivered into a large muscle (usually in the upper arm, thigh, or buttock) and is absorbed into the bloodstream through the capillaries serving the muscle. Intramuscular injections have slower absorption times than intravenous injections, but they can be administered more rapidly in emergency situations. Our exposure to intramuscular injections comes early in our lives when we receive the standard schedule of inoculations against diseases such as measles, diphtheria, and typhoid fever. Tetanus and flu shots are also administered in this way.

A third injection technique is **subcutaneous (s.c. or sub-Q)** delivery, in which a needle is inserted into the tissue just underneath the skin. Because skin has a less abundant blood supply relative to muscle, a subcutaneous injection has the slowest absorption time of all the injection techniques. It is best suited for situations in which it is desirable to have a precise control over the dosage and a steady absorption into the bloodstream. The skin, however, may be easily irritated by this procedure. As a result, only relatively small amounts of a drug can be injected under the skin, compared to the quantity that can be injected into a muscle or vein. When involved in drug abuse, subcutaneous injections are often referred to as *skin-popping*.

All injections require a needle to pierce the skin, so there is an inherent risk of bacterial or viral infection if the needle is not sterile. The practice of injecting heroin or cocaine with shared needles, for example, promotes the spread of infectious hepatitis and HIV (see Chapter 2). When administered orally, drugs do not have to be any more sterile than the foods we eat or the water we drink.

Inhalation

Next to ingesting a drug by mouth, the simplest way of receiving its effects is to inhale it in some form of gaseous or vaporous state. The alveoli within the lungs can be imagined as a huge surface area with blood vessels lying immediately behind them. Our bodies are so dependent on the oxygen in the air we breathe that we have evolved an extremely efficient system for getting oxygen to its destinations. As a consequence of this highly developed system, the psychoactive effect of an inhaled drug is even faster than a drug delivered through intravenous injection. Travelling from the lungs to the brain takes only five to eight seconds.

One way of delivering a drug through inhalation is to burn it and breathe in the smoke-borne particles in the air. Drugs administered through smoking include nicotine from cigarettes, opium, tetrahydrocannabinol (THC) from marijuana, free-base cocaine, crack cocaine, and crystallized forms of methamphetamine. Drugs such as paint thinners, gasoline, and glues can also be inhaled because they evaporate easily and the vapours travel freely through the air. In medical

intramuscular (i.m.): Into a muscle.
subcutaneous (s.c. or sub-Q): Underneath the skin.

© Roy Morsch/AGE Fotostock

Drugs administered by smoking and consumed by inhalation are absorbed extremely quickly, aided by a very efficient delivery system from the alveoli in the lungs to the bloodstream and from the bloodstream to the brain. Two men engaged in smoking crack cocaine are depicted here.

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settings, surgical anaesthetics are administered through inhalation because the concentration of the drug can be precisely controlled.

The principal disadvantage of inhaling smoked drugs, as you probably expect, arises from the long-term hazards of breathing particles in the air that contain not only the active drug but also tars and other substances produced by the burning process. In general, emphysema, asthma, and lung cancer can result from smoking (see Chapter 10). It is also possible, in any form of drug inhalation, that the linings leading from the throat to the lungs will be severely irritated over time.

Absorption Through the Skin or Membranes

Drug users over the ages have been quite creative in finding other routes through which drugs can be administered. One way is to sniff or snort a drug in dust or powder form into the nose. Once inside the nose, it adheres to thin mucous membranes and dissolves through the membranes into the bloodstream. This technique, referred to as an **intranasal** administration, is commonly used in taking snuff tobacco or cocaine. Prescription medications are becoming increasingly available in nasal-spray formulations, avoiding the need for needle injections or difficult-to-swallow pills.

Snuff tobacco, chewing tobacco, and cocaine-containing coca leaves can also be chewed without swallowing over a period of time or simply placed in the inner surface of the cheek and slowly absorbed through the membranes of the mouth. Nicotine chewing gums, available for those individuals who wish to quit tobacco smoking, work in a similar way. Nitroglycerin tablets for heart disease patients are typically administered **sublingually,** with the drug placed underneath the tongue and absorbed into the bloodstream.

At the opposite end of the body, medicines can be inserted as a suppository into the rectum, where the suppository gradually melts and the medicine is absorbed through thin rectal membranes into the bloodstream. This method is less reliable than oral administration, but it may be necessary if the individual is vomiting or unconscious at the time.

Another absorption technique involves a **transdermal patch,** which allows a drug to slowly diffuse through the skin. Transdermal patches have been used for long-term administration of nitroglycerin, estrogen, nicotine, and medications for motion sickness, Parkinson's disease, and Alzheimer's disease. Newly developed procedures to enhance the process of skin penetration include the promising technique of administering low-frequency ultrasound, which allows large molecules, such as those of insulin, to pass through the skin. Insulin administration is an especially interesting application because, until now, the only effective way of getting it into the bloodstream has been through needle injection.

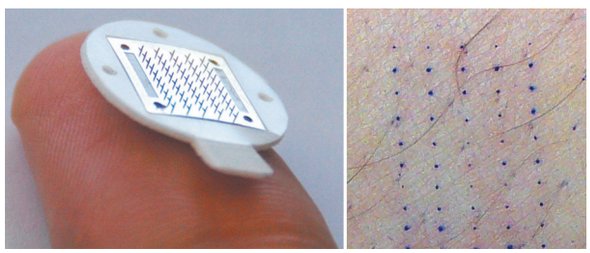
Alternative methods under development include small silicon chip patches containing a grid of microscopic needles that painlessly pierce the skin and allow the passage of large molecules into the bloodstream. Other techniques involve a mild electric current that propels the medication through the skin or the application of medication with special compounds that help the medication slip through skin pores. Advantages in nanotechnology have made it possible to provide "smart patches" that can be programmed to schedule specific doses of transdermal medication that match the fluctuating needs of the patient.[3]

Drugs . . . in Focus summarizes the various ways in which drugs can be administered into the body.

intranasal: Into the nasal cavity.

sublingual: Applied under the tongue.

transdermal patch: A device attached to the skin that slowly delivers the drug through skin absorption.



This skin patch contains a rectangular array of 50 microneedles, each 620 microns in length and thinner than a human hair. Tiny, painless epidermal punctures are created by pressing the needles against the skin. Each puncture acts as a conduit for medication to flow evenly from the skin patch into dermal capillaries and the bloodstream.

© 2012 National Academy of Sciences, U.S.A., Microneedles permit transdermal delivery of a skin-impermeant medication to humans. Daniel P. Wermeling, Stan L. Banks, David A. Hudson, Harvinder S. Gill, Jyoti Gumpta, Mark R. Prausnilz and Andra L. Sinchcomb. February 12, 2008, vol. 15, no. 6. www.pnasorg/cgi/doi/10.1073/pnas.0710355105. Photos courtesy Mark R. Prausnitz, Georgia Institute of Technology.

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DRUGS . . . IN FOCUS

Ways to Take Drugs: Routes of Administration

Oral Administration (by Mouth)

- Method: By swallowing or consuming in eating or drinking
- Advantages: Slow absorption time; possibility of rejecting poisons and overdoses
- Disadvantages: Slow absorption time; no immediate effect
- Examples: Medications in pill form, marijuana (baked in food), amphetamine and methamphetamine, barbiturates, LSD (swallowed or licked off paper), PCP, opium, methadone, codeine, caffeine, alcohol

Injection (by Hypodermic Syringe)

Intravenous Injection

- Method: By needle positioned into a vein
- Advantages: Very fast absorption time; immediate effects
- Disadvantages: Cannot be undone; risks of allergic reactions
- Examples: PCP, methamphetamine, heroin, methadone, morphine

Intramuscular Injection

- Method: By needle positioned into a large muscle
- Advantages: Quicker to administer than an intravenous injection
- Disadvantages: Somewhat slower absorption time than an intravenous injection; risk of piercing a vein by accident
- Examples: Vaccine inoculations

Subcutaneous Injection

- Method: By needle positioned underneath the skin
- Advantages: Easiest administration of all injection techniques
- Disadvantages: Slower absorption time than an intramuscular injection; risk of skin irritation and deterioration
- Examples: Heroin and other narcotics

Inhalation (by Breathing)

Smoking

- Method: By burning drug and breathing smoke-borne particles into the lungs
- Advantages: Extremely fast absorption time
- Disadvantages: Effect limited to time during which drug is being inhaled; risk of emphysema, asthma, and lung cancer from inhaling tars and hydrocarbons in the smoke; lung and throat irritation over chronic use
- Examples: Nicotine (from tobacco), marijuana, hashish, methamphetamine, ice or crystal methamphetamine, free-base cocaine, crack cocaine, PCP, heroin, and opium

Vaporous Inhalation

- Method: By breathing in vapours from drug
- Advantages: Extremely fast absorption time
- Disadvantages: Effect limited to time during which drug is being inhaled; lung and throat irritation over chronic use
- Examples: Surgical and dental anaesthetics, paint thinners, gasoline, cleaning fluid

Absorption (through Skin or Membranes)

- Method: By positioning drug against skin, inserting it against rectal membrane, snorting it against mucous membranes of the nose, or placing it under the tongue or against the cheek so it diffuses across into bloodstream
- Advantages: Quick absorption time
- Disadvantages: Irritation of skin or membranes
- Examples: Cocaine, amphetamine, methamphetamine, nicotine patches and gums, naltrexone (an opioid antagonist, see Chapter 5), snuff tobacco, coca leaves

How Drugs are Inactivated and Excreted

Having reviewed how a drug is absorbed into the bloodstream and, in the case of a psychoactive drug, into the brain, we can now consider the ways in which the body eliminates it. The most common means of elimination is through excretion in the urine after a series of actions in the liver and kidneys. Elimination also occurs through excretion in exhaled breath, feces, sweat, saliva, or (in the case of nursing mothers) breast milk.

The sequence of metabolic events leading to urinary excretion begins with a process called **biotransformation**, chiefly through the action of specific enzymes in the liver. The products of biotransformation, referred to as **metabolites**, are structurally modified forms of the original drug. Generally speaking, the goal of metabolism is to

biotransformation: The process of changing the molecular structure of a drug into forms that make it easier for the body to excrete it.

metabolite (me-TAB-oh-lite): A by-product resulting from the biotransformation process.

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make drugs water-soluble so they are passed along to the kidneys and eventually excreted in the urine. If they are less water-soluble, then they are reabsorbed into the intestines and excreted through defecation. On rare occasions, a drug may pass through the liver without any biotransformation at all and be excreted intact. The hallucinogenic drug *Amanita muscaria* (muscimol) is an example of this kind of drug (see Chapter 6).

A number of factors influence the process of biotransformation and urinary excretion and, in turn, the rate of elimination from the body. For most drugs, biotransformation rates will increase as a function of the drug's concentration in the bloodstream. In effect, the larger the quantity of a drug, the faster the body "tries" to get rid of it. An exception, however, is alcohol, for which the rate of biotransformation is constant, no matter how much alcohol has been ingested (see Chapter 8).

The activity of enzymes required for biotransformation may be increased or decreased by the presence of other drugs in the body. Enzymes are present throughout the body, but the most relevant to drug metabolism is a family of liver enzymes called cytochrome P450. Some drugs can act on these enzymes to reduce their activity and other increase their activity. *Enzyme induction* is when repeated drug taking results in a greater production of liver enzymes that metabolize the drug and other similar drugs. Conversely, *enzyme inhibition* is when repeated drug taking stops the action of specific liver enzymes, and metabolism of drugs slows down. A third scenario is *drug competition*, in which drugs taken in combination occupy all of the available liver enzymes, leaving the excess drugs nonmetabolized and resulting in dangerously toxic levels. An individual's age can also be a factor. Because enzyme activity levels in the liver decline after the age of 40, older people eliminate drugs more slowly than younger people. We will look at the consequences of drug interactions and individual differences in the next section of this chapter.

Finally, it is important to point out that drugs are gradually eliminated from the body at different rates simply on the basis of their chemical properties. In general, fat-soluble drugs are eliminated more slowly than water-soluble drugs. The index of how rapidly or slowly a particular drug is eliminated is referred to as its **elimination half-life**, defined as the amount of time it takes for the drug in the bloodstream to decline to 50% of its original concentration level. As an example, suppose the elimination half-life of Drug X is one hour. After one hour, the drug concentration would be one-half of the original; after two hours, it would be one-fourth of the original. After five hours, the concentration would be about 3% (1/32nd) of the original.

Many drugs, such as cocaine and nicotine, have elimination half-lives of only a few hours; marijuana and some prescription medications are examples of drugs with much longer half-lives.[4] Understanding the variation in the elimination rates of drugs and their metabolites is extremely important in the development of drug-testing procedures to detect drug-taking behaviour, a topic to be examined in Chapter 12.

Factors Determining the Behavioural Impact of Drugs

The type of delivery route into the bloodstream, as we have noted, places specific constraints upon the effect a drug may produce. Some drug effects are optimized by oral administration, whereas others require more direct access to the bloodstream. Other factors must be considered as well. If a drug is administered repeatedly, the timing of the administrations plays an important role in determining the final result. When two drugs are administered close together in time, we must also consider how these drugs might interact with each other in terms of their acute effects. The chronic effects of two drugs might interact as well. Finally, it is possible that two identical drugs taken by two individuals might have different effects, by virtue of the characteristics of the drug user at the time of administration. These four factors will now be considered.

Timing

All drugs, no matter how they are delivered, share some common characteristics when we consider their effects over time. There is initially an interval (the **latency period**) during which the concentration of the drug is increasing in the bloodstream but is not yet high enough for the behavioural effect of the drug to be detected. How long this latency period lasts is related generally to the absorption time of the drug. As the concentration of the drug continues to rise, the effect becomes stronger. A stage is eventually reached when the effect attains a maximum strength, even though the concentration in the blood continues to rise. This point

elimination half-life: The length of time it takes for a drug to be reduced to 50% of its equilibrium level in the bloodstream.

latency period: An interval of time during which the blood levels of a drug are not yet sufficient for a drug effect to be observed.

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is unfortunately the point at which the drug may produce undesirable side effects. One solution to this problem is to administer the drug in a time-release form (designated as controlled-release, extended-release, or sustained-release formulations). In this approach, a large dose is given initially to enable the drug effect to be felt; then smaller doses are programmed to be released at specific intervals afterward to postpone, up to 12 hours or so, the decline in the drug's concentration in the blood. The intention is to keep the concentration of the drug in the blood within a "therapeutic window"—high enough for the drug to be effective but low enough to avoid any toxic effects. When drugs are administered repeatedly, there is a risk that the second dose will boost the concentration of the drug in the blood too high before the effect of the first dose has had a chance to decline (Figure 3.1).

Drug Interactions

Two basic types of interactions may occur when two drugs are mixed together. In the first type, two drugs in combination may produce an acute effect that is greater than the effect of either drug administered separately. In some cases, the combination effect is merely *additive*. For example, if the effect of one drug alone is equivalent to a 4, and the effect of another drug is a 6, then the combined additive effect is equivalent to a value of 10.

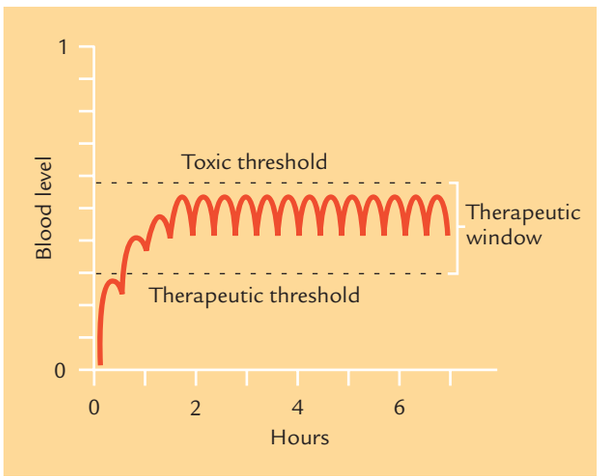

FIGURE 3.1

The therapeutic window. Time-release drugs are formulated to administer the drug in small amounts over time to stay above the threshold for a therapeutic effect but below the threshold for toxicity.

In other cases, however, the acute combination effect is *hyperadditive*, with the combined effect exceeding the sum of the individual drugs administered alone, as in the two drugs in the first example combining to a value of 13 or more. Any hyperadditive effect produced by a combination of two or more drugs is referred to as **synergism**. In some synergistic combinations, one drug may even double or triple the effect of another. It is also possible that one drug might have no effect at all unless it is taken simultaneously with another. This special form of synergism is called **potentiation**; it is as though a drug with no effect at all by itself, when combined with a drug having an effect of 6, produces a result equivalent to a 10. The danger of such interactions is that the combined effect of the drugs is so powerful as to become toxic. In extreme cases, this toxicity can be lethal.

In the second type of interaction, two drugs can be *antagonistic* if the acute effect of one drug is diminished to some degree when administered with another—a situation comparable to a drug with the effect of 6 and a drug with the effect of 4 combining to produce an effect of 3. Later chapters discuss drugs that are totally antagonistic to each other, in that the second exactly cancels out, or neutralizes, the effect of the first.

Cross-Tolerance and Cross-Dependence

If you were taking a barbiturate (a sedation-producing drug that acts to depress bodily functioning) for an extended length of time, and you developed a tolerance for its effect, you might also have developed a tolerance for another depressant drug, even though you had never taken the second one. In other words, it is possible for a tolerance effect for one drug to automatically induce a tolerance for another. This phenomenon, referred to as **cross-tolerance**, is commonly observed in the physiological and psychological effects of alcohol, barbiturates, and a class of antianxiety medications called benzodiazepines (Chapter 13).

synergism (SIN-er-jih-zum): The property of a drug interaction in which the combination effect of two drugs exceeds the effect of either drug administered alone.

potentiation: The property of a synergistic drug interaction in which one drug combined with another drug produces an enhanced effect when one of the drugs alone would have had no effect.

cross-tolerance: A phenomenon in which the tolerance that results from the chronic use of one drug induces a tolerance effect with regard to a second drug that has not been used before.

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As a result of cross-tolerance, an alcoholic will have already developed a tolerance for a barbiturate, or a barbiturate abuser will need a greater amount of an anesthetic when undergoing surgery.

We can view the interconnectedness of depressant drugs in another way as well. If withdrawal symptoms of one drug are relieved by administering another drug, then the two drugs show **cross-dependence**. In effect, one drug can substitute for whatever physiological effects have been produced by a second drug that has been discontinued. Unfortunately, cross-dependence provides a means for continuing an abused drug in the guise of a new one. If someone wanted to conceal a pattern of drinking from the family, for example, a dose of diazepam (Valium), an antianxiety medication, might suffice as a substitute for that "morning eye opener."[5]

Later in this chapter, we will examine the physiological mechanism that underlies the phenomena of cross-tolerance and cross-dependence.

Individual Differences

Some variations in drug effects may be related to an interaction between the drug itself and specific characteristics of the person taking the drug. One characteristic is an individual's weight. In general, a heavier person will require a greater amount of a drug than a lighter person to obtain an equivalent drug effect, all other things being equal. It is for this reason that drug dosages are expressed as a ratio of drug amount to a person's body weight. This ratio is typically expressed in metric terms, such as milligrams-per-kilogram (mg/kg).

Another characteristic is gender. Even if a man and a woman are exactly the same weight, differences in drug effects can still result on the basis of gender differences in body composition and sex hormones. Women have, on average, a higher proportion of fat, due to a greater fat-to-muscle ratio, and a lower proportion of water than men. When we look at the effects of alcohol consumption in terms of gender, we find that the lower water content (a factor that tends to dilute the alcohol in the body) in women makes them feel more intoxicated than men, even when the same amount of alcohol is consumed.

cross-dependence: A phenomenon in which one drug can be used to reduce the withdrawal symptoms following the discontinuance of another drug.

Relative to men, women also have reduced levels of enzymes that break down alcohol in the liver, resulting in higher alcohol levels in the blood and a higher level of intoxication.[6] We suspect that the lower level of alcohol biotransformation may be related to an increased level of estrogen and progesterone in women. Whether gender differences exist with regard to drugs other than alcohol is presently unknown.

Still another individual characteristic that influences the ways certain drugs affect the body is ethnic background. About 50% of all people of Asian descent, for example, show low levels of an enzyme called aldehyde dehydrogenase that normally breaks down alcohol in the liver shortly before it is excreted. With this particular deficiency, alcohol metabolites tend to build up in the blood, producing a faster heart rate, facial flushing, and nausea.[7] As a result, many Asians find drinking quite unpleasant.

Ethnic variability can be seen in terms of other drug effects as well. It has been found that Caucasians have a faster rate of biotransformation of antipsychotic and antianxiety medications than Asians and, as a result, end up with relatively lower concentrations of drugs in the blood. One consequence of this difference is in the area of psychiatric treatment. Asian schizophrenic patients require significantly lower doses of antipsychotic medication for their symptoms to improve, and they experience medication side effects at much lower doses than do Caucasian patients. Since other possible factors (such as diet, lifestyle, and environment) do not account for these differences, we can speculate that these differences have a genetic basis.[8]

In some cases, differences in the physiological response to a particular drug can explain differential patterns of drug-taking behaviour. For example, researchers have recently found that people of African descent who live in North America have a slower rate of nicotine metabolism following the smoking of cigarettes, relative to Caucasians. This finding might be the reason why African Americans, on average, report smoking fewer cigarettes per day than Caucasians. If we assume that an equivalent level of nicotine needs to be maintained in both populations, fewer cigarettes smoked but a higher level of nicotine absorbed per cigarette will produce the same effect as a greater number of cigarettes smoked but a lower nicotine level absorbed per cigarette. Consequently, African American smokers may be taking in and retaining relatively more nicotine per cigarette, and as a result not having to smoke as many cigarettes per day.[9]

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Quick Concept Check 3.1

Understanding Drug Interactions

Check your understanding of drug interactions by assuming the following values represent the effects of Drugs A, B, and C, when taken individually:

- Drug A 0
- Drug B 20
- Drug C 35

Identify the type of drug interaction when the following values represent the effect of two drugs in combination.

1. Drug A combined with Drug B 30
2. Drug B combined with Drug C 55
3. Drug A combined with Drug C 15
4. Drug B combined with Drug C 85
5. Drug B combined with Drug C 0
6. Drug A combined with Drug B 20

Answers: 1. potentiation 2. additive 3. antagonistic 4. synergistic (hyperadditive) 5. antagonistic 6. additive

Introducing the Nervous System

Before we can begin to deal with the specific impact of drugs on the brain, we need first to understand some basic facts about the overall organization of the *nervous system*, of which the brain is a part.

In simplest terms, the nervous system is designed to do two basic things: take in information from the environment around us and control our bodily responses so that we can live effectively in that environment. But, of course, we do a lot more than that. We interpret the information coming in, try to make sense of it, remember some of it for a later time, and more than occasionally generate some information on our own in a process called thinking.

We can understand these different functions in terms of divisions within the nervous system. In general, the nervous system is divided into the **central nervous system** (CNS), consisting of the brain and the spinal cord, and the **peripheral nervous system**, consisting of all the nerves and nerve fibres that connect the CNS to the environment and to our muscles and glands (Figure 3.2).

The Peripheral Nervous System

The peripheral nervous system (PNS) is responsible for taking sensory input from the outside world and sending it to the CNS. The CNS processes the information and, if a behavioural response is necessary, it sends output commands back to the PNS, which directly communicates with muscles and glands. On the input side, it includes the visual pathway, the auditory pathway, and other channels of sensory information about the world around us. On the output side, motor pathways in the PNS that control our reactions to that world generate two basic types of responses.

The first type, called a *somatic* response, is a voluntary reaction executed by skeletal muscles that are attached to bone. When you lift your arm, for example, you have executed a series of motor commands that ultimately results in contractions of flexor and extensor muscles. In this case, the movement is deliberate, conscious, and controlled.

central nervous system (CNS): The portion of the nervous system that consists of the spinal cord and the brain.

peripheral nervous system (PNS): The portion of the nervous system that consists of nerves and nerve fibres that carry information to the central nervous system and outward to muscles and glands.

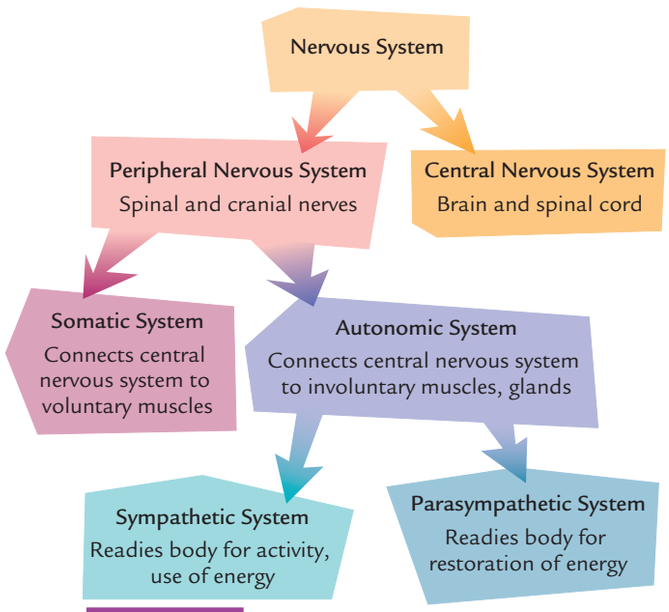

FIGURE 3.2

An "organizational chart" of the nervous system.

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A second type of reaction, called an *autonomic* response, is usually involuntary and executed by smooth muscles that form the walls of arteries, veins, capillaries, and internal organs, as well as cardiac muscles that form the walls of the heart. When you blush, for example, the capillaries are dilating, or enlarging, underneath the surface of your skin, an effect that produces a reddening colour and a feeling of warmth. As some of us know from personal experience, blushing often occurs when we do not want it to, and it is difficult to make it go away. And yet it is a reaction to a situation that has been processed through our sensory pathways and interpreted within the brain; in this case, some emotional content has triggered this autonomic response.

If we were to take the time to execute deliberate commands to breathe regularly, to have our hearts beat at an appropriate rate, or to carry out the thousands of changes that our internal organs make, we would not last very long. The autonomic control that has evolved is a product of the interplay of two subsystems, each delivered to smooth and cardiac muscles and to glands through its own set of nerve fibres. These subsystems of the PNS are referred to as the **sympathetic** and **parasympathetic** branches.

Sympathetic and Parasympathetic Responses

Autonomic responses are divided into two general categories (Figure 3.3). The first is oriented toward dealing with some kind of emergency or stress. If we are in a situation that is perceived as a threat to our internal

sympathetic nervous system: The portion of the autonomic nervous system that controls bodily changes that deal with stressful or emergency situations.

parasympathetic nervous system: The portion of the autonomic nervous system that controls the bodily changes that lead to increased nurturance, rest, and maintenance.

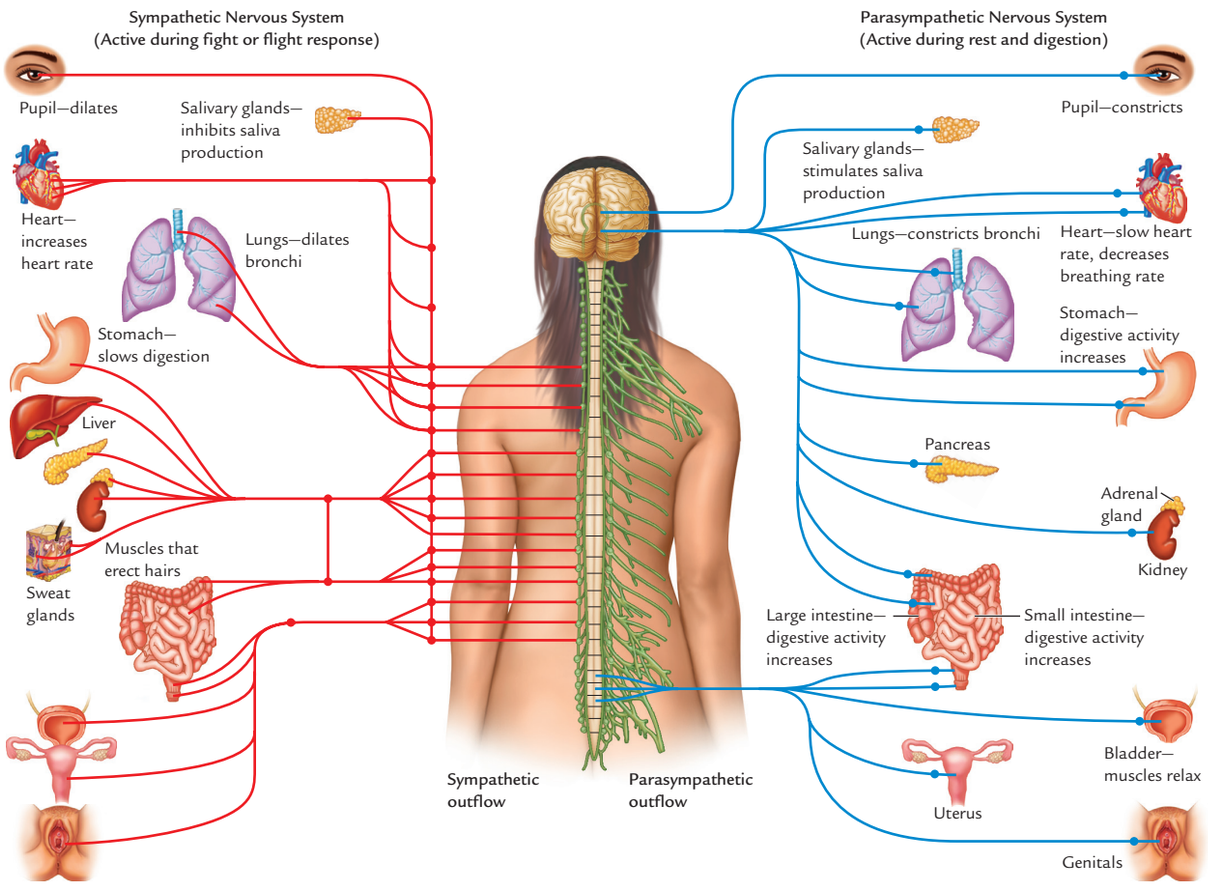

FIGURE 3.3

Functions of the sympathetic and parasympathetic branches of the autonomic nervous system.

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well-being or to our survival, the sympathetic system is in charge. During times of *sympathetic activation*, the heart rate goes up, blood pressure goes up, the bronchi in the lungs dilate to accommodate a greater amount of oxygen, the pupil dilates to allow more light into the eye, and other bodily systems alter their level of functioning so we are in a better position to fight, to flee, or simply to feel frightened. At the same time, the gastrointestinal tract is inhibited. It makes sense that we should not be digesting our lunch when we are battling for our lives.

The second category of response is totally opposite to the first. We cannot be "on alert" all our lives; we need some time to regroup our forces, to orient ourselves toward a state of calm and rest necessary for nurturance and internal maintenance. Heart rate and blood pressure now go down, bronchi and pupils constrict, and the gastrointestinal tract is now excited rather than inhibited. These and other changes constitute *parasympathetic activation*, and are an important counterpoint to the activation of the sympathetic system.

Some psychoactive drugs produce autonomic changes, in addition to their direct effects on the brain. They may produce a swing toward sympathetic activation (as with stimulants) or a swing toward parasympathetic activation (as with depressants).

The Central Nervous System

The central nervous system, located along the central axis of the body, consists of the *spinal cord* and the *brain*. It is here that interpretations of our sensory input occur, and the intricate processing of information is accomplished. Some of our sensory nerves, such as those originating at locations from the neck down, enter the CNS at the level of the spinal cord; others, such as those nerves coming from our eyes and ears, enter at the level of the brain. Complex information entering at the spinal cord is carried by neural pathways upward into the brain for further processing; the processing of simpler information may not involve the brain at all, resulting instead in merely reflexive responses.

The most important part of the CNS, of course, is the brain. It is nearly impossible to overestimate its role in our everyday lives. Every gesture we make, every feeling, every experience we have of our surroundings, every insight or memory, is a result of a complex, beautifully modulated pattern of activity among approximately 100 billion specialized cells called **neurons.** We owe our entire cognitive universe—all of what we are or think we are—to the functioning of these cells. It is here that psychoactive drugs do their work, for good or for bad.

Monkey Business Images/Shutterstock

During emergency situations, specific bodily changes are produced through stimulation of the sympathetic branch of the autonomic nervous system. First responders often function under prolonged sympathetic activation.

Understanding the Brain

Proceeding upward from the spinal cord, starting at the point where the CNS enlarges into the brain, neuroanatomists have classified brain tissue into three major sections: the *hindbrain*, the *midbrain*, and the *forebrain* (Figure 3.4). The older and more primitive systems of the brain tend to be underneath the newer and more sophisticated ones, so as we travel upward from hindbrain to midbrain to forebrain on our quick tour, we are dealing with structures that have evolved ever more recently and have greater involvement in complex behaviour. You can think of this arrangement in brain anatomy as similar to an archaeological dig, where the strata of previous civilizations extend downward into greater and greater antiquity. Understanding the brain in terms of the orderliness of its development over the span of evolutionary history helps to make sense of its complexity.

neuron: The specialized cell in the nervous system that receives and transmits information.

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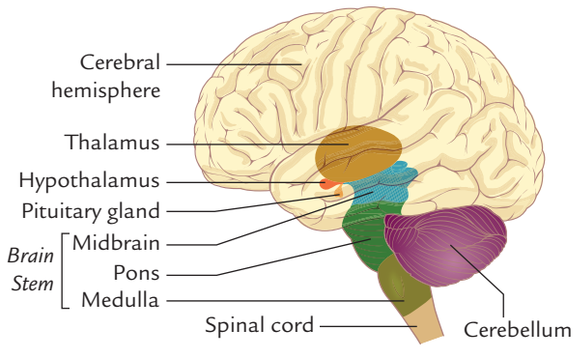

FIGURE 3.4

Basic structures of the human brain.

The Hindbrain

At the top of the spinal cord, neural tissue suddenly widens and enlarges into the hindbrain. The *medulla* lies at the point of the hindbrain where this enlargement has just begun. It is essentially the coordinator of the basic life-support systems in our body. Blood pressure is controlled here, as are the rhythms of breathing, heart rate, digestion, and even vomiting. Death would be seconds away were it not for the normal functioning of the medulla. Unfortunately, it is highly sensitive to opioids (Chapter 5), alcohol (Chapter 8), barbiturates, and other depressants (Chapter 13). When levels of any of these drugs are excessive in overdose cases, the respiratory controls in the medulla are inhibited, and death can result from asphyxiation (lack of breathing). Even if a person survives, the lack of oxygen in the blood while he or she is not breathing can result in severe brain damage. On a more positive note, the vomiting centre in the medulla is sensitive to the presence of poisons in the blood and is able to initiate vomiting to get rid of unwanted and potentially harmful substances.

Another hindbrain structure, situated just above the medulla, is the *pons*. We can view the pons in terms of our ability to maintain the necessary level of alertness to survive. Within the pons are structures that determine when we sleep and when we wake up, as well as the main portion of a structure called the *reticular formation* that energizes the rest of the brain to be alert to incoming information. Drugs affecting the patterns of our sleep influence centres in the pons and reticular formation.

Behind the medulla and the pons in the hindbrain is the *cerebellum*, an important structure for the maintenance of balance and for the execution of smooth movements of the body. The dizziness and lack of coordination we experience after consuming alcohol are attributable in large part to alcohol's depressive effect on the cerebellum.

The Midbrain

The midbrain, located just above the hindbrain, is a centre for the control of important sensory and motor reflexes, as well as for the processing of pain information.

Without a specific region of the midbrain called the *substantia nigra*, we would not be able to control the movements of our bodies effectively. The muscular tremors and other motor difficulties characteristic of Parkinson's disease is a result of degeneration of the substantia nigra. Unfortunately, symptoms that resemble Parkinson's disease have been frequently observed in patients taking antipsychotic medications for the treatment of schizophrenia. Efforts to develop antipsychotic medications without this adverse side effect will be explored in Chapter 15.

The Forebrain

Finally, in the uppermost section of the brain are the most recently evolved systems in the brain, collectively referred to as the forebrain. One of these forebrain systems, lying immediately above the midbrain, includes the *hypothalamus* and the *limbic system*. It is through these structures that we are able to carry out the motivational and emotional acts that ensure our survival as a species. Feeding behaviour, drinking behaviour, and sexual behaviour are controlled by the hypothalamus.

The limbic system surrounds the hypothalamus and plays a central role in organizing emotional behaviour during times of stress. Experimental lesions in points within the limbic system can turn a tame animal into a raging monster or a wild animal into a docile one. Not surprisingly, theories about the basis for psychological dependence have focused on the limbic system. Some of these ideas will be explored later in the chapter. Drugs that deal with symptoms of anxiety, depression, and schizophrenia affect regions within the limbic system.

The second forebrain system, and the most important from the standpoint of understanding human behaviour, is a two-sided, wrinkled sheet of neural tissue, with a thickness approximately equivalent to the height of a capital letter on this page. Overhanging nearly all of the brain, the hemispheres of the **cerebral cortex** resemble a giant walnut, an association that

cerebral cortex: The portion of the forebrain responsible for higher level information processing.

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prompted early physicians in the Middle Ages to prescribe walnuts as medicine for diseases of the brain (obviously a nutty idea).

When we arrive at the cerebral cortex (or neocortex, for short), we have arrived at the pinnacle of the brain both functionally and spatially. Specific regions of the cerebral cortex are concerned with processing visual, auditory, and somatosensory (touch) information, while other regions control the organization of complex and precise movements.

A large percentage of cortical tissue is devoted to the task of associating one piece of information with another. In the human brain, more than 80% of the cortex, called the *association cortex*, concerns itself with the integration of information. Of all the areas within the association cortex, the most recently evolved is a region closest to the front of the brain called the *prefrontal cortex*. Our higher-order, intellectual abilities (often referred to as *executive* functioning), as well as our personality characteristics, emerge from activity in this region. It has been speculated that a dysfunction in the prefrontal cortex may be associated with a loss of personal control with respect to the abuse of alcohol and other drugs.[10]

Quick Concept Check 3.2

Understanding Drugs and Brain Functioning

Check your understanding of the relationship between certain psychoactive drugs and functions of the brain by matching the part of the brain most likely to be affected by a given drug, given the description of its behavioural effects.

PSYCHOACTIVE DRUG EFFECTS	BRAIN AREAS AFFECTED
1. Drug X changes the pattern of your sleep.	cerebral cortex
2. Drug Y interferes with your intellectual functioning.	medulla
3. Drug Z raises your general arousal level.	cerebellum
4. Drug U interferes with your ability to control food intake.	pons
5. Drug V interferes with your ability to breathe.	hypothalamus
6. Drug W makes you very dizzy.	reticular formation

Answers: 1. pons 2. cerebral cortex 3. reticular formation 4. hypothalamus 5. medulla 6. cerebellum

Understanding the Neurochemistry of Psychoactive Drugs

Gaining some perspective about brain anatomy lays the foundation for an understanding of *where* certain psychoactive drugs are active, but it does not help us to understand *how* they work. To answer this second question, we need to know something about neurons themselves, the specialized cells that communicate information within the nervous system. As we will see, our understanding of neuronal communication has been critical for the insights we have gained into the nature of drug abuse.

Introducing Neurons

It is hard to imagine the enormous complexity of the human brain on a cellular level. There are an estimated 100 billion neurons in the adult brain, and an estimated 10 to 100 trillion structures (called synapses) where these neurons communicate with each other. A cubic millimetre of cerebral cortex alone contains roughly a billion synapses![11]

Not surprisingly, the brain is the most complex organ of the body. So how can we possibly begin to understand the brain amidst such complexity? Or rather, are our own brains sophisticated enough to understand how our brains work?

Fortunately, the task is not as insurmountable as it seems. The neuron itself, as the basic unit of the nervous system, can be understood in relatively simple terms. Imagine the neuron at any moment in time as a tiny device that can turn on or off, like a light switch. In terms of the neuron, the "on" state is accomplished by the generation of an **action potential**, sometimes referred to as a nerve impulse. Just as the neuron is the basic unit that forms the structure of the nervous system, the action potential is the basic event that forms the language of the nervous system.

The unique role of the neuron is to receive information and to transmit information, a task that it carries out through its three principal components: the *cell body*, the *dendrites*, and the *axon* (Figure 3.5). The cell body comprises the bulk of the neuron, and contains

action potential: an electrical message generated at the cell body that moves down the axon and causes release of neurotransmitters.

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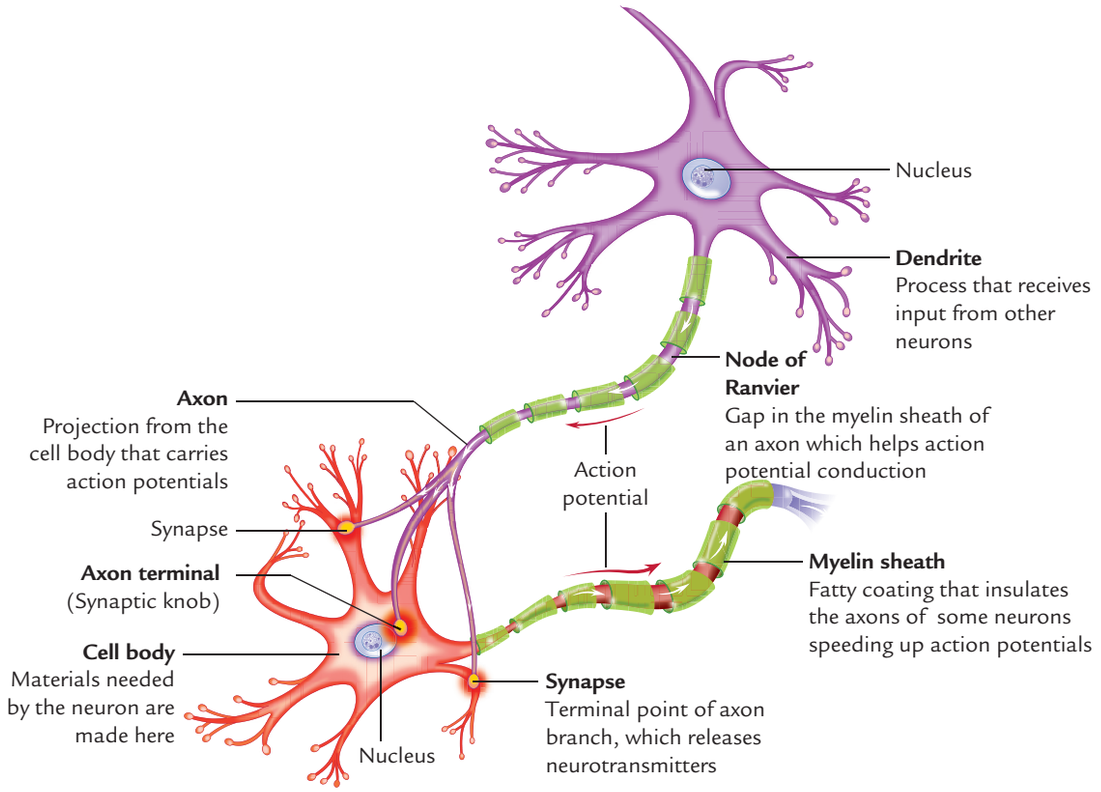

FIGURE 3.5

Basic structure of a neuron. The axon is shown surrounded by the myelin sheath, which increases the transmission speed of nerve impulses.

the nucleus, mitochondria, endoplasmic reticulum, and other organelles that are in other types of cells (such as muscle cells, skin cells, and blood cells).

The feature that makes the neuron specialized for communication purposes is its ability to signal to other neurons with electro-chemical signals. Neurons have unique appendages that extend from the cell body, some of them rather short and one quite long. The short ones are called dendrites, and represent the part of the neuron that receives information from the other neurons The long appendage, called the axon, is the part that transmits the action potential from the cell body to the end of the axon, called **presynaptic terminals.**

Action Potential

The neuron is the basic signalling device in the nervous system that uses individual signals called action potentials. The outside of a neuron, called the extracellular space, is covered with a distribution of positively charged and negatively charged ions that is different from the distribution of positive versus negatively charged ions inside the neuron. Many more sodium (Na^+) and chloride (Cl^-) ions are concentrated on the outside of a neuron, whereas more potassium (K^+) ions are concentrated on the inside of the neuron. This sets up a potential difference in electricity between the inside and outside of a neuron when the neuron is at rest. This is called the **resting membrane potential** and can range from about -40 to –90 mV depending on the type of neuron. When the neuron becomes active (more about this later) there are specific ion channels that open up and allow particular ions in or out. For example, voltage-dependent sodium channels can open up when the membrane potential becomes more positive, or depolarized, and allow Na^+ ions to flow into the neuron (Figure 3.6), which

presynaptic terminals: The end of the axon, where neurotransmitters are released.

resting membrane potential: The difference in electrical charge between the inside and the outside of the neuron (about –70 mV) when the neuron is not being stimulated or inhibited.

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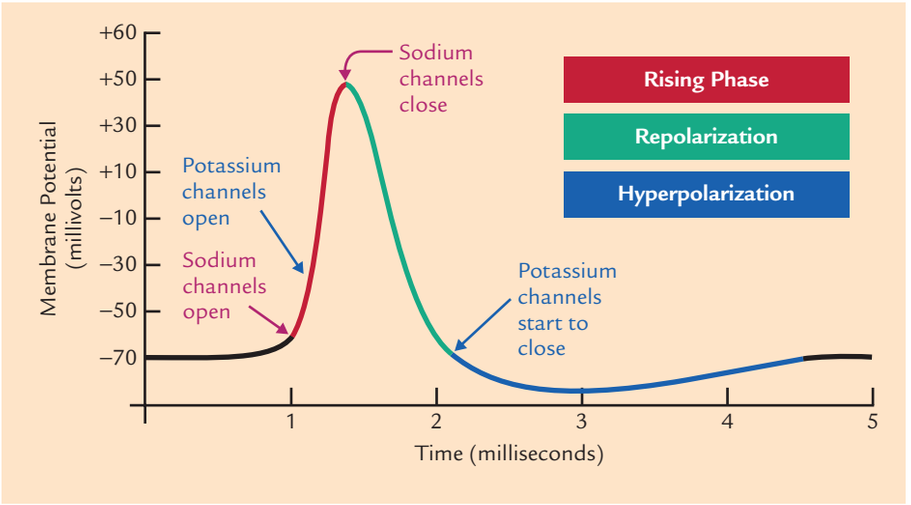

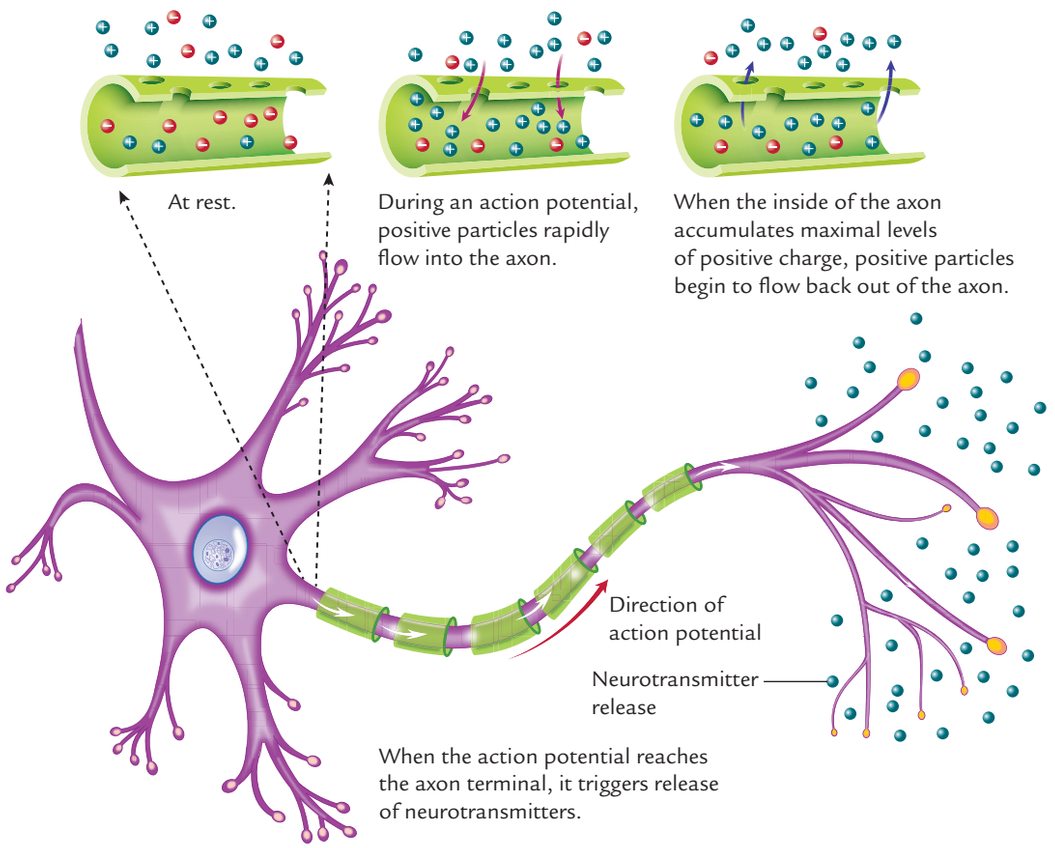

FIGURE 3.6

The action potential begins when positively charged Na^+ ions move into the axon during the rising phase. Potassium channels open slowly during the rising phase and become most active when the sodium channels close at the end of the rising phase. K^+ ions flow out of the axon, an action that brings the membrane potential back down (repolarization) and overshoots past the resting membrane potential (hyperpolarization). The action potential moves down the axon until it reaches the presynaptic terminals and causes neurotransmitter release.

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allows the action potential to move down the axon. During an action potential voltage-dependent potassium channels also open (although later and slower than the sodium channels) and allow K^+ ions to leave. The removal of a positive ion brings the membrane potential back to its polarized state and can even overshoot (that is, go below resting membrane potential), called hyperpolarization (Figure 3.6). When Na^+ channels open in the axon they trigger adjacent Na^+ channels to open, which moves the signal down the axon in a relatively all-or-none process all the way to the presynaptic terminal. The uneven balance of Na^+ and K^+ ions after an action potential is brought back to normal by a Na^+/K^+ pump that moves Na^+ back out and K^+ back in.

When an action potential is generated, it travels down the length of the axon at speeds up to 120 metres per second (432 km/h) until it reaches the axon's terminals. If we followed the nerve impulse down the length of the axon, starting from the cell body (sometimes a distance of as long as a metre), we would see that, toward its end, the axon diverges like the branches of a tree. These branches are called *axon collaterals*. At the terminal point of each of these branches are the small button-like *presynaptic terminals*. If nothing else happened here, the action potential would sputter out like a wet fuse. But, of course, there is more to the story. By virtue of junctures between neurons called **synapses**, action potentials from one neuron can influence the generation of action potentials in other neurons. This process is referred to as *synaptic transmission*, where the electrical signal—the action potential—becomes a chemical signal that is carried by neurotransmitters.

Synaptic Transmission

The neuronal changes that result from most psychoactive drugs occur because they alter at least one of the basic stages of synaptic transmission (Figure 3.7):

- The action potential moves into the axon terminal and causes specialized pores called *voltage-gated calcium channels* in the membrane to open. As their name implies, when they are opened by voltage change (caused by the action potential), they allow Ca^{2+} ions to move into the presynaptic terminal.
- Located inside the presynaptic terminals are enzymes that build chemical molecules called **neurotransmitters**. Specialized transporters package millions of the newly synthesized neurotransmitters into *synaptic vesicles*. When Ca^{2+} ions enter the terminal, they signal the synaptic vesicles to release their contents into the synapse.

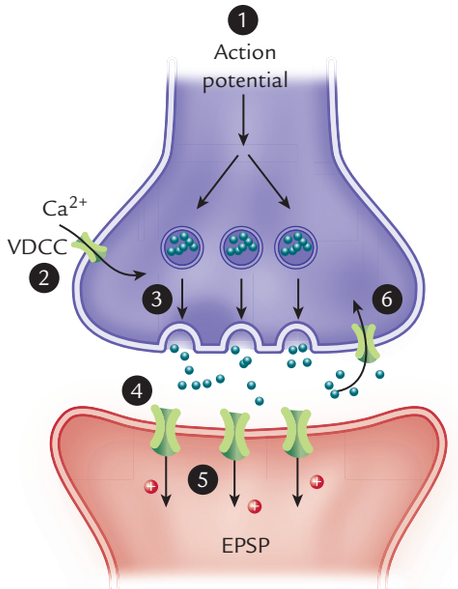

FIGURE 3.7

A close-up view of a single synapse and the steps in synaptic transmission. (1) Action potential invades the presynaptic terminal. (2) VDCCs open and Ca^{2+} ions move into the terminal. (3) Ca^{2+} ions trigger the synaptic vesicles to release their contents into the synapse. (4) The neurotransmitters move across the synapse and bind to their appropriate receptors (ionotropic glutamate receptor shown here). (5) The ionotropic or metabotropic receptors are activated and cause changes at the postsynaptic terminal (excitation shown here). (6) The neurotransmitters are taken back up into the presynaptic terminal or are broken down by enzymes in the synapse.

Source: Created by Trevor Hamilton.

- The neurotransmitters move to the postsynaptic terminal on the dendrite of the receiving neuron and each binds, like a key in a lock, to its specific receptor (Figure 3.8). If there are no receptors for the neurotransmitter, or those receptors are occupied by another substance, synaptic transmission will stop here. There are two subtypes of receptors that are very different in their structure and function and will be discussed in the next section.

synapse (SIN-apse): The juncture between neurons. It consists of a presynaptic terminal, the intervening gap, and a *postsynaptic terminal* containing receptor sites on the receiving neuron.

neurotransmitter: A chemical substance that a neuron uses to communicate information at the synapse.

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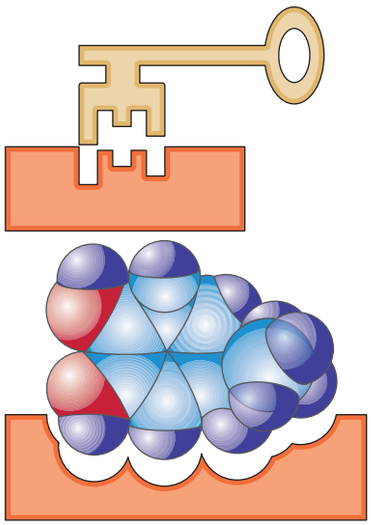

FIGURE 3.8

The lock-and-key model of neurotransmitter binding.

- Once the neurotransmitter binds to the receptor, it is expelled and transported back to the presynaptic terminal. This process, called **reuptake**, is essentially a way of getting the neurotransmitter back to the presynaptic terminal, where it can be packaged into another synaptic vesicle and released again (Figure 3.7). Neurotransmitters can also be broken down by enzymes in the synapse or taken up by adjacent glial cells.

Ionotropic and Metabotropic Receptors

When a neurotransmitter binds to a receptor the properties of the receptor itself will determine what happens in the dendrite of the postsynaptic neuron. There could be a fast excitation or inhibition, or a longer lasting intracellular event. Two general types of receptors can be present on the postsynaptic terminal (Figure 3.9).

Ionotropic receptors have a hollow pore (channel) that will open with neurotransmitter binding and allow specific ions through. One type of ionotropic receptor is a *ligand-gated ion channel*, and is very similar to a voltage-dependent channel, except these are activated by a molecule (ligand), rather than a voltage change. For example, glutamate is the most common excitatory neurotransmitter and when it binds to its ionotropic receptors, Na^+ ions flow into the dendrite. When an excitatory ion flows into the postsynaptic terminal it is called an *excitatory postsynaptic potential* (EPSP). On the contrary, when the neurotransmitter GABA, the most common inhibitory neurotransmitter, binds to its ionotropic receptor, Cl^- ions flow in, and this is called an *inhibitory postsynaptic potential* (IPSP). Many

reuptake: The process by which a neurotransmitter is transported from the synapse back up into the presynaptic terminal.

ionotropic receptor: A cell membrane receptor-ion channel complex that allows specific ions to pass through when the receptor is activated.

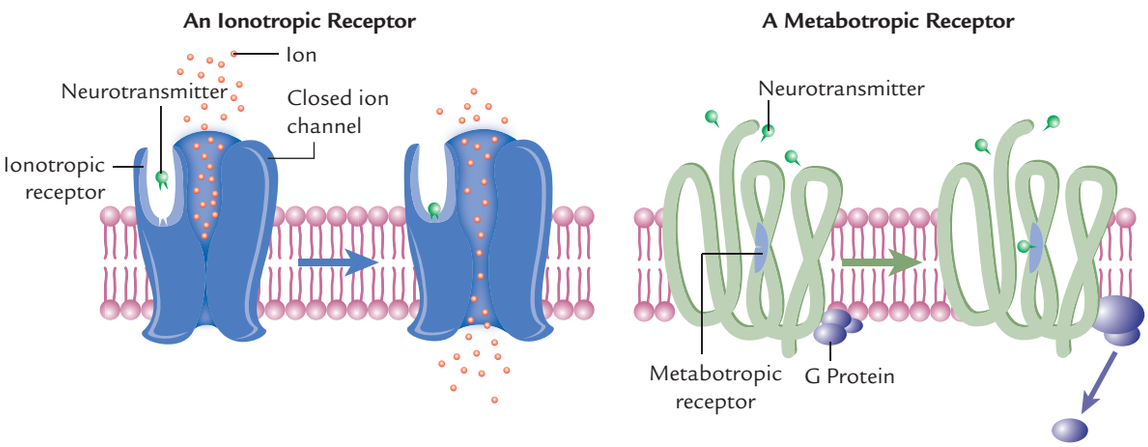

FIGURE 3.9

Ionotropic and metabotropic receptors. *A* When a neurotransmitter binds to an ionotropic receptor, this can result in the fast opening of ion channels that are specific to different types of ions. The direction of ion flow will depend on the concentration of the ions inside and outside of the neuron and the membrane potential. This can result in excitation or inhibition of the neuron. *B* When neurotransmitters bind to metabotropic receptors, a signalling protein activates other molecules called G proteins. These G proteins can move inside the neuron and cause many different slow intracellular changes, like the closing of an ion channel or the activation of a second messenger.

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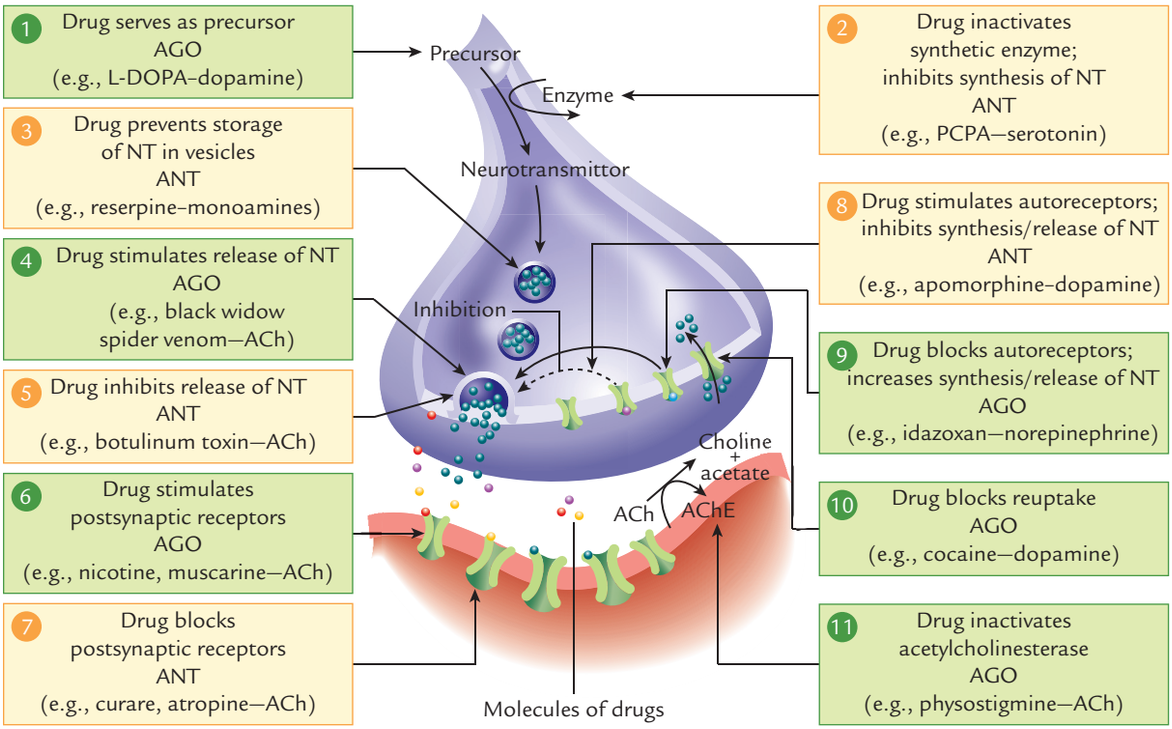

FIGURE 3.10

Drug alteration of synaptic transmission. There are many ways that an agonist (AGO, blue boxes) can facilitate synaptic transmission. Conversely, there are many ways that an antagonist (ANT, red boxes) can decrease synaptic transmission.

EPSPs that occur on the dendrites and travel passively to the cell body can trigger an action potential in the axon hillock (Figure 3.10). IPSPs can act to decrease the strength of EPSPs, and thus prevent action potentials from happening. Remember that each neuron gets input from thousands of other neurons at least, so it is the combination of EPSPs and IPSPs that will determine whether that neuron will fire. When EPSPs from multiple synapses in the dendritic tree act together, it is called *spatial summation*. A similar additive mechanism called *temporal summation* is when synapses repeatedly fire, causing a much larger EPSP.

Metabotropic receptors do not have an ion channel that opens or closes. Instead, they are connected to G proteins (guanosine-triphosphate-sensitive proteins). When metabotropic receptors are activated, they trigger the G protein to break into subunits that move about the inside of the neuron. These subunits can have a variety of functions including the alteration of the function of other receptors and the creation of second messengers. Generally, the activation of these receptors causes relatively slow intracellular changes with a wide variety of effects. *Autoreceptors* are metabotropic receptors that are located on the presynaptic terminal; *autoreceptors* are specialized structures that respond to the neurotransmitter that the neuron releases. This seems backward, but autoreceptors play an important role in detecting the amount of neurotransmitter present in the synapse. Their activation feeds back into the presynaptic terminal and can decrease future neurotransmitter release.

Agonists and Antagonists

When a drug causes a change in behaviour, on a fundamental level, this change likely occurs because the drug has bound to a receptor and altered synaptic transmission. For example, when an addict takes cocaine intranasally it increases the amount of dopamine, serotonin,

metabotropic receptor: A cell membrane receptor that is linked to a G protein. Activation results in the production of a second messenger that can have a variety of intracellular functions.

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and norepinephrine in the synapse, and this causes many of the stimulant effects. This is an example of an **agonist**, which is a substance that can act like a neurotransmitter and can bind to a receptor to cause a facilitation of synaptic transmission. Figure 3.10 shows many of the ways that drugs can act as agonists (notice not all agonists bind to receptors). An **antagonist** has the opposite action; it decreases synaptic transmission. An example of an antagonist is botulinum toxin that prevents the release of acetylcholine. Some celebrities have this injected cosmetically because it reduces muscle contraction, and therefore stops facial wrinkles. An example of an agonist that may be more familiar to you is alcohol, which activates GABAA receptors, and causes sedation and in extreme cases, death. Again, there are many ways that a drug can act as an antagonist (Figure 3.10).

Major Neurotransmitters

Glutamate is a small amino acid that is the most common *excitatory* neurotransmitter and has both ionotropic and metabotropic receptors. When glutamate binds to one of its ionotropic receptors (AMPA, kainite, or NMDA) it causes depolarization of the postsynaptic terminal, and there is an increased probability that the neuron will fire an action potential. In fact, the NMDA receptor is very important in two cellular forms of learning and memory called *long-term potentiation* and *long-term depression*. There is also a close connection between glutamate activity and the abuse potential of several psychoactive drugs. The action of two dissociative anaesthetics with hallucinogenic properties, phencyclidine (PCP, also known as angel dust) and ketamine, are associated with the blocking of NMDA receptors (see Chapter 6). On the other hand, recent pharmacological research has pointed to the activation of subtypes of metabotropic glutamate receptors as a critical element in drug craving and drug-abuse relapse with respect to cocaine, nicotine, alcohol, and heroin. As a result, the current development of new drugs that block glutamate receptors of the latter type shows great promise in drug-abuse treatment.[12]

Gamma aminobutyric acid (GABA) is a small amino acid like glutamate and is the most common *inhibitory* neurotransmitter throughout the brain. GABA also has both ionotropic ($GABA_A$) and metabotropic ($GABA_B$) receptors. Antianxiety medications, also called *anxiolytics*, stimulate $GABA_A$ receptors, providing a reduction in feelings of stress and fear, as will be discussed in Chapter 13. Since this neurotransmitter is a major source of inhibition in the brain, it should not be surprising that anticovulsant medications that increase action at GABA receptors are commonly prescribed to treat epileptic seizures.

Acetylcholine was the first molecule to have been firmly established as a neurotransmitter by Otto Loewi in 1921. It is released at all synapses between neurons and muscles, called *neuromuscular junctions*, as well as throughout the brain. Both ionotropic and metabotropic receptor sites are sensitive to acetylcholine.

Muscarinic acetylcholine receptors (mAChRs) are metabotropic receptors that are named because they are responsive to the drug muscarine. If a drug is antimuscarinic, it means it interferes with the role of acetylcholine in stimulating parasympathetic reactions of the body. Examples are atropine and scopolamine (see Chapter 6). A short-acting atropine-like solution, topically applied to the eyes, is used by ophthalmologists during an eye examination to cause the pupils to dilate by inhibiting the parasympathetic tendency for the pupils to constrict, making it possible to examine the retina.

Nicotinic acetylcholine receptors (nAChRs) are ionotropic and so named because they are responsive to nicotine (see Chapter 10). They are found near the end points of motor neurons, where skeletal muscles are innervated, as well as throughout the cerebral cortex. Some nicotinic antagonists, such as the poison *curare*, affect these motor neurons so dramatically that the body can become paralyzed within seconds. Deficiencies in acetylcholine or in nicotinic receptors have been tied to Alzheimer's disease, a condition resulting in memory loss and disorientation.

Norepinephrine, or **noradrenaline**, is concentrated in the hypothalamus and limbic system but is also found throughout the brain. In the peripheral nervous system, it is the principal neurotransmitter for sympathetic

agonist: A substance that facilitates synaptic transmission.

antagonist: A substance that decreases synaptic transmission.

glutamate (GLU-ta-mate): The most common excitatory neurotransmitter in the brain. Glutamate receptors are associated with actions of PCP and ketamine and with feelings of drug craving.

gamma aminobutyric acid (GABA) (GAM-ma a-MEEN-o-byoo-TEER-ik ASS-id; GAB-AH): The most common inhibitory neurotransmitter in the brain. Antianxiety and anticonvulsant drugs tend to facilitate the activity of GABA receptors in the brain.

acetylcholine (a-SEE-til-KOH-leen): A neurotransmitter active in the parasympathetic autonomic nervous system, cerebral cortex, and peripheral somatic nerves.

norepinephrine (NOR-ep-ih-NEH-frin), or **noradrenaline:** A neurotransmitter active in the sympathetic autonomic nervous system and in many regions of the brain.

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autonomic activation, but its role there is independent of its effects in the brain. Norepinephrine helps to regulate our mood states; Chapter 15 will discuss how drugs that boost the levels of norepinephrine also help relieve symptoms of depression.

Dopamine binds to metabotropic dopamine receptors that affect three important aspects of our behaviour. The first aspect is motor control: the ability to start a movement when we want to; to stop it when we want to; and to execute the movement in a smooth, precisely determined manner. Specifically, Parkinson's disease is a result of a degeneration of dopamine-releasing neurons in the substantia nigra of the midbrain. The second aspect is action in the limbic system, where dopamine can influence learning and memory, and emotionality.[13] Problems in dopamine-releasing neurons in the cortex and limbic system are strongly suspected to be at the root of schizophrenia. The role of dopamine in schizophrenia and efforts to develop drugs that relieve schizophrenic symptoms will be discussed in Chapter 15. Third, as we will see shortly, dopamine in the brain plays a major role in producing the craving that encourages a continuing pattern of compulsive drug-taking behaviour.

dopamine (DOPE-ah-meen): A neurotransmitter in the brain whose activity is related to emotionality and motor control.

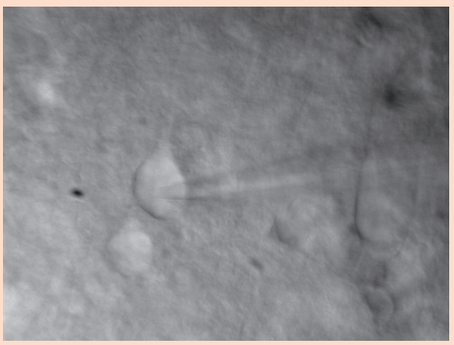
FPO

PORTRAIT

Quentin Pittman—Understanding Neuronal Communication One Cell at a Time

Researchers can investigate how a drug works by observing its impact on behaviour, which can provide many insights. However, other pharmacologists investigate the impact that drugs have on the brain by studying individual living neurons. Quentin Pittman and his neurophysiology laboratory at the University of Calgary do just this.

With a specialized technique called intracellular patch-clamp recording, researchers can look under a microscope and move a tiny, hollow, glass electrode close to an individual neuron (see picture below). Once they are close enough, they form a tight seal with the neuron, then puncture the membrane, and can record electrical activity (action potentials, EPSPs, IPSPs) from only that neuron. This is because the electrode is filled with an artificial solution that mimics the inside contents of the neuron, which keeps it alive. Once the researchers accomplish this goal, they can begin investigating how this neuron behaves.



Trevor Hamilton

One of the Pittman laboratory's many areas of research is investigating the action of the receptors activated by cannabis (marijuana), called cannabinoid receptors. The Pittman research lab has discovered that in an area of the hypothalamus called the supraoptic nucleus, endocannabinoids naturally help to control the release of important hormones into the bloodstream. This mechanism is essential for keeping natural homeostasis in the body, including regulation of eating behaviour. Pittman researchers have also identified a new form of a cannabinoid receptor that has never before been found in the brain.

Quentin Pittman is a Professor in the Department of Physiology and Pharmacology at the University of Calgary and an education director for the Hotchkiss Brain Institute, and was inducted into the Royal Society of Canada (RSC) in 2010 for his contributions to neuroscience and physiology. The RSC was established in 1882 as Canada's National Academy of distinguished scholars, artists, and scientists, and now contains about 2000 Canadians. Other famous members include Sir Sandford Fleming, who developed worldwide standard time zones and made the first postage stamp in Canada, and Sir William Osler, who was a revolutionary physician who shaped much of modern medicine and had over 1500 scientific publications.

Sources: Crosby, K. M., Inoue, W., Pittman, Q. J., & Bains, J.S. (2011). Endocannabinoids gate state-dependent plasticity of synaptic inhibition in feeding circuits. *Neuron*, *71*(3), 529–541. doi:10.1016/j.neuron.2011.06.006; McDonald, N. A., Kuzmiski, J. B., Naderi, N., Schwab, Y., & Pittman, Q.J. (2008). Endogenous modulators of synaptic transmission: cannabinoid regulation in the supraoptic nucleus. *Prog Brain Res*, *170*, 129–136. doi:10.1016/S0079-6123(08)00412-3. Review.

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Serotonin, or **5-Hydroxytryptophan** (**5-HT**) is concentrated in the pons and medulla, in the limbic system, and in the cortex. At the level of the hindbrain, serotonin plays an important role in regulating patterns of sleep. At the level of the limbic system, it shares with norepinephrine responsibility for establishing appropriate mood levels, avoiding wild swings upward that result in mania or wild swings downward that result in depression. As you can predict, many drugs that relieve mania and depression act upon serotonin-releasing neurons. Several hallucinogenic drugs, such as LSD, stimulate serotonin-releasing neurons in the cortex, a topic that will be explored further in Chapter 6.

Endorphins are a group of natural brain-produced painkillers and bear a remarkable resemblance to morphine. Endorphins play an important role in the emotional aspects of our lives. Chapter 5 will discuss how the discovery of endorphins has helped us understand more clearly the nature of opiate dependence.

Another group of brain-produced chemicals called **endocannabinoids** bear a close resemblance to the active ingredient in marijuana (Portrait on Quentin Pittman, and see Chapter 7). An understanding of neurochemicals such as endorphins and endocannabinoids helps to shed light on the mechanisms for the psychoactive effects of opioids and marijuana respectively (see Drugs . . . in Focus).

serotonin (5-HT) (SER-ah-TOH-nin), or **5-Hydroxytryptophan (5-HT):** A neurotransmitter in the brain whose activity is related to emotionality and sleep patterns.

endorphins (en-DOR-fins): A class of chemical substances, produced in the brain and elsewhere in the body, that act on the same opiate receptors as morphine, heroin, and codeine.

endocannabinoids (EN-doh-ca-NAB-ih-noids): Brain-produced chemicals that mimic the effects of the active ingredient in marijuana and other cannabis products.

DRUGS . . . IN FOCUS

Endorphins, Endocannabinoids, and the "Runner's High"

There has been great progress in our understanding of how specific psychoactive drugs (opioids and marijuana, respectively) work at a biochemical level in the brain. The essential message from neuroscience research is that these drugs produce their physiological and behavioural effects by virtue of triggering chemicals and receptors that have existed in our brains throughout our evolutionary history. They shed light on how the brain works on a day-to-day basis and at crucial times in our lives.

Endorphins, for example, have been related to the underlying process of pain control. In stressful circumstances, people can become temporarily analgesic (relatively insensitive to pain) without any external drugs. There are well-documented cases of soldiers who have ignored their injuries during the heat of battle, athletes who are unaware of their pain until the game is over, and individuals in primitive societies who endure painful religious rituals without complaint. Increased levels of endorphins are believed to contribute to these phenomena.

In another line of evidence, the effects of the Chinese technique of analgesic acupuncture (the inserting of needles into the skin at precisely defined points in the body to relieve pain) have been found to be completely reversible by naloxone (a specific antagonist to endorphins, see Chapter 5). It is reasonable, therefore, to conclude that the beneficial effects of acupuncture result from increased levels of endorphins.

Endorphin levels measured in the placental bloodstream of pregnant women near to the time of childbirth are greatly elevated from levels normally present in nonpregnant women, and they reach a peak during labour itself. It is believed that, as a result, women in labour are enduring less pain than they would experience if these endorphin levels were unchanged. In other words, endorphins may protect them against an even greater amount of discomfort.

With respect to the "runner's high," the feeling of calm and euphoria that many individuals report following prolonged exercise, endorphins may play a role. But recently, attention has been drawn to another group of brain-produced chemicals called endocannabinoids, so-called because they mimic the physiological effects of cannabis products such as marijuana. The *endo* prefix in both endorphins and endocannabinoids refers to the fact that these chemicals are produced within the body rather than exogenous substances like drugs that are brought in from outside the nervous system.

It has been found that 50 minutes of hard running on a treadmill or riding a stationary bicycle significantly increases levels of endocannabinoids in the blood. Since endocannabinoids are small molecules, they can pass through the blood–brain barrier (to be described later in the chapter) and produce the calming and free-form sense of well-being that is associated with marijuana. Experiments have yet to be carried out that would establish a causal link between activation of endocannabinoids in the brain and the subjective experience of a "runner's high," but the circumstantial evidence is certainly intriguing.

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Physiological Aspects of Drug-Taking Behaviour

There are three important concepts related to drug-taking behaviour that arise from the physiology of the nervous system. The first is the blood–brain barrier, the second is the physiological basis for drug tolerance, and the third is the current hypothesis that psychological dependence is directly related to activity in a specific area of the brain.

The Blood–Brain Barrier

Mentioned earlier in the chapter was a barrier that restricts the passage of drugs and other molecules from the bloodstream to the brain. This exclusionary system is called the **blood–brain barrier**. Because it is important to supply the brain with nutrients (oxygen, glucose, and amino acids) and to remove waste, but also to keep out dangerous toxins and large molecules, we are quite fortunate to have this "gatekeeper." This keeps the environment of the brain free from the biochemical ups and downs that are a fact of life in the bloodstream. The key factor in determining whether a drug passes through the blood–brain barrier is the degree to which that drug is *lipid-soluble*.

Despite the obstacles, many types of drugs easily pass into the brain: nicotine, alcohol, cocaine, barbiturates, and caffeine, to name a few. Among the opiates, heroin, which is highly lipid-soluble, crosses the blood–brain barrier faster and more completely than morphine. Penicillin, by contrast, does not cross the blood-brain barrier because it is not fat-soluble. Consequently, penicillin can be used as an antibiotic treatment only for infections outside the brain.[14]

The presence of a blood–brain barrier is an issue not only for the study of psychoactive drugs but also for certain medical treatments. For example, one of the effective treatments for Parkinson's disease is administration of the drug L-Dopa, a shortened name for levodopa. The reason for using this drug stems from the root cause of Parkinson's disease: death of neurons in the substantia nigra that make dopamine. Taking dopamine itself is of no help, since its lack of lipid-solubility excludes it from getting to the brain. Fortunately, L-Dopa, a metabolic precursor to dopamine, is lipid-soluble. Therefore, L-Dopa can enter the brain and then get converted into dopamine. As a result, there is a rise in dopamine levels in the brain, and the symptoms of Parkinson's disease are relieved. Unfortunately, as Parkinson's disease progresses L-Dopa treatment becomes increasingly ineffective.[15]

It has recently become possible to create lipid-soluble molecules in the laboratory rather than finding them in nature. Pharmacologists have succeeded in combining protein-based drugs that are presently excluded by the blood–brain barrier with a fatty acid, enabling the drugs to slip through into the brain. It may be possible in the future to design special proteins ("smart proteins") that not only ferry drugs across the barrier but also regulate the release of the drugs once they are in the brain.[16]

Biochemical Processes Underlying Drug Tolerance

The last chapter considered the phenomenon of drug tolerance as a behavioural effect accomplished through Pavlovian conditioning. Tolerance can also be examined in terms of two types of physiological processes, one occurring in the liver and the other occurring in the neuron itself.

In the first type, called *metabolic* (*dispositional*) *tolerance*, a drug may facilitate, over repeated administrations, the processes that produce the drug's biotransformation in the liver. The rate of alcohol elimination, for example, increases over time if alcohol is ingested repeatedly over an extended period. When the liver breaks down the drug faster than it had initially, a smaller amount is left available for absorption into the blood. In the case of alcohol, the habitual drinker feels less of an alcoholic effect and compensates by increasing the amount consumed (see enzyme induction earlier in this chapter).

In the second type of physiological process, called *cellular* (*pharmacodynamic*) *tolerance*, changes occur in the synapses of neurons themselves. Receptors that have been stimulated by the drug over time may become less sensitive or removed from the synapse altogether, called *receptor down-regulation*. The result is a decreased effect of the drug. On the contrary, repeated blocking of receptors by a drug over time may cause a compensatory reaction, such as an increase in the number of receptors or an increase in the amount of neurotransmitter released (*receptor up-regulation*).[17]

Instances of cross-tolerance and cross-dependence can be explained by the fact that we are dealing with multiple drugs that bind to the same receptors in the brain. Imagine that two or more drugs activated different sites on the same receptor; the receptor itself would then not be able to "tell them apart." As far as the receptor was concerned, the effect would be the same. The neuronal effects of the drugs over an extended period of time would be equivalent and interchangeable, producing the effects of cross-tolerance and cross-dependence. In general, drugs that have similar psychoactive effects share common receptors.

blood–brain barrier: A specialized separation between the bloodstream and central nervous system that keeps toxins and large molecules out of the brain.

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Physiological Factors in Psychological Dependence

Amphetamines, cocaine, heroin, alcohol, and nicotine may be very different from a pharmacological standpoint, but they are remarkably similar in the way people and animals react to them. There is a tremendous feeling of satisfaction as these drugs enter the bloodstream and the brain, and an intense craving for repeating the experience. The parallels are numerous enough to suggest the existence of a common physiological process in the brain that links them all together. It is not a coincidence that there is a system of neurons near the hypothalamus and limbic system that animals will work hard to stimulate electrically. We cannot say how they are feeling at the time, but their behaviour indicates that they want to "turn on" this region of their brains.

Two of the key elements in the rewarding effect of these psychoactive drugs are dopamine and a grouping of neurons lying in a region of the limbic system called the **nucleus accumbens**. In 1954, at McGill University in Montreal, James Olds and Peter Milner discovered that electrical stimulation of this brain area acted like a rewarding signal.[18] Other studies found that when animals are injected with amphetamines, heroin, cocaine, alcohol, or nicotine, there is a release of dopamine in the nucleus accumbens.[19]

Administration of any substance that interferes with the action of dopamine in this region eliminates the desire of animals to work for the self-administration of these abused drugs. Although we cannot say, of course, that these animals no longer experience feelings of craving as a result, you will recall that self-administration behaviour in animals closely parallels the pattern of human behaviour that characterizes psychological dependence. Therefore, these studies can be used to understand the neural changes caused by drug abuse. Considering the evidence now in hand, a persuasive argument can be made that dopamine-related processes in the nucleus accumbens underlie the reinforcing effects of many abused drugs. There is also research showing an involvement of the nucleus accumbens with compulsive gambling and compulsive eating disorders.[20]

It is not hard to see the applications to the real-world treatment of drug dependence. Drugs that affect activity in the nucleus accumbens are currently being developed to reduce the feelings of craving that cause drug-dependent individuals to relapse (Health Line).[21]

nucleus accumbens (NEW-clee-us ac-CUM-buns): A region in the limbic system of the brain considered to be responsible for the rewarding effects of many drugs of abuse.

Health Line Drug Craving and the Insula of the Brain

They were 32 former cigarette smokers, reporting a minimum of five cigarettes a day for two years or more. They had all suffered some degree of brain injury. They had all reported how difficult it was to stop smoking. Sixteen of the smokers, however, found themselves capable of stopping easily following their injury. Why were these particular 16 individuals so lucky?

It turns out that it was considerably more likely for these smokers to quit smoking if brain damage had included a prune-shaped area under the frontal lobes of the cerebral cortex called the *insula*. Twelve out of 13 with insula damage quit easily, whereas only four out of 19 with damage that did *not* include the insula were able to do so. The insula-damage group had an odds ratio, regarding their likelihood of smoking cessation, of approximately 22 (see Chapter 2). In other words, they were 22 times more likely to stop cigarette smoking than the non-insula-damage group.

This relatively small study, reported in 2007, has had a major impact on our understanding of the neurological basis for drug dependence. A neuroimaging study in a group of drug abusers, for example, showed increased insula activity to be correlated with subjective feelings of drug craving when they viewed a series of drug-related images. In a study of animals made dependent on amphetamine, the inactivation of the insula in their brains was shown to prevent their urge to seek out amphetamine in a laboratory environment. An accumulating body of research points to the importance of the insula in the neural circuitry that maintains substance dependence, but also to the complex decision-making process that underlies urges for pleasurable outcomes in our lives.

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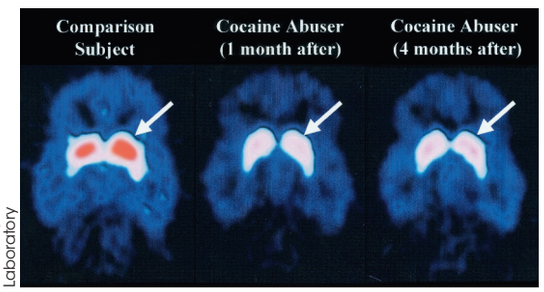
Research on the influence of dopamine and dopamine receptors in drug dependence has provided insight into the question of why some individuals may be more susceptible than others to drug-taking behaviour. In one study, 23 drug-free men with no history of drug abuse were given doses of methylphenidate (brand name: Ritalin), a psychoactive stimulant when ingested by adults. Twelve of the men experienced a pleasant feeling, nine felt annoyed or distrustful, and two felt nothing at all. Measurements of a subclass of dopamine receptors in the brains of these subjects showed a consistent pattern. The men with the lowest concentration of dopamine receptors were the ones experiencing pleasant effects. It is reasonable to hypothesize that those individuals with the fewest dopamine receptors might be the most vulnerable to drug abuse. A reasonable hypothesis is that their drug-taking behaviour is a matter of compensating for an inadequate number of dopamine receptors necessary to experience pleasurable feelings without drugs.[22]

We now understand that individual differences observed in dopamine receptor concentrations are, in part, genetically based. In the case of nicotine, it is estimated that genetics accounts for about 75% of the inclination to begin smoking, for about 60% of the tendency to become dependent on nicotine, and for about 54% of the ability to quit. Analyses of the human genome have revealed specific gene sites that increase the risk of alcohol abuse and the risk of abuse of a variety of illicit substances, including marijuana.

On the other hand, it is clear that there is an interplay between genetic and environmental influences in this area, and the total picture is bound to be complex. For example, genetic influences in substance abuse in general have been found to be more prominent among people in early to middle adulthood and less prominent among adolescents, for whom social environmental factors are dominant.[23]



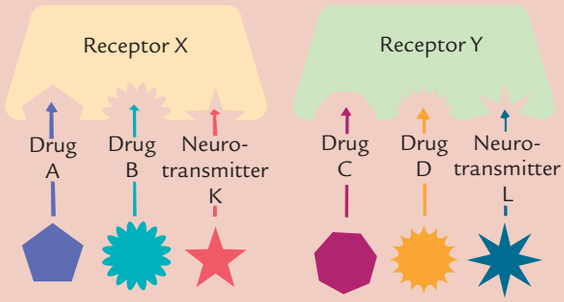
Courtesy of Brookhaven National Laboratory

This is literally "your brain on drugs." PET scans from a drug-free subject (left), a detoxified cocaine abuser one month after detoxification (middle), and a detoxified cocaine abuser four months after detoxification (right). The absence of orange-coloured areas in the PET scans in the middle and on the right indicates lower levels of dopamine activity.

Quick Concept Check 3.3

Understanding Cross-Tolerance and Cross-Dependence

Check your understanding of cross-tolerance and cross-dependence by answering the following questions. Suppose you have two receptors in the brain, as shown here.



Notice that Receptor X has three binding sites, one for drug A, one for drug B, and one for neurotransmitter K. Receptor Y also has three binding sites, one for drug C, one for drug D, and one for neurotransmitter L.

On the basis of this information, indicate whether the following pairs of drugs show cross-tolerance and cross-dependence with each other.

1. Drug A and drug B	yes	no
2. Drug A and drug C	yes	no
3. Drug B and drug C	yes	no
4. Drug C and drug D	yes	no
5. Drug B and drug D	yes	no
6. Drug A and drug D	yes	no

Answers: 1. yes 2. no 3. no 4. yes 5. no 6. no

Psychological Factors in Drug-Taking Behaviour

This chapter has considered the physiological effects of psychoactive drugs, down to the level of a single neuron in the brain. It has also pointed out that certain physiological factors (such as weight and gender)

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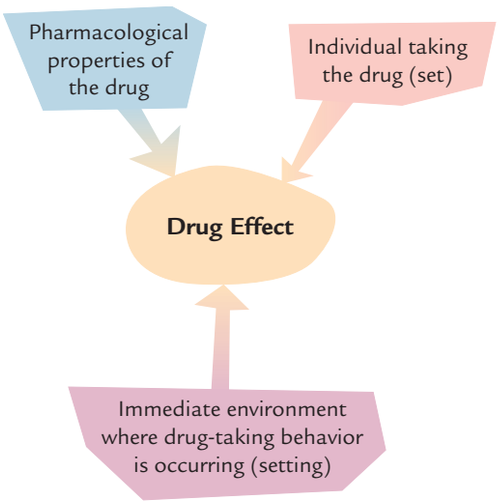

FIGURE 3.11

Viewing a psychoactive drug effect as a three-way interaction.

must be taken into account to predict particular drug effects. Yet even if we controlled these factors completely, we would still frequently find a drug effect in an individual person to be different from time to time, place to place, and situation to situation. Predictions about how a person might react would be far from perfectly accurate.

Therefore, a good way of thinking about an individual's response to a particular drug is to consider the drug effect as a three-way interaction of the drug's pharmacological properties (the biochemical nature of the substance), the individual taking the drug (set), and the immediate environment within which drug-taking behaviour is occurring (setting) (Figure 3.11). Whether one or more of these factors dominate in the final analysis seems to depend on the dosage level. Generally speaking, the higher the drug dose, the greater the contribution made by the pharmacology of the drug itself; the lower the dose, the greater the contribution of individual characteristics of the drug-taker or environmental conditions.[24]

Expectation Effects

One of the most uncontrollable factors in drug-taking behaviour is the set of expectations a person may have about what the drug will do. If you believe that a drug will make you drunk or feel sexy, the chances are increased that it will do so; if you believe that smoking a marijuana joint makes you high, the chances are increased that it will. In the most extreme case, you might experience a drug effect even when the substance you ingested is completely inert—that is, pharmacologically ineffective. Any inert (inactive) substance is referred to as a **placebo**, and the physical reaction to it is referred to as the *placebo effect*.

Of course, the reverse is true as well. You can imagine the impact of negative expectations in drug-taking behaviour. When feelings are strong that a drug will have *no effect* on you, the chances are lessened that you will react to it.

The concept of a placebo goes back to the earliest days of pharmacology. The bizarre ingredients prescribed in the Ebers Papyrus (see Chapter 1) were effective to the extent that people *believed* that they were effective, not as a consequence of any known factor in these ingredients. No doubt, the placebo effect was strong enough for medical symptoms to diminish. During the Middle Ages, in one of the more extreme cases of the placebo effect, Pope Boniface VIII reportedly was cured of kidney pains when his personal physician hung a gold seal bearing the image of a lion around the pope's thigh.[25] However, it would be a mistake to think of the placebo effect as involving totally imaginary symptoms or totally imaginary reactions. Physical symptoms, involving specific bodily changes, can occur on the basis of placebo effects alone. How likely is it that a person will react to a placebo? The probability varies from drug to drug, but in the case of morphine, the data are very clear. A 1959 review of studies in which morphine or a placebo was administered in clinical studies of pain concluded that a placebo-induced reduction in pain occurred 35% of the time. Considering that morphine itself had a positive result in only 75% of the cases, the placebo effect was a very strong one.

In a more recent placebo study reported in 2008, volunteer subjects were asked to judge the intensity of electric shocks before and after ingesting a pill that contained no active ingredients. Half of the subjects were told the pill was a drug selling for $2.50 each, and the other half were told the pill cost a "discounted" 10 cents. The percentage of subjects reporting a reduction in pain was greater with the expensive pill (85%) than with the cheaper pill (62%). In both cases, a placebo effect was observed. Higher-priced pills were assumed to be more effective than cheaper pills,

placebo (pla-SEE-bo): Any inert substance that produces a psychological or physiological reaction.

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Marcin Balcerzak/Shutterstock

The likelihood of a placebo effect is maximized when the patient has a substantial level of trust in the expertise of the physician prescribing a drug.

even though in both cases they were physiologically inert. Evidently, the attitude that "you get what you paid for" is alive and well, even in the context of drug-taking behaviour.[26]

Unfortunately, it is difficult to predict exactly whether a person will react strongly or weakly to a placebo. We do know, however, that the level of enthusiasm of the prescribing physician plays a major role. In other words, the credibility of the messenger enhances the credibility of the message. In one study that varied the attitude of the physician toward a particular medication, negative attitudes toward the medication resulted in the least benefits, whereas positive attitudes resulted in the most. The colour of a placebo can also be a factor. A yellow antidepressant pill is more likely to evoke a "sunnier" outlook on life; a red pill is more likely to have a stimulating effect; a green pill is more likely to reduce anxiety; and, not surprisingly, a pill with a trademark brand imprinted on it is more likely to be effective in general than a generic version.[27]

It is not at all clear how the placebo effect is accomplished. In the case of pain relief, there is evidence that we have the natural ability to increase levels of endorphins in the bloodstream and the brain from one moment to the next, but the nature of our ability to alter other important substances in our bodies is virtually unknown. Placebo studies have shown a 33% increase in lung capacity among asthmatic children who inhaled a bronchodilator containing a placebo instead of medication and the development of skin rashes in people who have been exposed to fake poison ivy, to name a few examples of placebo-induced physiological reactions. Placebo research forces us to acknowledge the potential for psychological control over physiological processes in our bodies.[28]

Drug Research Procedures

Given the power of the placebo effect in drug-taking behaviour, it is necessary to be very careful when carrying out drug research. For a drug to be deemed truly effective, it must be proved to be better not only in comparison to a no-treatment condition (a difference that could conceivably be attributed to a placebo effect) but also in comparison to an identical-looking drug that lacks the active ingredients of the drug being evaluated. For example, if the drug under study is in the shape of a round red pill, another round red pill without the active ingredients of the drug (called the *active placebo*) must also be administered for comparison.

The procedures of these studies also have to be carefully executed. Neither the individual administering the drug or placebo nor the individual receiving the drug or placebo should know which substance is which. Such precautions, referred to as a **double-blind** procedure, represent the minimal standards for separating the pharmacological effects of a drug from the effects that arise from one's expectations and beliefs.[29] We will return to the issue of interactions between drug effects and expectations in Chapter 8 when we consider behaviour associated with alcohol intoxication.

double-blind: A procedure in drug research in which neither the individual administering a chemical substance nor the individual receiving it knows whether the substance is the drug being evaluated or an active placebo.

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Summary

How Drugs Enter the Body

- There are four basic ways to administer drugs into the body: oral administration, injection, inhalation, and absorption through the skin or membranes. Each of these imposes constraints on which kinds of drugs will be effectively delivered into the bloodstream.

How Drugs Exit the Body

- Most drugs are eliminated from the body through urinary excretion. Drugs are broken down for elimination by the action of enzymes in the liver. An index of how long this process takes is called the elimination half-life.

Factors Determining the Behavioural Impact of Drugs

- Factors that influence the physiological effect of a drug include the time elapsed since its administration, drug interactions when it is administered with other drugs at about the same time, and the personal characteristics of the individual consuming the drug.
- An individual's weight, gender, and ethnic background can play a definite role in the behavioural and physiological effects of a drug.

Introducing the Nervous System

- Understanding the organization of the nervous system helps us to understand where psychoactive drugs are working in our bodies.
- The nervous system consists of the peripheral nervous system and the central nervous system, with the latter divided into the brain and the spinal cord. Autonomic nerves control our cardiac and smooth muscles to respond either to stress (sympathetic activation) or to demands for nurturance and renewal (parasympathetic activation).

Understanding the Brain

- Within the brain are three major divisions: the hindbrain, midbrain, and forebrain. The forebrain is the most recently evolved region of the brain; it controls the most complex behaviours and processes the most complex information.
- Many drugs affect all levels of the brain, in one way or another.

Neuronal Communication and Drug Effects

- Understanding the functioning of neurons and their interaction through neuronal communication helps us to understand how psychoactive drugs work in our bodies.
- In general, drugs work at the neuronal level by altering the three basic stages of neuronal communication: (1) neurotransmitter release; (2) receptor binding; and (3) the returning of the neurotransmitter back to the synaptic knob for future use.
- There are dozens of neurotransmitters that accomplish this task. The seven major neurotransmitters are acetylcholine, norepinephrine, dopamine, serotonin, gamma aminobutyric acid (GABA), glutamate, and a group of neurochemicals called endorphins.

Physiological Aspects of Drug-Taking Behaviour

- Three important issues need to be understood in looking at the physiological effect of drugs: the extent to which drugs pass from the bloodstream to the brain, the extent to which tolerance effects occur, and the extent to which a drug influences neuronal activity in the region of the nucleus accumbens in the brain.

Psychological Factors in Drug-Taking Behaviour

- Although the physiological actions of psychoactive drugs are becoming increasingly well understood, great variability in the effect of these drugs remains, largely because of psychological factors.
- The most prominent psychological factor is the influence of personal expectations on the part of the individual consuming the drug. The impact of expectations on one's reaction to a drug, a phenomenon called the placebo effect, is an important consideration in drug evaluation and research.

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Key Terms

acetylcholine, p. xx
action potential, p. xx
agonist, p. xx
antagonist, p. xx
biotransformation, p. xx
blood–brain barrier, p. xx
central nervous system (CNS), p. xx
cerebral cortex, p. xx
cross-dependence, p. xx
cross-tolerance, p. xx
dopamine, p. xx
double-blind, p. xx
elimination half-life, p. xx
endocannabinoids, p. xx
endorphins, p. xx
gamma aminobutyric acid (GABA), p. xx
glutamate, p. xx
intramuscular (i.m.), p. xx
intranasal, p. xx
intravenous (i.v.), p. xx
latency period, p. xx
metabolite, p. xx
neuron, p. xx
neurotransmitter, p. xx
norepinephrine (noradrenaline), p. xx
nucleus accumbens, p. xx
parasympathetic branch of the autonomic nervous system, p. xx
peripheral nervous system, p. xx
placebo, p. xx
potentiation, p. xx
presynaptic terminals, p. xx
resting membrane potential, p. xx
reuptake, p. xx
serotonin (5-Hydroxytryptophan), p. xx
subcutaneous (s.c. or sub-Q), p. xx
sublingual, p. xx
sympathetic branch of the autonomic nervous system, p. xx
synapse, p. xx
synergism, p. xx
transdermal patch, p. xx

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