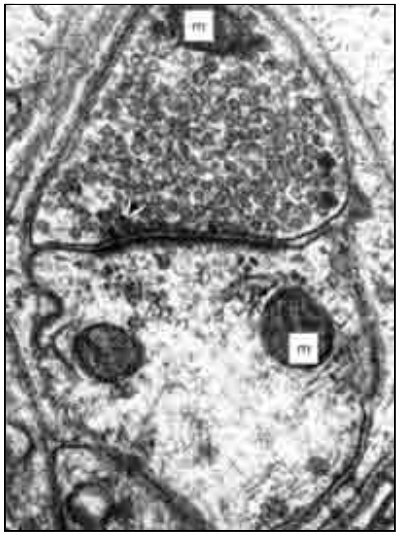
Lesson 3— Drugs Change the Way Neurons Communicate

At a Glance

Overview

Students build upon their understanding of neurotransmission by learning how different drugs of abuse disrupt communication between neurons. Students then conduct an activity investigating the effect of caffeine on their heart rate. Finally, students analyze data on how the way a drug is taken into the body influences its effect.



Source: Principles of Neural Science*, 3rd edition, Eric R. Kandel, James H. Schwartz, Thomas M. Jessell ©The McGraw-Hill Companies. (m = mitochondria)*

Major Concept

Drugs affect the biology and chemistry of the brain.

Objectives

By the end of these activities, the students will

- understand that certain drugs interfere selectively with neurotransmission and
- realize that the effect of a drug is dependent upon dosage and route of administration.

Basic Science–Health Connection

Drugs of abuse are valuable tools for investigations of brain function because they can mimic or block actions of neurotransmitters, and thus exert effects on homeostasis and behavior.

Background Information

Drugs Disrupt Neurotransmission

How do drugs cause their effects on the brain and behavior? Lesson 1 introduced students to the idea that a specific brain region, the reward system (part of the limbic system), regulates feelings of pleasure and that this region is activated by drugs of abuse. But what do drugs actually do in that brain region? Drugs interfere with neurotransmission. More specifically, drugs of abuse

produce feelings of pleasure by altering neurotransmission by neurons in the reward system that release the neurotransmitter dopamine.[1 (references.html#L31),2 (references.html#L32)] Thus, drugs of abuse alter the communication between neurons that is mediated by dopamine. Because the synapse is so complex, there is a variety of sites at which drugs may affect synaptic transmission. One way to affect synaptic transmission is to increase the amount of neurotransmitter released into the synaptic space. Drugs like alcohol, heroin, and nicotine indirectly excite the dopamine-containing neurons in the ventral tegmental area (VTA) so that they produce more action potentials.[1 (references.html#L31),2 (references.html#L32)] As the number of action potentials increases, so does the amount of dopamine released into the synapse. Amphetamines (e.g., methamphetamine, crystal, crank) actually cause the release of dopamine from the vesicles. This is independent of the rate of action potentials and, depending on dose, can cause a relatively quick and prolonged rise of extracellular dopamine levels.

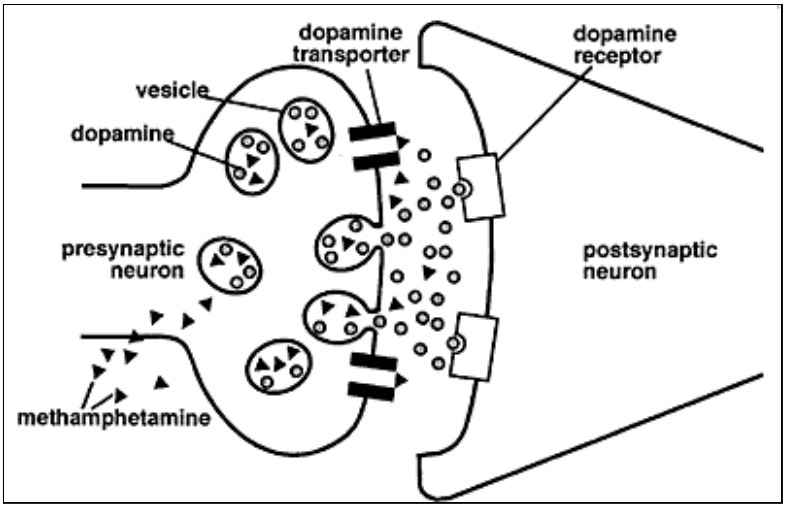


Figure 3.1: *Methamphetamine alters dopamine neurotransmission in two ways. Methamphetamine enters the neuron by passing directly through nerve cell membranes. It is carried to the nerve cell terminals by transporter molecules that normally carry dopamine or norepinephrine. In the nerve terminal, methamphetamine enters the dopamine- or norepinephrine-containing vesicles and causes the release of neurotransmitter. Methamphetamine also blocks the dopamine transporter from pumping dopamine back into the transmitting neuron. Methamphetamine acts similarly to cocaine in this way.*

Nicotine not only acts at the cell body in the VTA to increase the number of action potentials and number of vesicles released from a neuron, but it also acts by another mechanism to alter dopamine release. When nicotine binds to nicotine receptors on the dopamine-containing axon terminals in the nucleus accumbens, more dopamine is released with each action potential.[1 (references.html#L31)]

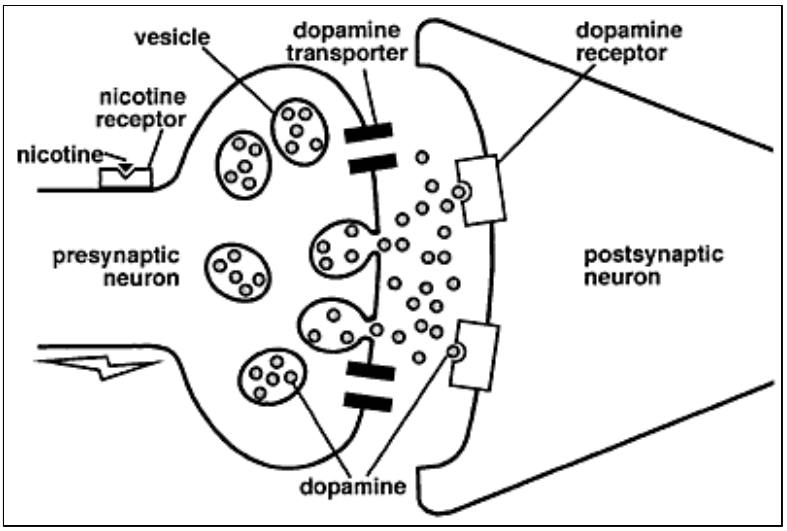


Figure 3.2: *Nicotine binds to specific receptors on the presynaptic neuron. When nicotine binds to receptors at the cell body, it excites the neuron so that it fires more action potentials (electrical signals, represented by jagged shape in lower left of figure) that move toward the synapse, causing more dopamine release (not shown in figure). When nicotine binds to nicotine receptors at the nerve terminal (shown above), the amount of dopamine released in response to an action potential is increased.*

Drugs may also alter synaptic transmission by directly affecting the postsynaptic receptors. Some drugs activate receptors, and others block them.

While THC (the main psychoactive chemical in marijuana) and morphine activate specific receptors, other drugs block specific receptors. Caffeine, the mild stimulant found in coffee and some soft drinks, exerts its effects by preventing a neurotransmitter/neuromodulator called adenosine from binding to its receptor. Normally, the binding of adenosine to its receptor causes sedation; it is a natural sleep-inducer. Instead of causing sedation, the blocking of the adenosine receptors with caffeine leads to an increase in activity and arousal levels.[1 (references.html#L31),3 (references.html#L33)]

The actions of some drugs are very complex. LSD, for example, acts on serotonin receptors. Serotonin, an important neurotransmitter in many brain regions, is involved in regulating a wide variety of functions, including mood and basic survival functions such as sleeping and eating. Scientists continue to study how hallucinogens act, but apparently LSD activates some serotonin receptors (LSD acts as a receptor agonist) and blocks other serotonin receptors (LSD acts as a receptor antagonist).[1 (references.html#L31)]

A third way to affect synaptic transmission is to alter the removal of neurotransmitters from the synapse. Cocaine and amphetamines work this way (this is the second way amphetamines can alter neurotransmission).[1 (references.html#L31),3 (references.html#L33)] Both drugs block the dopamine transporter (reuptake pump) that removes dopamine from the synapse. The result is a fairly rapid and persistent rise of dopamine in the synapse, leading to feelings of euphoria and well-being. Most drugs of abuse don't block enzymatic destruction of neurotransmitters, although smoking has been shown to reduce levels of an enzyme that breaks down neurotransmitters, monoamineoxidase.

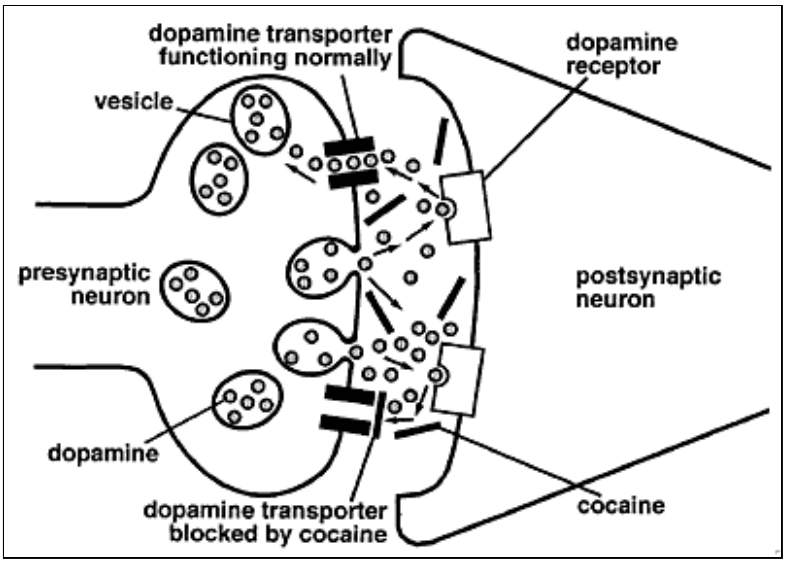


Figure 3.3: *When cocaine enters the brain, it blocks the dopamine transporter from pumping dopamine back into the transmitting neuron, flooding the synapse with dopamine. This intensifies and prolongs the stimulation of receiving neurons in the brain's pleasure circuits, causing a cocaine high.*

Alcohol affects the brain's neurons in several ways. It alters their membranes and ion channels, enzymes, and receptors, and it also binds directly to the receptors for acetylcholine, serotonin, and GABA and the NMDA receptors for glutamate. GABA normally reduces the activity of neurons by allowing chloride ions to enter the postsynaptic neurons. This effect is amplified when alcohol binds to the GABA receptor and the neuron's activity is further diminished, which explains the sedative effect of alcohol.

Alcohol also reduces glutamate's excitatory effect by blocking the receptor activated by glutamate, the NMDA receptor. NMDA receptors are known to be involved in synaptic plasticity, a cellular mechanism for learning and memory. However, chronic consumption of alcohol gradually makes the NMDA receptors *hypersensitive* to glutamate while desensitizing the GABA receptors.

Alcohol also helps increase the release of dopamine, by a process that is still poorly understood but that appears to involve curtailing the activity of the enzyme that breaks dopamine down.

Drugs Mimic Natural Body Chemicals

The ability of drugs to interrupt normal synaptic transmission may seem odd. After all, if receptors have such great specificity for a single type of binding partner, how can drugs disrupt the process? The answer lies in the similarity in conformation, or structure, of the drugs to natural body chemicals. For example, the receptors in the brain that bind morphine and other opioids recognize natural opioid peptides called endorphins and enkephalins that are made by our brains and used as neurotransmitters.[4 (references.html#I.34)] It is an evolutionary coincidence that these receptors recognize a plant-derived chemical (drug) as well. This coincidence is a double-edged sword. Opioid compounds that come from plants are both the most potent analgesics (pain relievers) available and some of the most potent addictive drugs as well. Morphine continues to be one of the most effective drugs to relieve the pain associated with many chronic diseases. When abused, opioids are often taken at higher-than-prescribed doses or in ways other than as prescribed (for example, injected vs. orally), which, by stimulating the dopamine cells in the VTA, can cause

profound feelings of pleasure (euphoria). Tetrahydocannabinol (THC), the active ingredient in marijuana, binds to specific receptors in the brain called cannabinoid receptors, which were discovered because scientists were trying to understand how marijuana works. Subsequently, natural (endogenous) transmitters that bind these receptors were identified—one of which is called anandamide. The cannabinoid system is distributed widely in the brain and the body and is thought to play a role in a wide variety of physiological activities, including memory, appetite, pain perception, and immune regulation. The discovery of this system may enable scientists to develop medications (without the abuse and other health liabilities of marijuana) for a variety of diseases, including obesity, schizophrenia, multiple sclerosis, and addiction.

Drugs of abuse share a common action: they act on the brain's reward system. Within that system, they all (except perhaps for LSD) share the ability to increase the levels of dopamine in the nucleus accumbens. This almost certainly accounts for the rewarding (pleasurable) effects of abused drugs.

The effects of drugs are not limited to the reward pathway in the brain. Drugs can act in various regions of the brain to exert their effects, but their ability to alter dopamine neurotransmission in the ventral tegmental area (VTA) and the nucleus accumbens is the initial and one of the most important factors driving continued drug use.

Many factors determine how a drug affects an individual. Some of these are biological. For example, genetics can affect a person's sensitivity to a drug or how quickly the drug is metabolized and cleared from the body. But environmental factors can also be important—stress or trauma can alter a person's experience with drugs. Two factors that are especially important are the dose of the drug and the route of administration, which affects how fast it reaches the brain.

The Dose Changes the Drug's Effects

For a drug to work, it must be taken into the body, absorbed in the bloodstream, and delivered to the brain. Drugs can be taken in a range of doses—from low, having no detectable effect, to moderate, producing the drug's desired effect, to large and unpleasant, or even toxic (Figure 3.4). Not everyone will respond the same way to a given drug dose—many factors can influence this, including those mentioned above, as well as age, gender, and the person's history of using that drug or other related drugs. However, most drugs, when taken at high doses, produce effects that are both undesirable and potentially harmful to health (overdose).

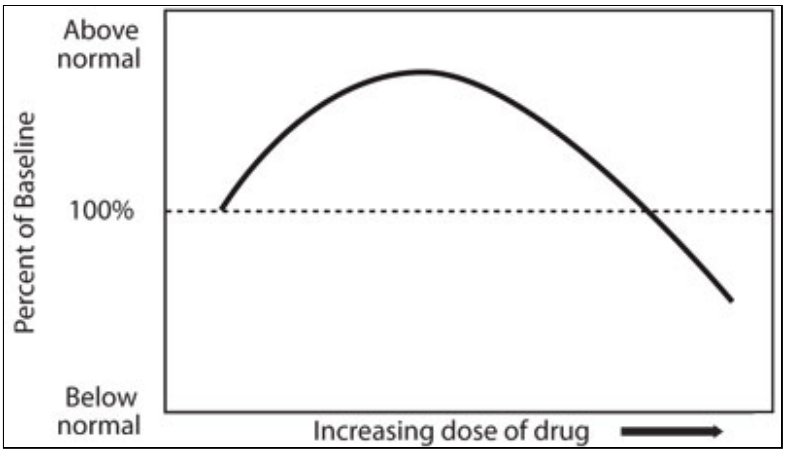


Figure 3.4: *Effects of a drug depend on the dose.*

Drugs Enter the Brain in Different Ways

In addition to dose, the manner in which a drug is taken can profoundly alter the response to the drug. A drug that is inhaled (smoked) reaches the brain very quickly. The inhaled drugs go directly from the lungs into the left side of the heart, where they enter the arterial circulation that carries them to the brain. Marijuana and nicotine are examples of drugs that are commonly taken into the body by inhalation (smoking). The intensity of the effect of inhaled drugs may be slightly less than that for injected drugs because less of the drug gets into the brain; some of the drug will be exhaled with the rest of the components of the smoke. A drug that is injected intravenously also travels quickly to the brain, where it can exert its effects. The rapid passage of injected heroin, for example, brings a high risk of overdose. In some cases, the heroin can reach lethal levels faster than medical help can be obtained to reverse the overdose. A third route of drug administration is by snorting or snuffing. A drug that is snorted or snuffed is taken in through the nose, where it is absorbed through the mucous membranes lining the nasal passages. Television and movies often depict cocaine being snorted. The effects of drugs taken by this method will be less intense than by injection or inhalation because it takes longer for the drug to get into the brain.

Routes of Administration
Ingestion Inhalation Injection Snorting/Snuffing Through the skin

Figure 3.5: *Drugs enter the brain by different routes.*

Another route of administration is by oral ingestion. Most people are familiar with taking a medicine, either as a solid or a liquid, by mouth. People can also take drugs of abuse this way. Drugs commonly taken orally include stimulants and depressants. Drugs taken orally enter the bloodstream more slowly than by any of the other routes. The drugs that are swallowed reach the stomach and intestine, where they are absorbed into the bloodstream. Not only do they take longer to act, but the body begins to metabolize them before they can act on the brain. Enzymes in the stomach, intestines, and liver begin breaking down the drugs so they can be cleared from the body.

As shown in Figure 3.6, the route of administration causes dramatic differences in the onset, intensity, and duration of a drug's effect. Methamphetamine, for example, can be smoked,

snorted, ingested orally, or injected. If the drug is smoked or injected, the user almost immediately experiences an intense rush or "flash" that lasts a few minutes. Snorting methamphetamine produces feelings of euphoria within three to five minutes, while oral ingestion produces effects within 15 to 20 minutes. The high resulting from snorting or ingestion is not as intense as that resulting from injecting or smoking the drug.[5 (references.html#L35)]

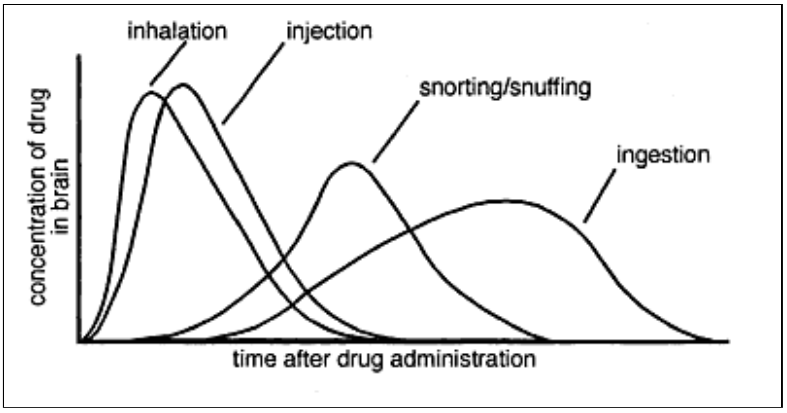


Figure 3.6: *Drugs of abuse enter the body by different routes. The intensity of a drug's effect depends on how the drug is taken.*