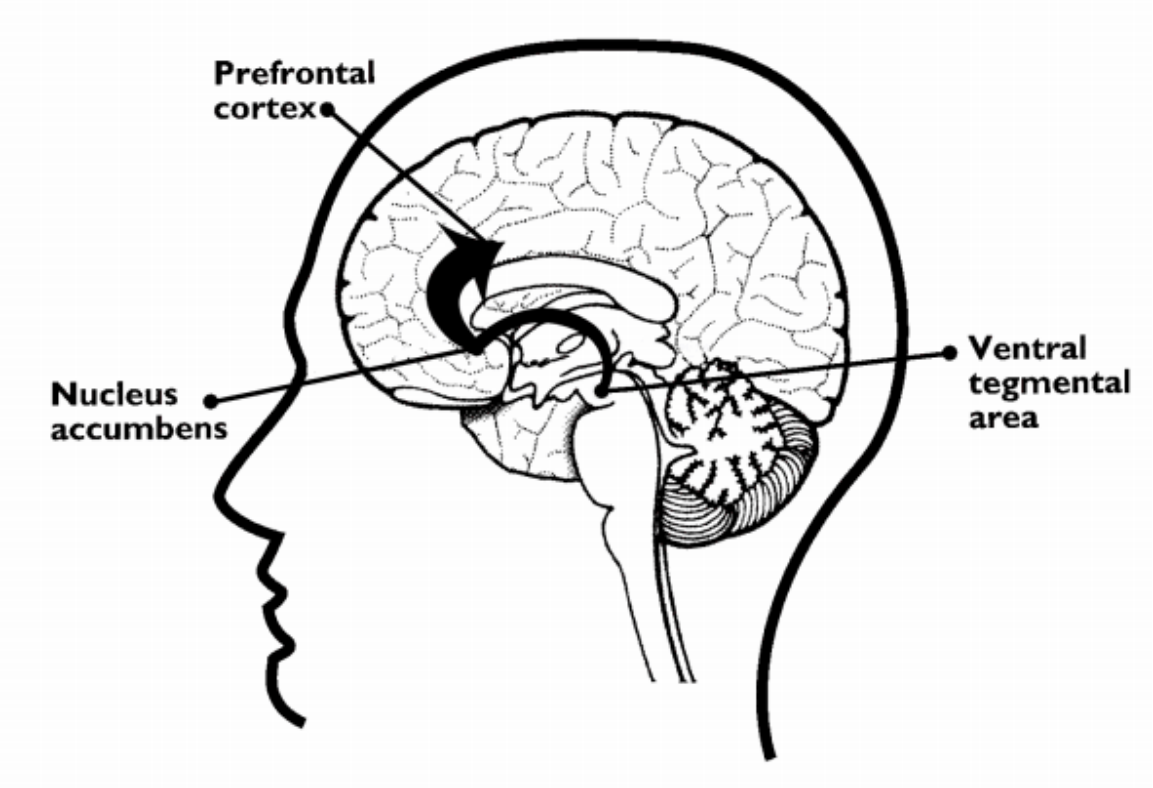
# The Reward System




Drawing of a brain cut in half, showing the reward system.

# Drugs: What You Should Know


These days, drugs can be found everywhere, and it may seem like everyone's doing them. Lots of people are tempted by the excitement or escape that drugs seem to offer. But learning the facts about drugs can help you see the risks of chasing this excitement or escape. Here's what you need to know.

## The Deal on Substances

Thanks to medical and drug research, there are thousands of drugs that help people. Antibiotics and vaccines have revolutionized the treatment of infections. Medicines can lower blood pressure, treat diabetes, and reduce the body's rejection of new organs. Medicines can cure, slow, or prevent disease, helping us to lead healthier and happier lives. But there are also lots of illegal, harmful drugs that people take to help them feel good or have a good time.

How do drugs work? Drugs are chemicals or substances that change the way our bodies work. When you put them into your body (often by swallowing, inhaling, or injecting them), drugs find their way into your bloodstream and are transported to parts of your body, such as your brain. In the brain, drugs may either intensify or dull your senses, alter your sense of alertness, and sometimes decrease physical pain.

A drug may be helpful or harmful. The effects of drugs can vary depending upon the kind of drug taken, how much is taken, how often it is used, how quickly it gets to the brain, and what other drugs, food, or substances are taken at the same time. Effects can also

vary based on the differences in body size, shape, and chemistry.

Although substances can feel good at first, they can ultimately do a lot of harm to the body and brain. Drinking alcohol, smoking tobacco, taking illegal drugs, and sniffing glue can all cause serious damage to the human body. Some drugs severely impair a person's ability to make healthy choices and decisions. Teens who drink, for example, are more likely to get involved in dangerous situations, such as driving under the influence or having unprotected sex.

## Why People Take Drugs

And just as there are many kinds of drugs available, there are as many reasons for trying them or starting to use them regularly. People take drugs just for the pleasure they believe they can bring. Often it's because someone tried to convince them that drugs would make them feel good or that they'd have a better time if they took them.

Some teens believe drugs will help them think better, be more popular, stay more active, or become better athletes. Others are simply curious and figure one try won't hurt. Others want to fit in and take drugs due to peer pressure. A few use drugs to gain attention from their parents.

Many teens use drugs because they're depressed or think drugs will help them escape their problems. The truth is, drugs don't solve problems — they simply hide feelings and problems. When a drug wears off, the feelings and problems remain, or become worse. Drugs can ruin every aspect of a person's life.

# How Drugs Work in Your Body

*By Michael Bihari, MD*
*Updated August 19, 2008*

Drugs work in your body in a variety of ways. They can interfere with microorganisms (germs) that invade your body, destroy abnormal cells that cause cancer, replace deficient substances (such as hormones or vitamins), or change the way that cells work in your body.

There are more than 8,000 medications available either by prescription or over-the-counter. Some can be used to treat several different health conditions. Aspirin, for example, can be used to treat pain, inflammation, and fever. In addition, aspirin can prevent heart attacks if taken on a regular basis. The following information is a basic overview of how some drugs work to improve your health.

## Fighting Infections

An infection occurs when microorganisms, such as bacteria or viruses, invade your body. Medications used to treat infections can kill germs directly or prevent them from multiplying and growing.

Some medications used to treat infections include:

- Augmentin (amoxicillin/clavulanic acid), used to treat ear infections
- Bactrim (trimethoprim-sulfamethoxazole), used to treat urinary tract infections
- Lamisil (terbinafine), used to treat ringworm
- Pen-Vee K (penicillin), used to treat strep throat
- Valtrex (valacyclovir), used to treat herpes infections

## Targeting Cancer Cells

There are three types of medications used to treat cancer. Chemotherapy attacks cancer cells directly and stops or slows their growth and spread. Biological therapy helps your body's immune system fight cancer. Lastly, antiangiogenic therapy blocks the growth of new blood vessels to a tumor, which may cut off a tumor's supply of oxygen and nutrients. Some cancers are treated with a combination of these medications.
Some medications used to treat cancer are:

- Adriamycin (doxorubicin), a chemotherapy agent used to treat a number of cancers, including bone, breast, stomach, lung, bladder, leukemia and lymphoma
- Avastin (bevacizumab), an antiangiogenic therapy used to treat cancers of the colon, rectum, or lung
- Intron-A (interferon alpha), a biological therapy used to treat malignant melanoma
- Herceptin (trastuzumab), a biological therapy used to treat breast cancer
- Platinol (cisplatin), a chemotherapy agent used to treat many types of cancer including bladder, lung, and head and neck

## Replacing Missing or Deficient Substances

Your body needs certain levels of amino acids (or proteins), vitamins and minerals to work properly. If these substances are deficient or missing, you can develop health conditions such as scurvy (vitamin C deficiency), anemia (iron deficiency), and pernicious anemia (vitamin B12 deficiency). Recent medical studies have suggest that a lack of vitamin D may increase the risk of heart attack in men. Your physician, therefore, may recommend a vitamin D supplement.

You also can develop a deficiency disorder caused by a lack of hormones in your body. Hormones regulate many of the functions in your body, and a deficiency in one or more

hormones can cause serious health problems. Diabetes (insulin deficiency), hypothyroidism (thyroid hormone deficiency), and short stature (growth hormone deficiency) are some examples.

Some medications used to treat hormone deficiency disorders are:

- Androgel (testosterone), used to treat hypogonadism (low testosterone in men)
- Humalog (insulin lispro), used to treat diabetes
- Humatrope (somatropin), used to treat short stature due to growth hormone deficiency
- Premarin (conjugated estrogens), used to treat symptoms of menopause
- Synthroid (levothyroxine), used to treat hypothyroidism

## Changing How Cells Work

Most common chronic diseases – such as asthma, type 2 diabetes, hypertension, arthritis, heart disease, and some types of mental illness – are caused by an abnormality in how the cells in your body function. These abnormalities may be caused by aging of cells, genetics, wear and tear on the body, and lifestyle issues such as smoking, lack of exercise, poor eating habits, and environmental stress and pollution.

Most medications prescribed or sold over the counter target one or more of these cell abnormalities. For example, some medications used to treat pain and inflammation interfere with the production of chemical substances that are released by cells in response to tissue damage. These chemical substances, also known as mediators, are responsible for the pain and swelling in arthritis and injuries.

Some medications used to treat depression work by increasing the amount of a chemical messenger in the brain. Additionally, some other medications make cells more or less

sensitive to hormones in the body. Beta blockers, such as Tenormin (atenolol) and Toprol XL (metoprolol), are used to treat hypertension by making heart cells less sensitive to the body's adrenaline. Some oral diabetes medications, such as Actos (pioglitazone) and Avandia (rosiglitazone), make muscle cells more sensitive to insulin.

Some medications that alter the function of body cells are:

- Arthrotec (diclofenac, misoprostol), used to treat arthritis
- Lipitor (atorvastatin), used to treat high cholesterol
- Nexium (esomeprazole), used to treat GERD (heartburn)
- Viagra (Sildenafil), used to treat erectile dysfunction
- Zoloft (sertraline), used to treat depression

**Sources:**

About bacteria & antibiotics. Alliance for the Prudent Use of Antibiotics. 03 July 2008.

Angiogenesis Inhibitors Therapy: Questions and Answers. National Cancer Institute. 03 July 2008.

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How Medications Work. Johns Hopkins Prescription Drugs Reports. 03 July 2008.

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# Drugs and the brain: A quick guide to brain chemistry

**Get the low-down on some of the major chemicals that govern activity in our brains, how they work, and why certain drugs have the effects they do. *By Barry Gibb.***

Beneath every thought, dream or action lies a remarkable chemical dance. Molecules called neurotransmitters are in constant flux throughout the brain. Manufactured and released by the billions of neurons a human brain possesses, they bring order to human existence. But for the mind to work effectively, neurotransmitters need a port in which to dock - a receptor. Here, we'll take a look at some of the major neurotransmitters in the brain, their own special receptors and a few of the other chemicals, or drugs, that bind them.

**Not sure what a word means? Check our glossary:**

- Ion: An atom or molecule that has lost or gained electrons to become either negatively or positively charged.
- Ion channel: A protein or assembly of several proteins in a cell membrane that opens and closes to let ions move in and out of cells.
- Neuron: A nerve cell.
- Neurotransmitter: Chemicals made in the brain that pass signals between different nerve cells.
- Receptor: A protein or assembly of several proteins in a cell membrane that a molecule (such as a neurotransmitter, hormone or drug) can bind to.

**Glutamate: What goes up...**

Glutamate is the brain's 'on switch'. Known as an 'excitatory neurotransmitter', this tiny molecule does pretty much what it says on the tin - wherever it finds a receptor to dock with, it causes the hosting neuron to become excited. An excited nerve is one that's more likely to 'fire', resulting in the release of its own unique mix of neurotransmitters.

Glutamate receptors are a varied bunch, and can be split into two main families. Ionotropic receptors are so-called because they form channels for ions to move through when glutamate binds to them. Ionotropic glutamate receptors are: NMDA (the same receptor ketamine blocks), kainate (a stimulant originally found in seaweed) and AMPA. Metabotropic glutamate receptors perform a little

more indirectly.

Chances are, you're already an expert on glutamate as it crops up in foods either alone (it tastes savoury), or in its flavour enhancing form - monosodium glutamate, MSG.

**GABA: ...must come down**

Not a reference to hardcore techno, GABA is the neurotransmitter acting as glutamate's lazy twin, its sole purpose being to slow things down, dampen and inhibit nervous activity. Like glutamate, the GABA (gamma-aminobutyric acid) receptors are split into two types. The GABA A receptors respond to GABA binding by allowing the flow of ions across nerve membranes. The GABA B receptors involve intermediaries in the process.

Drugs that stimulate these receptors tend to slow the brain down, so it's no surprise to discover alcohol affects these receptors. Drugs activating GABA receptors are found everywhere - liquid ecstasy, or GHB, has become well known as a 'date rape drug' while other activators, such as the benzodiazapenes, are used in clinical contexts to help people get more sleep or lessen anxiety, for example.

**Serotonin: Feeling groovy**

Originally extracted from gut cells, serotonin has numerous roles throughout the body. Within the brain, however, it's become associated with mood - a person's overall state of mind, how they feel about themselves and the external world at a point in time. As you might expect, laying the burden of something as complex as mood on a single molecule could be oversimplifying a little, but remarkably, this simple molecule does have a big impact on your mind.

The link between serotonin and how you feel is down to the large variety of serotonin (also known as 5-HT or 5-hydroxytryptamine) receptors throughout the brain. Part of the reason behavioural complexity can arise from such apparent simplicity is due to the breadth of different serotonin receptor types and their downstream effects. These effects include causing the levels of numerous other neurotransmitters to be increased or decreased throughout different brain regions. Like a throwing a pebble into a lake, serotonin causes ripples of effect.

A lack of serotonin in the brain is associated with depression, which is why drugs called SSRIs (selective serotonin reuptake inhibitors) such as fluoxetine (Prozac), are commonly prescribed to help treat depression. Such drugs cause an increase in the overall levels of serotonin in the brain

leading, in many cases, to diminished symptoms. Certain illegal drugs, such as MDMA ('ecstasy') and LSD ('acid') can also stimulate different serotonin receptors, leading to altered or extreme moods.

**Acetylcholine: Remember me?**

Among other things, acetylcholine appears to play an important role in learning and memory. The neurons that produce this neurotransmitter - cholinergic neurons - are found in several regions of the brain where, when stimulated, they release their stores of neurotransmitter onto waiting neurons. But to have any effect, those neurons need to have the right receptors; in this instance, the nicotinic and muscarinic receptors.

Nicotinic receptors, named after one of their most potent activators, nicotine (and the reason cigarettes are so addictive), allow ions to quickly pass through them when either acetycholine - or nicotine - binds to them. Muscarinic receptors (from muscarine, a receptor stimulant and poison extracted from certain mushrooms) act on a slower time frame than the nicotinic receptors. One of the most common blockers of the muscarinic receptors is atropine, a natural compound found in certain plants, such as deadly nightshade or mandrake.

**Dopamine: The pleasure principle**

Without pleasure we would not be here. Eating, sex and happiness are all things that feel good - as a consequence, we seek them out. Of all the neurotransmitters in the brain, dopamine is the one most associated with pleasure. And with good reason - everything that makes you feel good is down to this key neurotransmitter and the effect it has on the brain. Moreover, every addictive substance known affects dopamine release in what's known as the brain's 'reward pathway', the equivalent of a neurological circuit connecting experience with feeling good.

Regulating dopamine's effects throughout the brain are its receptors, of which there are five known main variants: D1-D5. Alongside pleasure, these receptors ensure the involvement of dopamine in a range of activities, from movement to memory. Drugs, such as cocaine and amphetamines, lead to a sharp, temporary, rise in dopamine within the brain.

**Cannabinoids: Natural highs?**

It's no mystery that the brain responds to cannabis - the question is why would the brain evolve the ability to bind to this drug? Could it be the human body makes its own version of the plant-derived

substance responsible for the effects of cannabis, tetrahydrocannabinol (THC)?

Endocannabinoids are the human version of what nature has created within certain plants. These fatty chemicals move freely between cells until they find their receptors. The two known ones are CB1 and CB2. Once activated, a number of pathways are activated, resulting in a diverse array of effects, from our experience of pain to movement of the digestive tract.

**Opioids: Poppy-derived painkilling**

The colourful poppy is the source of the alkaloid drug, opium (an opiate - literally meaning poppy tears), a property that led to the eventual discovery of the numerous opioid receptors that bind such compounds within the nervous system. One well-known opiate commonly used today for the treatment of severe pain, is morphine (after Morpheus the Greek god of dreams).

Distributed throughout the nervous system, the opioid receptors, OP1-OP4, are involved in all of the calming effects we might expect, such as pain relief and reduction in anxiety - but are taken to extremes by illegal drugs, such as heroin. The natural partners to the opioid receptors are the endorphins, released during certain activities, such as running (thought responsible for the 'runner's high'), pain and orgasm.

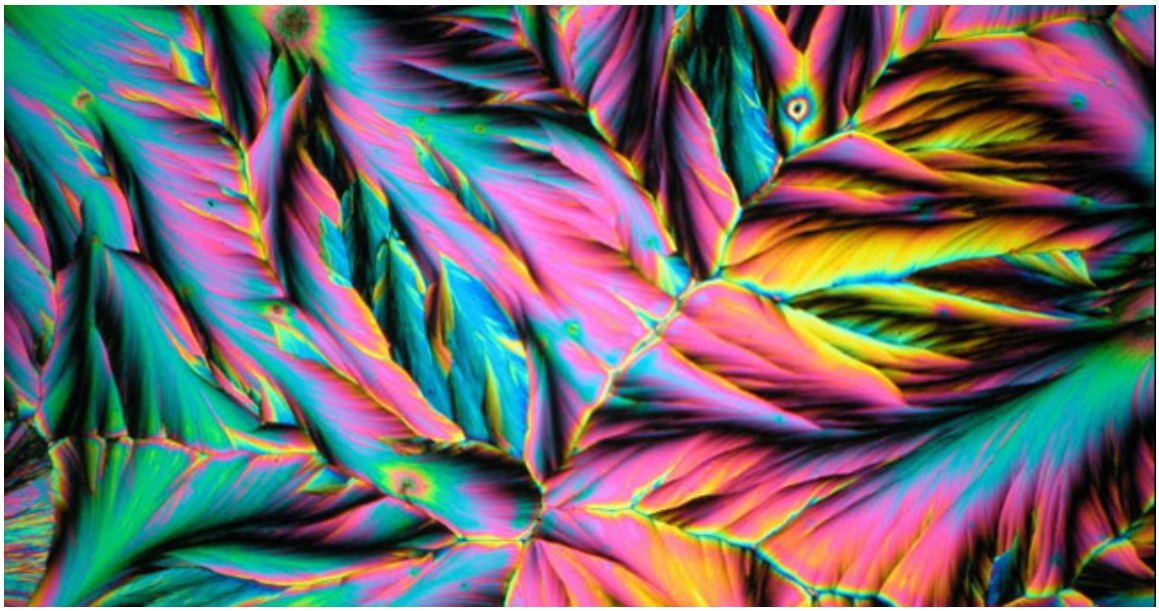
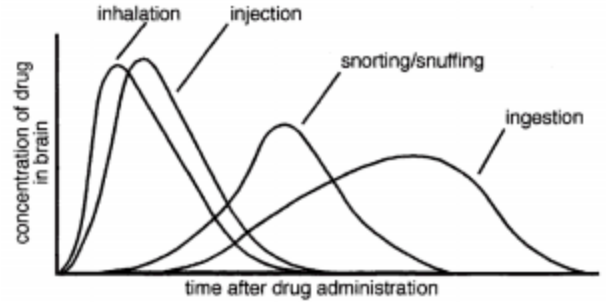


*Image: Dopamine crystals viewed with polarised light. Credit: Spike Walker, Wellcome Images.*

This article is part of the exclusive online content for 'Big Picture: Addiction'. Published twice a year, 'Big Picture' is a free post-16 resource for teachers that explores issues around biology and medicine. Find out more about the 'Big Picture' series. http://www.wellcomecollection.org/whats-on/exhibitions/high-society/essays/drugs-and-the-brain.aspx

# How Do Drugs Get Into the Brain?

Use the information in the graph below to help you answer the questions.




1. Four people who abuse drugs each take a drug. One person injects 100 milligrams (mg) of it into a vein, one person smokes 100 mg, one person snorts 100 mg, and one person swallows or ingests 100 mg. Who will experience the greatest effect of the drug? The individual with the greatest concentration of drug in the brain will have the greatest effect.

2. Who will experience the quickest effect from the drug?

3. Who will experience the least behavioral effect from the drug?

4. Who will experience the slowest effect from the drug?

5. Tobacco smokers can use nicotine patches to help them quit smoking. The nicotine patches help the smoker slowly lower the amount of nicotine that enters the body. How does the nicotine in the patch enter the body?

6. Explain why the different ways of taking drugs cause different behavioral responses.

# Long-Term Effects of Drugs on the Brain

So, why are drugs so bad? After all, the high or rush only lasts a little while, right? What else could be happening in the brain of a person who abuses drugs? Consider that the brain is continuously changing. After all, learning occurs because neurons are forming new synapses. Scientists say that the brain is plastic and call this “neuroplasticity.” That doesn’t mean the brain is made of a chemical plastic like a credit card, but it refers to the brain’s ability to modify connections in response to experience. When a person learns something or has new experiences, some new synapses may form or existing synapses may get stronger. Other synapses may disappear.

When a person takes drugs repeatedly, the brain changes in response to this experience. If a person takes drugs and then stops, he or she will crave the drug. In other words, the individual will have a strong desire to take more of the drug. Scientists can actually see evidence of cravings in the brain. If someone addicted to cocaine sees pictures of drug paraphernalia, PET scans show that a part of the brain that is important for emotional memory (called the amygdala) is activated, and the person reports feelings of drug craving. If he or she sees a video with mountains, trees, and animals, the amygdala is not stimulated. Thus, just seeing pictures of drugs or things associated with drugs can trigger an uncontrollable urge for drugs.

After taking drugs for a period of time, a person may need to take a higher dose of the drug to have the same experience that he or she did when first taking the drug. This is called tolerance. The brain has adapted to having a certain amount of drug present and does not respond the same way it did initially. That is why people who abuse and who are addicted to drugs take increasingly higher amounts of an abused drug. Tolerance may develop because the body may become more efficient at eliminating the chemical from the body, or because the cells of the body and brain become less responsive to the effect of the drug.

Scientific studies have shown clearly that certain drugs can cause dramatic changes in the brain, but not all questions have been answered. Drugs can change the structure of the brain. Perhaps one of the most dramatic long-term effects of a drug is to kill neurons. Many people have heard that drinking alcohol will kill brain cells. It's true. If alcohol is abused over a period of time, neurons in the brain can die. Some neurons in the brain are more sensitive to alcohol than others. Neurons that make up the mammillary bodies (small round structures on the brain's undersurface) and hippocampus, areas in the brain that are important for memory, are more vulnerable to the effects of alcohol than are some other neurons in the brain. The neurons in the cerebral cortex, the part of the brain that controls most of our mental functions and endows us with consciousness, may also die if a person frequently abuses alcohol in high doses.

Another drug that can be toxic to neurons is an amphetamine derivative called MDMA, or ecstasy. In rats and nonhuman primates, MDMA damages the axon terminals of neurons that release serotonin, a neurotransmitter that is involved in regulating appetite, sleep, emotions, and so on. In some parts of the brain, the axons of some of these neurons may regenerate (or re-grow) after drug use is stopped, but the new growth of the neurons is not normal. Some areas are not reinnervated (nerve fibers do not grow back into the area), and some areas have abnormally high regrowth of the neurons. Either way, the neurons do not look normal. Studies have not yet been able to determine whether MDMA has this same effect on humans.

Cocaine also changes the brain in ways that may last for a long time. PET scans of human brains have shown that glucose metabolism is reduced even three months after the last use of cocaine. Remember that glucose metabolism is an indicator of how active the brain cells are. If the neurons are using less glucose in certain areas, they are not as active. The changes that cocaine causes in the brain last much longer than the pleasurable feelings it produces. Other drugs cause similar decreases in brain activity. Even two years after the last use of amphetamines, PET images show that the brain of a

person who has abused drugs is less active than the person's who never used drugs.

Scientists, for many reasons, don't know all of the effects that a drug has. First, the brain is such a complicated organ that, despite great scientific advances, understanding all that it does will take many more years. Second, individuals may respond differently to drugs due to genetic and other differences among people. Third, many people who abuse drugs abuse more than one drug. Many individuals who take cocaine, for example, also drink alcohol. The combination of the drugs makes it difficult to determine what the effect of one drug alone may be. Another complication is that people addicted to drugs may have other health problems in addition to their drug problem. People addicted to heroin, for example, spend most of their energy and activity trying to get their next "fix." Consequently, they do not eat well and may have impaired immune systems. Also, drug-addicted people often suffer from mental illnesses, such as depression. The changes that occur in the brain because of mental illness make it difficult to determine what changes the drugs have caused.

The brain is an incredibly complex organ. This complexity will keep scientists working for many years to understand how the brain works. Someday, scientists will answer questions about what happens in the brain to cause addiction, which will then help scientists understand how to prevent addiction.

On a separate sheet of paper, answer the following questions:

1. What are some of the ways that drugs cause long-term changes in the brain?
2. How does the brain adapt to the presence of drugs?
3. How may the abuse of drugs relate to the plasticity of the brain?
4. What are some problems that scientists have when they investigate the effects of drugs on the brain?

# Exercise, pleasure and the brain

## Understanding the biology of "runner's high"

Yes, exercise can activate the brain's pleasure circuit. And so, like nicotine ororgasm or food or gambling, it can become a substrate for addiction as well. This can indeed be a genuine addiction, not merely one as expressed in a common usage like, "I'm addicted to sleeping on 600-thread-count sheets." Real exercise addicts display all of the hallmarks of substance addicts: tolerance, craving, withdrawal, and the need to exercise "just to feel normal." Does this make exercise a virtue, a vice, or a little of both?

Sustained physical exercise, whether it be running or swimming or cycling or other aerobic activity, has well-known health benefits, including improvements in the function of the cardiovascular, pulmonary, and endocrine systems. Voluntary exercise is also associated with long-term improvements in mental function and is the single best thing one can do to slow the cognitive decline that accompanies normal aging. Exercise has a dramatic antidepressive effect. It blunts the brain's response to physical and emotional stress. A regular exercise program produces a large number of changes in the brain, including the new growth and branching of small blood vessels and increases in the geometric complexity of some neuronal dendrites. It is associated with a host of interrelated biochemical changes as well, including increases in the level of a key protein called BDNF (brain-derived neurotrophic factor). At present we have little understanding of which of these morphological or biochemical changes underlie the beneficial effects of voluntary exercise on brain function, but this is an area of active research.

In addition to the beneficial long-term effects of a sustained exercise program, there are also short-term benefits of exercise that wear off after an hour or two. These include an increased pain threshold, reduction of acute anxiety and "runner's high." Runner's high (which can occur following any intense aerobic exercise, not just running) is a short-lasting, deeply euphoric state that's well beyond the simple relaxation or peacefulness felt by many following intense exercise. Careful surveys have revealed it to be rather rare: The majority of athletes, whether amateur or professional, never experience it at all, and those who do, only do so intermittently. Indeed, many distance runners or swimmers feel merely drained or even nauseated at the end of a long race, not blissful. Since the 1970s runners high has been attributed in the popular imagination to the exercise-triggered production of endorphins, the brain's own morphine-like molecules. This idea was initiated by a series of studies in which blood was drawn from subjects before and after intense exercise. Analysis revealed an exercise-associated increase in the level of a particular endorphin, called beta-endorphin, in the blood.

There's a major problem, however, in trying to link runner's high with circulating beta-endorphin . Beta-endorphin almost completely fails to cross the cellular barrier that separates the bloodstream from the brain. If beta-endorphin in the bloodstream were indeed responsible for runner's high, then it would have to increase levels of some other chemical messenger that would then cross into the brain to exert its effects. Alternatively, there are different types of endorphins (and their related molecules called enkephalins, which together with endorphins are called "endogenous opioids") that are synthesized within the brain and therefore could cause euphoria without crossing the blood-brain barrier.

One way to address this question would be to perform a spinal tap on people before and after exercise to see if opioid levels rose in the cerebrospinal fluid that bathes the brain and spinal cord. However, because a spinal tap is painful and carries a small risk of complications, human subjects review boards at most institutions have ruled that it is not ethical to conduct that type of experiment. Dr. Henning Boecker

and his coworkers at the University of Bonn in Germany realized that they could investigate runner's high without resorting to spinal taps by measuring brain opioid levels with a brain scanner. They recruited ten amateur distance runners who had previously reported experiencing runner's high. Each subject received a baseline brain scan using a radioactively tagged drug designed to measure the secretion of all forms of endogenous opioid (it bound to all types of the brain's many opioid receptors) and completed a survey of mood. After the subjects had a two-hour-long run followed by a thirty-minute cool-down period, the brain scan and mood survey were repeated. The researchers found that this long run was associated with increased opioid release in the runner's' brains, particularly in the prefrontal cortex (a planning and evaluation center) and the anterior cingulate cortex and insula (which serve to interface pain and pleasure with emotions). In addition, those subjects who reported the highest levels of euphoria after running also had the highest levels of opioid release.

This study is an interesting first step, but much more remains to be done in the area. One useful line of work will be to repeat the experiment using more specific opioid receptor drug probes in an attempt to implicate a particular endogenous opioid in runner's high. Then drugs that block those receptors could be given to see if runner's high could be attenuated. It's likely that runner's high is not entirely mediated by the opioid system: Exercise also increases the levels of endocannabinoids, the brain's natural cannabis-like molecules, in the bloodstream. Unlike beta-endorphin, which cannot readily pass the blood-brain barrier, endocannabinoids easily move throughout the body. Thus exercise-induced increases in endocannabinoid levels in blood are presumably mirrored in the brain and could also contribute to the euphoria of runner's high.

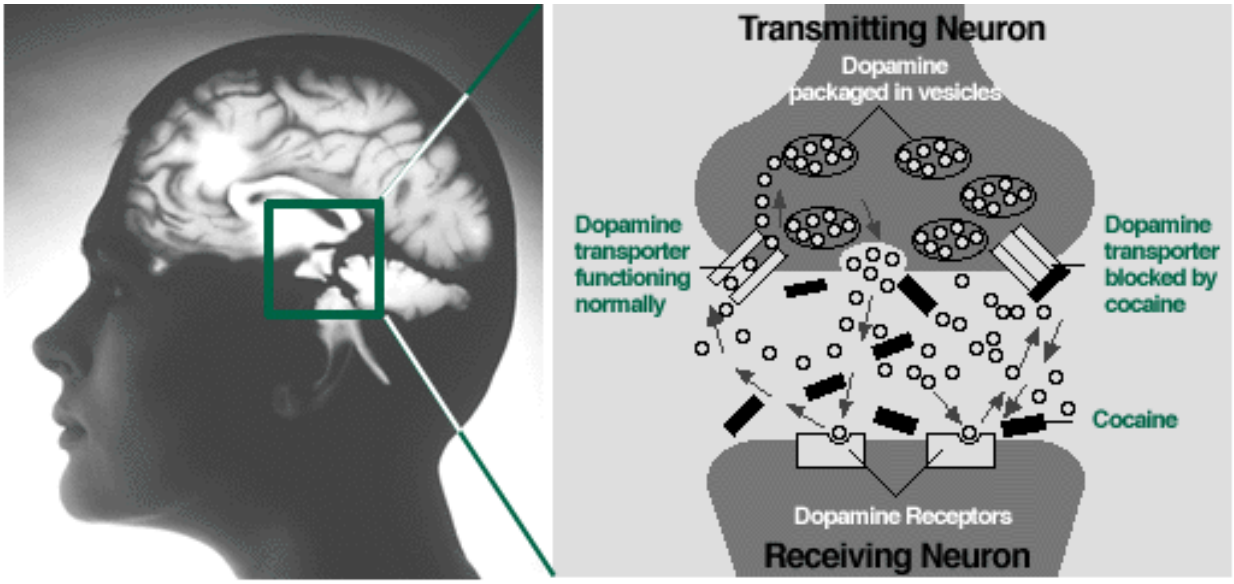
Putting some of the pieces together, we know that intense exercise can bring about short-term euphoria, reduction of anxiety, and increases in pain threshold. This is coincident with increases in the levels of brain opioids and, presumably, endocannabinoids, both of which can produce all of these short-term psychoactive

effects. We also know that endocannabinoids and opioids can indirectly activate dopamine cells of the ventral tegmental area (the VTA, a key portion of the pleasure circuit) and thereby stimulate the medial forebrain pleasure circuit. We know that exercise can be addictive and that other substances and behaviors that are addictive have increased dopamine release in VTA target regions as a common property. In rats, sustained wheel-running can cause dopamine release in the nucleus accumbens and other VTA target regions. Rats also show some signs of exercise addiction . For example, they can be trained to work hard (i.e., perform many lever presses) for access to a running wheel.

All these observations taken together suggest that intense exercise will activate release from VTA dopamine neurons, a process that will underlie at least some portion of runner's high. Unfortunately, to date there is little evidence to support this theory in humans. Gene-Jack Wang and his colleagues at Brookhaven National Laboratory used a brain scanner to image dopamine release in the nucleus accumbens and dorsal striatum of twelve subjects before and after thirty minutes of vigorous treadmill running, followed by a ten-minute cool-down period. They found no differences in D2 dopamine receptor occupancy (their measure of dopamine release) associated with this exercise regimen. No mood scale ratings were performed, so we cannot know if these subjects experienced runner's high. It would be useful to repeat this experiment together with mood scale ratings and more intense exercise, as Boecker and coworkers did for their endogenous opioid measurements.

Published on April 21, 2011 by David J. Linden, Ph.D. in The Compass of Pleasure
http://www.psychologytoday.com/blog/the-compass-pleasure/201104/exercise-pleasure-and-the-brain

# The Brain's Reward System




Central to the rewarding excitatory effects of psychoactive drug use and the possible eventuality of drug addiction is the role of the brain's dopaminergic neurotransmitter system. Neurons in this system are critical in the mediation of reinforcement; i.e. behaviors that stimulate brain-reward regions rich with dopaminergic neurons are likely to be repeated due to the intrinsic reward value they possess. Stimulation to these systems elicits a range of motivational emotions and responses that encourage adaptive behavior; eating, exercise, sexual behaviors, and personal accomplishments stimulate reward centers and provide motivation for a repeat performance. When systems within reward centers go awry due to injury, stress, genetics, or drug use, however, behavior may become dysfunctional, leading to affective, eating or sexual disorders and other compulsive and excessive behaviors.

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http://criminology.fsu.edu/crimtheory/week5.htm

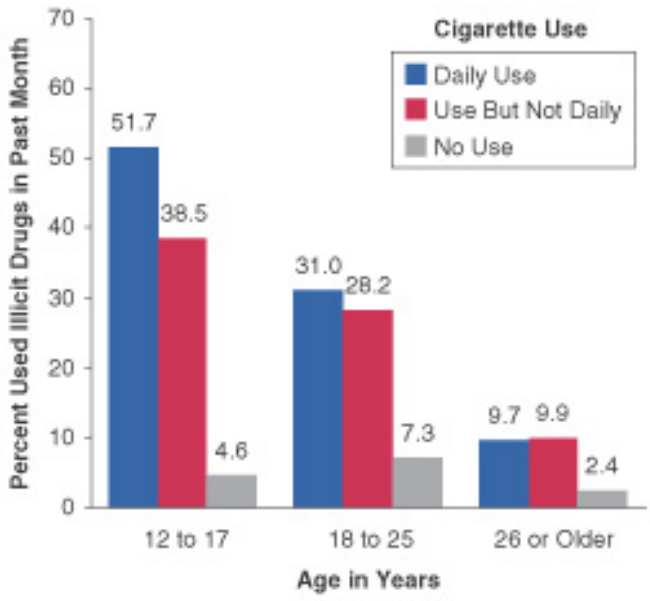


**Figure 1. Percentages of Persons Aged 12 or Older Reporting Past Month Illicit Drug Use,** by Level of Past Month Cigarette Use and Age Group: 2000**

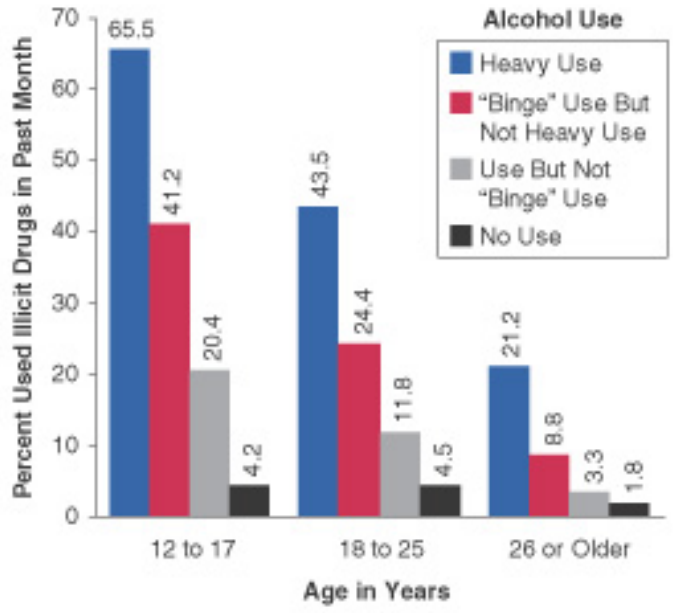


**Figure 2. Percentages of Persons Aged 12 or Older Reporting Past Month Illicit Drug Use,** by Past Month Alcohol Use and Age Group: 2000**

**Table and Figure Notes:**

* "Binge" Alcohol Use is defined as drinking five or more drinks on the same occasion on at least 1 day in the past 30 days. By "occasion" is meant at the same time or within a couple hours of each other. Heavy Alcohol Use is defined as drinking five or more drinks on the same occasion on each of 5 or more days in the past 30 days.

**Illicit Drug Use indicates use at least once of marijuana/hashish, cocaine (including crack), heroin, hallucinogens (including LSD and PCP), inhalants, or any prescription-type psychotherapeutic used nonmedically.

Source (table and figures): SAMHSA 2000 NHSDA.

# Perception of Marijuana as a 'Safe Drug' Is Scientifically Inaccurate, Finds Review of Teen Brain Studies

The nature of the teenage brain makes users of cannabis amongst this population particularly at risk of developing addictive behaviors and suffering other long-term negative effects, according to researchers at the University of Montreal and New York's Icahn School of Medicine at Mount Sinai.

*The nature of the teenage brain makes users of cannabis amongst this population particularly at risk of developing addictive behaviors and suffering other long-term negative effects. (Credit: © EJ White / Fotolia)*

"Of the illicit drugs, cannabis is most used by teenagers since it is perceived by many to be of little harm. This perception has led to a growing number of states approving its legalization and increased accessibility. Most of the debates and ensuing policies regarding cannabis were done without consideration of its impact on one of the most vulnerable populations, namely teens, or without consideration of scientific data," wrote Professor Didier Jutras-Aswad of the University of Montreal and Yasmin Hurd, MD, PhD, of Mount Sinai. "While it is clear that more systematic scientific studies are needed to understand the long-term impact of adolescent cannabis exposure on brain and behavior, the current evidence suggests that it has a far-reaching influence on adult addictive behaviors particularly for certain subsets of vulnerable individuals."

The researchers reviewed over 120 studies that looked at different aspects of the relationship between cannabis and the adolescent brain, including the biology of the brain, chemical reaction that occurs in the brain when the drug is used, the influence of genetics and environmental factors, in addition to studies into the "gateway drug" phenomenon. "Data from epidemiological studies have repeatedly shown an association between cannabis use and subsequent addiction to heavy drugs and psychosis (i.e. schizophrenia). Interestingly, the risk to develop such disorders after cannabis exposure

is not the same for all individuals and is correlated with genetic factors, the intensity of cannabis use and the age at which it occurs. When the first exposure occurs in younger versus older adolescents, the impact of cannabis seems to be worse in regard to many outcomes such as mental health, education attainment, delinquency and ability to conform to adult role," Dr Jutras-Aswad said.

Although it is difficult to confirm in all certainty a causal link between drug consumption and the resulting behavior, the researchers note that rat models enable scientists to explore and directly observe the same chemical reactions that happen in human brains. Cannabis interacts with our brain through chemical receptors (namely cannabinoid receptors such as CB1 and CB2.) These receptors are situated in the areas of our brain that govern our learning and management of rewards, motivated behavior, decision-making, habit formation and motor function. As the structure of the brain changes rapidly during adolescence (before settling in adulthood), scientists believe that the cannabis consumption at this time greatly influences the way these parts of the user's personality develop. In adolescent rat models, scientists have been able to observe differences in the chemical pathways that govern addiction and vulnerability – a receptor in the brain known as the dopamine D2 receptor is well known to be less present in cases of substance abuse.

Only a minority (approximately one in four) of teenage users of cannabis will develop an abusive or dependent relationship with the drug. This suggests to the researchers that specific genetic and behavioral factors influence the likelihood that the drug use will continue. Studies have also shown that cannabis dependence can be inherited through the genes that produce the cannabinoid receptors and an enzyme involved in the processing of THC. Other psychological factors are also likely involved. "Individuals who will develop cannabis dependence generally report a temperament characterized by negative affect, aggressivity and impulsivity, from an early age. Some of these traits are often exacerbated with years of cannabis use, which suggests that users become trapped in a vicious cycle of self-medication, which in turn becomes a dependence,"

Jutras-Aswad said.

The researchers stress that while a lot remains unknown about the mechanics of cannabis abuse, the body of existing research has clear implications for society. "It is now clear from the scientific data that cannabis is not harmless to the adolescent brain, specifically those who are most vulnerable from a genetic or psychological standpoint. Identifying these vulnerable adolescents, including through genetic or psychological screening, may be critical for prevention and early intervention of addiction and psychiatric disorders related to cannabis use. The objective is not to fuel the debate about whether cannabis is good or bad, but instead to identify those individuals who might most suffer from its deleterious effects and provide adequate measures to prevent this risk" Jutras-Aswad said. "Continuing research should be performed to inform public policy in this area. Without such systematic, evidenced-based research to understand the long-term effects of cannabis on the developing brain, not only the legal status of cannabis will be determined on uncertain ground, but we will not be able to innovate effective treatments such as the medicinal use of cannabis plant components that might be beneficial for treating specific disorders," Dr Hurd said.

**Story Source:**

The above story is based on materials provided by **Universite de Montreal**, via Newswise.

**Journal Reference**:

1. Yasmin L. Hurd, Michael Michaelides, Michael L. Miller, Didier Jutras-Aswad. **Trajectory of adolescent cannabis use on addiction vulnerability**. *Neuropharmacology*, 2013; DOI: 10.1016/j.neuropharm.2013.07.028