Psychopharmacology

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Chapter 9: The Pharmacology of Scheduled Psychoactive Drugs: Psychostimulants, Psychedelics, and Marijuana

This chapter and the next examine the pharmacology of a wide range of drugs that have both clinical and recreational significance. These drugs range from the mild psychostimulant caffeine which is found in coffee, tea, and chocolate, to some of the most addictive and destructive substances known including crack cocaine and methamphetamine. The pharmacology of the opiates will be described in a separate chapter.

> *Katherine had a relatively normal childhood. She grew up in a family of four. He father was a successful real-estate broker in Seattle and her mother, who was an elementary school teacher before she had children, remained at home during the early years before she and her twin brother started school. Late in elementary school Katherine discovered she could easily influence those around her using her popularity and good looks. She matured more quickly than other girls her age and took advantage of the attention she drew. By middle school Katherine was attracted to older boys and enjoyed the thrills of occasional cigarettes and alcohol that they could provide. She was able to evade most of the trouble her risky lifestyle taunted until she became pregnant during her junior year of high school. Her gothic style of dress kept this a secret from her friends and parents through the first four months of pregnancy. The secret ended when Katherine developed a serious infection from gonorrhea and needed*

medical attention. Because of the advanced stage of infection Katherine was encouraged to have an abortion. After this Katherine's life began to change in significant ways. Her relationship with her parents deteriorated quickly and she was no longer attending school. Katherine found the company of an older boy who afforded a nice downtown apartment by selling marijuana, methamphetamine, and crack cocaine whenever it was available. It wasn't long before Katherine was using meth regularly and assisting her friend in its distribution. By the time she was 18, Katherine was addicted and no longer a desirable partner to her companion and business partner. Once their relationship ended Katherine found it more and more difficult to obtain the meth she craved. She returned home for a few weeks and convinced her father she needed a loan to begin cosmetology school and to secure an apartment near its campus. With $8,000 Katherine moved back downtown and quickly reestablished a source for meth. Her stint at school lasted less than a month and it was clear that $8000 wouldn't last much longer. At this point Katherine's life was consumed by methamphetamine. Most of her days began late after shrugging off a drug hangover and trying to locate methamphetamine or crack cocaine. Even though Katherine knew the streets well her drug cravings often pushed her for miles in the rain to finally locate a seller. On days drugs were unavailable Katherine returned to her apartment to fight off the severe headaches and nausea of withdrawals and hopefully sleep. In order to keep her apartment, and the drug supply that now cost almost $100 per day, Katherine turned to petty theft and prostitution. At first she found it easy to attract high-paying clients through an agency in Seattle. However, as the meth began to takes its toll her appearance deteriorated quickly and her agency and once-easy clients were no longer interested. Predictably, Katherine, along with several other young girls, was arrested late one night in a prostitution sting. Not knowing who else to call, she woke her mother who was able to secure her release. Shocked by her appearance and stuporous condition her mother rushed her to a hospital. Katherine had lost over 30 lbs from her previously healthy weight, her forearms had scars from numerous injections and scratching, and she had hepatitis from contaminated needles and unprotected sex. In the course of just over 18 months Katherine had transformed from an attractive and popular high school student to a young woman hovering over death with a methamphetamine addiction. Katherine was admitted to a private recovery clinic in Seattle where she spent the next 30 days living at the facility with few opportunities to leave. The exceptions were brief excursions with her parents for dinner or a quick shopping spree. After her in-house stay Katherine was allowed to move back to her parent's home and to attend college part time. She is now in her second semester with plans to study psychology. During our interview Katherine admitted that, although she hasn't used drugs since her release, she has felt the intense urge. While recently driving the streets she had once walked in search of meth the frightening and exhilarating anticipation of seeing a

seller all rushed back to her. The next few hours were filled with the confusion of racing thoughts and the severe temptation to use just one more time. In all likelihood Katherine's addiction will win out within a year as it unfortunately does with most drug addicts. The recidivism rate for meth addiction is over 80% within the first year of abstinence. Most recovered addicts will have sought help several times before finally quitting meth for good.

Katherine's case is neither surprising nor is it typical, as there is no characteristic course or set of experiences that leads one to drug addiction. Katherine flirted with risky behavior from early in middle school, but other drug addicts may begin using at a much older age even after they have started a career and family. We begin this chapter, however, reviewing the pharmacology of a wide range of drugs with potential for abuse in addition to their significant clinical importance.

The use of drugs by youth in our country had been rising at an alarming and steady rate prior to 1999. At that time, approximately 42.1% of high school seniors had used an illicit drug during the previous year. Since 1999, however, illicit drug use by teenagers has gone down slightly each year. The most recent statistics, from the National Survey on Drug Use and Health, estimates the annual prevalence of illicit drug use to be just under 36%--a decline of about 1% each year. The same descending trend over these years has also been observed with alcohol and tobacco use. The only upward trend has been a gradual increase in the illegitimate use of prescription pain medication. About 15% of high school seniors used Vicodin or OxyContin during the past year without a prescription, which represents an increase of about 1.5% over the past 8 years.

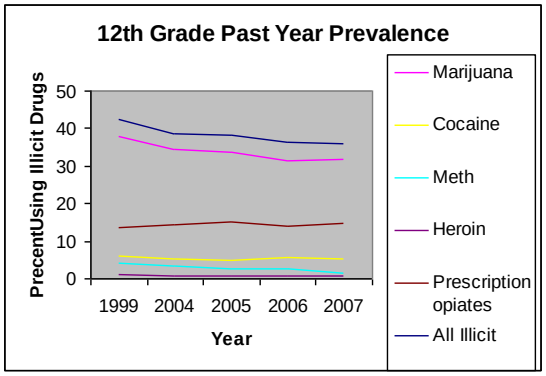


Figure 1: *Annual prevalence of drug use by 12th graders from the highest prevalence rates recorded in 1999 through 2007. Since 1999 there has been a very slight decline in all illicit drug use with the exception of the use of opiate prescription drugs (Vicodin & OxyContin) which increased slightly. From the National Survey on Drug Use and Health, 2007.*

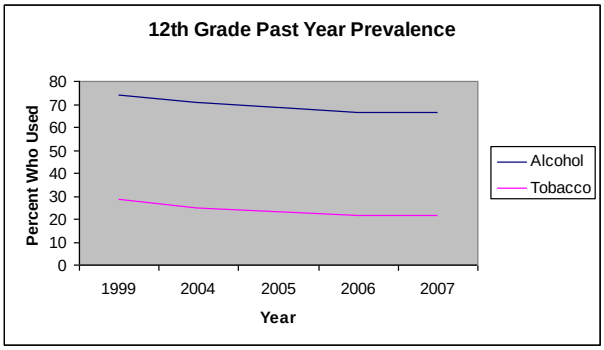


Figure 2*: Annual prevalence of alcohol and tobacco use by 12th graders. Both alcohol and tobacco use has declined about 1% each year for the past 8 years. From the National Survey on Drug Use and Health, 2007.*

The use of psychoactive drugs is not a recent phenomenon as many of the drugs discussed in this chapter have uses dating back hundreds or even thousands of years. Caffeine, nicotine, cocaine, opium, psychedelic mushrooms, marijuana, and alcohol all have uses that can all be traced back to ancient times. Other, more modern drugs are either derivatives of these ancient substances or they have been discovered or synthesized more recently. For example, amphetamines were more recently extracted from the Ephredra plant, LSD from the ergot fungus which grows on grain, and morphine extracted from opium. For convenience these psychoactive drugs will be separated into two categories: scheduled drugs and unscheduled drugs and substances.

The term **drug schedule** refers to a drugs classification based on its potential for abuse as described by the **Controlled Substance Act** of 1970. The Controlled Substance Act identified five schedules, or classifications of drugs ranging from Schedule I to Schedule V. Schedule I drugs, for instance, were those with little or no clinical significance but with a great potential for abuse. Included in Schedule I are LSD, marijuana, and heroin. Schedules II through V classified drugs with decreasing abuse potential and with some clinical importance. The drug schedules created by the Controlled Substance Act are summarized in Table 1 with a few examples within each classification. The use of scheduled drugs is highly regulated by the **Drug Enforcement Administration** (DEA) and they are only available by prescription from a licensed practitioner or through a special license issued by the DEA to scientists and laboratories for the purpose of conducting research.

Schedule	Description	Examples of Drugs and Substances
I	Drugs have a high potential for abuse, have no accepted medical use, and there is a lack of safety information regarding their use.	heroin, LSD, mescaline, psilocybin, marijuana
II	Drugs have a high potential for abuse, have accepted medical uses, but their use may lead to severe dependence.	morphine, codeine, cocaine, amphetamine, methamphetamine, nabilone (synthetic THC)
III	Drugs have a potential for abuse, have accepted medical uses, and their use may lead to low or moderate dependence.	anabolic steroids, pentobarbital, Marinol (synthetic THC)
IV	Drugs have a low potential for abuse, have accepted medical uses, and they have a lower risk of dependence than Schedule III drugs.	Benzodiazepines, Phenobarbital, Ambien and similar sleep aides
V	Drugs have a low potential for abuse, have accepted medical uses, and the have a lower risk of dependence than Schedule IV drugs	Codeine and opiate preparations for cough or diarrhea

Table 1*: The classification of controlled substances by the Controlled Substance Act of 1970. A complete list of scheduled drugs is available from the Drug Enforcement Administration (www.usdoj.gov/dea).*

Scheduled Psychoactive Drugs

The scheduled drugs discussed in this section include cocaine, amphetamines, marijuana, and psychedelic drugs. All of these drugs fall into either Schedule I or II for controlled substances. It is important to point out that the assignment of a drug schedule may be more influenced by politics than by pharmacology. Marijuana and LSD are two such examples. Neither of these drugs has been shown to have a high abuse potential and marijuana, arguably, has medical benefits. The barbiturates and benzodiazepines which

fall into Schedules III and IV were described in Chapter 5 on anxiety disorders and the opiates, in Schedules I and II, are described in a later chapter.

Psychostimulants: Cocaine

Cocaine is extracted from the coca plant (*Erythroxylum coca*) which readily grows in the mountainous regions of South America. Although most of the illicit cocaine comes from Columbia and Peru, significant amounts are also grown in Bolivia and Ecuador.

Coca leaves have been used by the indigenous people of South America for thousands of years. These leaves, when chewed, produce a sense of well-being and confidence as well as relief from fatigue. The practice of chewing coca leaves appears to have been widespread in South America and evidence for its use has even been found in ancient Peruvian tombs. While chewing coca is still popular in some South American regions, most cocaine is exported as cocaine sulfate or cocaine hydrochloride.

Cocaine compounds are extracted from the coca leaf by crushing the leaves in a solvent such as kerosene, benzene, or alcohol to extract the cocaine. Traditionally the leaves were crushed by stomping on them in large vats, but mechanical crushing has essentially replaced stomping as it is a much quicker and more efficient way to macerate the leaves for cocaine extraction. The liquid mixture that is produced is processed with heat and sulfuric acid to isolate the cocaine alkaloids and remove the waxy residue from the leaf extract. This process results in a cocaine sulfate paste that can contain as much as 60% cocaine. Cocaine paste can be further processed with dilute hydrochloric acid to produce a water soluble crystalline compound called cocaine hydrochloride.

Not only have large cocaine processing facilities in South America provided customers around the world with cocaine, they have begun to devastate the ecology of streams and rivers where these solvents are dumped after cocaine extraction. Numerous formerly pure streams in Columbia and Peru are now polluted with extraction solvents such as kerosene, gasoline, and benzene as well as sulfuric and hydrochloric acids.

Figure 3*: Coca shrubs grow readily in mountainous regions throughout South America. The coca leaves from these shrubs can be harvested several times each year.*

Figure 4*: Processed cocaine hydrochloride. This water soluble compound can be snorted, injected, or converted into crack cocaine for smoking.*

As shown in Figure 1, the use of cocaine among high school seniors has been essentially stable for the past 8 to 10 years. However, in 2006 it was estimated that over 35 million Americans over age 12 had used cocaine at least once and that there are about 2 million regular users of cocaine. In the United States a gram of cocaine hydrochloride (about 60-70% pure) cost just over $100, but the price can vary widely depending on

location. This is enough cocaine to provide about 5-10 doses of snorted, or 10-15 doses of intravenous cocaine to users who have not developed significant tolerance.

While the amount of cocaine produced in South America is difficult to determine, the Office of National Drug Control Policy estimates that 970 metric tons were produced in 2006 and most of this was bound for the U.S. In that year over 150 metric tons were seized by law enforcement agencies in the United States.

History of Cocaine Use

The stimulant effects of coca were recognized and well described long before cocaine was identified as its active ingredient. The cocaine alkaloid was first isolated in 1855 by the German chemist Freidrich Gaedcke who named it erythroxyline. It was another German scientist, Albert Niemann, who actually named it cocaine after carefully describing its extraction and purification process. Soon after its isolation, cocaine became widely used as a local anesthetic, particularly for surgeries of the eyes and nose. Cocaine was also added to tonics and beverages because of its stimulating effects. In 1863 the wine tonic Vin Mariani was marketed in the U.S. and soon after cocaine was added to the original Coca-Cola recipe, thus its name. By the early 1900s cocaine could be purchased in local drugstores and was included in a variety of tonics and remedies.

Sigmund Freud's interest in cocaine began in the early 1880s after reading scientific reports about its effects. Freud claims to have used cocaine frequently during this period,

> *"I take very small doses of it regularly against depression and against indigestion, and with the most brilliant success."*

His experiences as well as recommendations for its uses were soon published in a series of scientific papers and letters called the *Cocaine Papers*. The first of this sequence, Über Coca (About Cocaine), was published in 1884. A selection from this work describes some of his experiences

> *"The psychic effect of cocaïnum muriaticum in doses of 0.05–0.10g consists of exhilaration and lasting euphoria, which does not differ in any way from the normal euphoria of a healthy person. The feeling of excitement which accompanies stimulus by alcohol is completely lacking; the characteristic urge for immediate activity which alcohol produces is also absent. One senses an increase of self-control and feels more vigorous and more capable of work; on the other hand, if one works, one misses that heightening of the mental powers which alcohol, tea, or coffee induce. One is simply normal, and soon finds it difficult to believe that one is under the influence of any drug at all."*

Freud enthusiastically promoted the use of cocaine to his friends and his fiancée in spite of concerns by those close to him that he may have become addicted to it. Freud continually denied that cocaine had any harmful effects and whether or not he was actually addicted during this time remains unknown.

> *"It seems to me noteworthy – and I discovered this in myself and in other observers who were capable of judging such things – that a first dose or even repeated doses of coca produce no compulsive desire to use the*

stimulant further; on the contrary, one feels a certain unmotivated aversion to the substance."

It wasn't until the passage of the **Harrison Narcotic Tax Act** in 1914 that cocaine was prohibited in all of its forms and mistakenly described as a dangerous narcotic. After its prohibition cocaine was only available to licensed practitioners for medicinal and research uses. Its use as a local anesthetic continues to the present although other local anesthetics like lidocaine (Xylocaine) and procaine (Novocaine) are much more commonly used.

*Pharmacology of Cocain*e

Cocaine hydrochloride (cocaine-HCl) is a water soluble compound that once administered readily separates into cocaine-H^+ and Cl^- ions in the blood. The protonated (positively charged) cocaine ion (cocaine-H^+) quickly passes through cell membranes and enters the brain. How rapidly cocaine enters the brain depends on its route of administration. Snorted and orally ingested cocaine enter the brain more slowly and incompletely than either intravenous administration or the inhalation of vaporized cocaine. For example, peak levels of cocaine are reached within 5 minutes of an iv injection compared to nearly an hour after intranasal administration.

Figure 5: *Crack (freebase) cocaine (methylbenzoylecgonine) is produced by heating cocaine hydrochloride in water and sodium bicarbonate. The crystals or "rocks" are then vaporized for inhalation by further heating.*

Crack Cocaine Beginning in the 1980s, cocaine users began converting cocaine hydrochloride (an acid) into a base by dissolving it in mild ammonia (NH_3) solution. This results in the compound **methylbenzoylecgonine** which could be vaporized for inhalation. During the production process a cracking sound is made, thus the name **crack**. Crack cocaine can also be manufactured by heating cocaine hydrochloride in water and sodium bicarbonate (baking soda). The cocaine rocks (called freebase cocaine) produced by these methods are then heated until they vaporize. Inhaling the vapors of freebase cocaine is an efficient and rapid method of cocaine delivery. Peak plasma levels are reached within 5 minutes by inhalation.

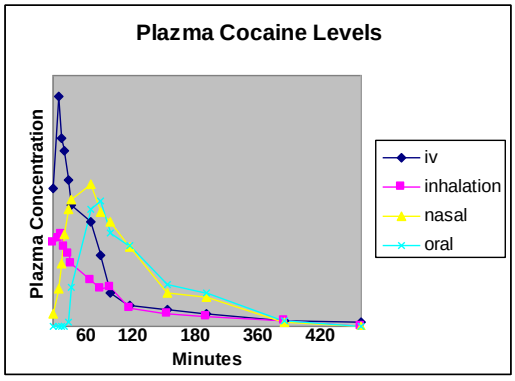


Figure 6: *Cocaine concentrations in plasma depend upon route of administration. The highest concentrations follow iv administration or inhalation in about 5 minutes.*

Cocaine is widely distributed throughout bodily tissues and is metabolized quickly by both blood and liver enzymatic hydrolysis. The metabolic half-life of cocaine varies between 1 to 1.5 hours. The principle metabolites of cocaine are **benzoylecgonine** and **ecgonine**, both of which can be detected in the blood and other tissues for several weeks. Benzoylecgonine can also be detected in the hair of regular users for the life of a particular hair cell or until it is cut and only sections grown since the last drug use are exposed. If cocaine is used with alcohol the active compound **cocaethylene** is formed which is believed to be an even more potent euphoric than cocaine itself. Cocaethylene has a half-life of approximately 2.5 hours, nearly doubling the duration of the toxic and psychoactive effects of cocaine. Cocaethylene is particularly toxic to cardiac functioning. It causes severe hypertension, ventricular arrhythmia, and decreased blood flow—any of which can have unpredictably fatal consequences to otherwise healthy individuals (Wilson et al., 2002).

Mechanisms of Cocaine Action

Cocaine readily passes through cell membranes in the brain and acts by binding to the **dopamine transporter** (DAT) on the presynaptic membrane. Because of its high affinity for the transporter protein cocaine blocks the normal reuptake of dopamine from the synaptic gap resulting in prolonged dopamine activity on postsynaptic receptors. Cocaine has similar effects on transporters for both norepinephrine and serotonin. However, cocaine's effects on the dopamine transporter are believed to be the most important for is psycho stimulating and reinforcing effects. In human studies the subjective, euphoric effects of cocaine appear to be directly related to its degree of DAT

binding. At least 47% of dopamine transporters need to be blocked before subjects perceive the euphoric effects of cocaine and doses that typically induce euphoria in cocaine users occupy between 60 and 80% of DATs (Volkow et al., 1997).

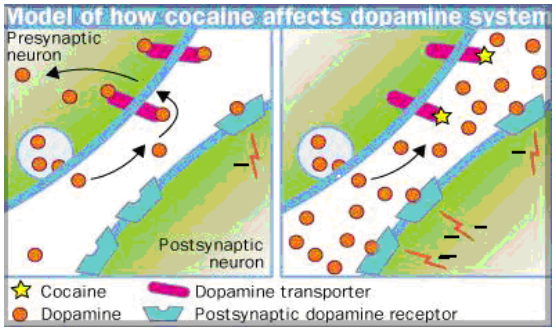


***Figure 7**: Cocaine acts by blocking the reuptake transporters for dopamine, serotonin, and norepinephrine on the presynaptic terminal.*

It is important to note, however, that DAT blockade by itself is not sufficient to account for cocaine's euphoric effects. The drug methylphenidate (Ritalin), which was described in the chapter on attention disorders, also blocks DATs to an extent similar to that of cocaine. The critical difference between methylphenidate and cocaine is how rapidly DAT blockade occurs after administration. Cocaine quickly enters the brain and blocks DATs while orally administered methylphenidate only does so slowly (Volkow et al., 2003). A rapid increase in dopamine activity in the **mesolimbic system** is believed to be critical for the euphoric and reinforcing potential of cocaine and other addictive substances.

As stated above, cocaine also blocks norepinephrine and serotonin transporters and these systems may also contribute to cocaine's reinforcing and euphoric effects. To examine this, mice with genetic deletions of the DAT gene (knockout mice) have been tested for cocaine's reinforcing effects. If cocaine reinforcement is mediated solely by

dopamine transporter blockade, DAT knockout mice would not be expected to demonstrate cocaine reinforcing effects. A popular method to investigate drug reinforcement is to repeatedly administer cocaine to animals in the same side of a dual chambered apparatus (see Figure 7). Later, animals are given a choice to explore both chambers and the time animals spend on each side is a measure of their conditioned place preference. This procedure is referred to as **place preference conditioning** (PPC). Typically animals prefer spending time in the chamber associated with cocaine administration.

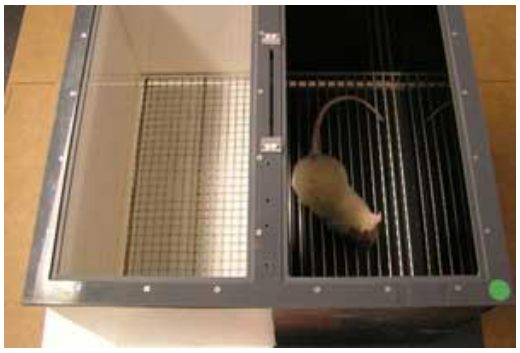


Figure 8: *Place preference conditioning (PPC) apparatus used to investigate the reinforcing effects of drugs. Animals tend to prefer spending time in the chamber associated with cocaine administration. Place preference conditioning is a demonstration of Pavlovian conditioning where context cues serve as conditioned stimuli (CSs) and drug onset serves as an unconditioned stimulus (US). Conditioned responses (CRs) are increases in motivation and arousal expressed as preferences for the drug-associated context.*

Dopamine transporter knockout mice retain cocaine's reinforcing effects in spite of the fact that they don't express the dopamine transporter. It is believed that in these mice cocaine effects on serotonin neurons within the **ventral tegmental area** (VTA) contribute to enhance dopamine activity in the mesolimbic system, particularly in the

nucleus accumbens (Hnasko et al., 2007; Mateo et al., 2004; Sora et al., 2001; Thanos et al., 2008).

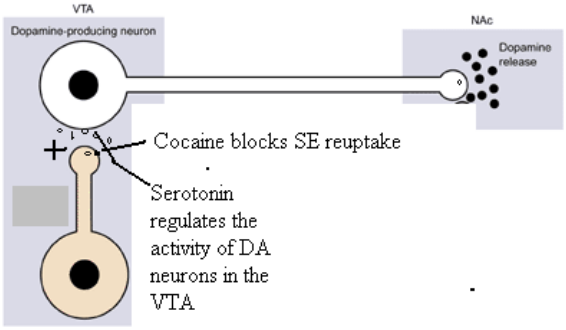


Figure 9: *Serotonin-dopamine interactions in the ventral tegmental area (VTA). Serotonin, and perhaps norepinephrine, regulate the activity of dopamine neurons in the VTA and can contribute to increased dopamine release in the nucleus accumbens (NAc).*

In summary, cocaine's euphoric and reinforcing effects are primarily mediated by enhanced dopamine concentrations in synapses in the nucleus accumbens and in the basal ganglia. In DAT **knockout animals** these effects appear to be mediated upstream of the nucleus accumbens, in the ventral tegmental area (VTA) of the midbrain where these dopamine neurons originate. Serotonin in the VTA appears to regulate dopamine activity and may contribute to increased dopamine release in the nucleus accumbens.

Figure 10: *Cocaine was widely used as a local anesthetic before 1914 when it was prohibited in tonics and remedies.*

Cocaine as a local anesthetic and Na^+ channel blockade

Cocaine has a long history of use as an **anesthetic** for surgery of the eyes, mouth, and nose. Its ability to not only dull pain but to constrict local blood flow makes it ideal for these uses. Cocaine disrupts the propagation of action potentials by blocking voltage-gated Na^+ channels. As action potentials propagate along an axon, voltage-gated sodium channels open as the membrane depolarizes allowing Na^+ influx and a continuation of the action potential. When cocaine enters these channels it effectively blocks Na^+ influx and prevents further depolarization. Because protonated cocaine (cocaine-H^+) more easily enters a sodium channel when it is open, the anesthetic effects of cocaine are greatest when local pain transmitting neurons are rapidly firing. Cocaine is most often used as a **local anesthetic** whenever its actions are to be restricted to its site of administration. In surgery of the eye, for example, cocaine may either be applied directly to the eye or injected to tissues surrounding the eye. Cocaine does have **analgesic** properties when administered systemically (an iv injection, for example), but these effects are not

considered local anesthetic effects even though the anesthetic effects is still mediated by Na^+ channel blockade.

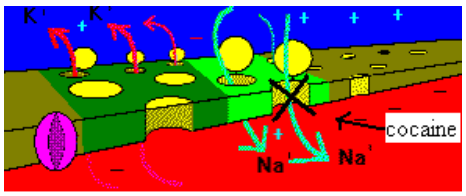


***Figure 11**: Cocaine's anesthetic effects are mediated by sodium channel blockade, thereby disrupting the propagation of action potentials. Protonated cocaine (cocaine-H^+) readily enters Na^+ channels when pain transmitting neurons are firing.*

Cocaine use is occasionally associated with cardiac toxicity including myocardial infarction, arrhythmias, and occasional sudden death. It is believed that Na^+ channel blockade in neurons controlling cardiac functioning may be a contributing factor in these abnormalities. Cocaine's respiratory depressant effects are also believed to be mediated by Na^+ channel blockade in neurons within the chemosensitive sites of the medulla. Normally these neurons respond to decreases in blood pH by triggering ventilatory responses. Cocaine, as well as the opiates, barbiturates, and alcohol can all inhibit respiratory responses, although by different means, and can lead to respiratory failure and sudden death.

Psychostimulants: Amphetamine and Methamphetamine

The amphetamines are a collection of closely related compounds that resemble the neurotransmitter dopamine in chemical structure. The first of these compounds to be used was ephedrine which is extracted from the *ephedra sinica* plant, also known as ma huang from ancient Chinese medicine. Ma huang has been used as an herbal remedy for

at least 5,000 years to treat a variety of ailments including asthma and allergic reactions as well as congestion resulting from the common cold.

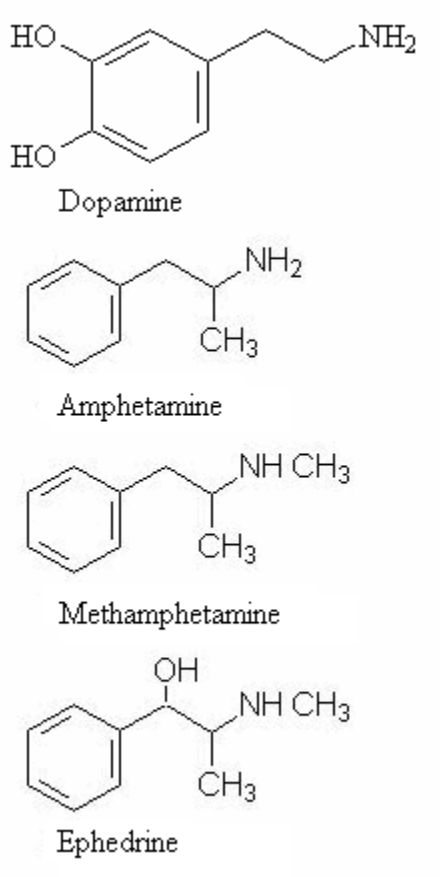


Figure 12: *Molecular structures of dopamine, amphetamine, methamphetamine, and ephedrine. All of these compounds share a similar core structure.*

More recently **ephedra** has been marketed as a diet aid for weight loss, to increase wakefulness, and as a performance enhancer. Its effectiveness as a weight loss and performance enhancing supplement remain controversial, but it has nevertheless been banned by many sport organizations as well as by the International Olympic Committee.

Because of several highly publicized fatalities related to ephedra in the late 1990s, it was finally banned altogether by the FDA in 2004.

Amphetamine was first synthesized by the Romanian chemist Lazăr Edeleanu in 1887. It wasn't until the mid 1930s, however, that amphetamine was finally marketed as an inhalant antihistamine under the trade name Benzedrine. Soon after, the structurally related amphetamine **dextroamphetamine** (Dexedrine) was introduced to treat narcolepsy, attention disorders, nasal congestion, and obesity. By the late 1940s amphetamines were used to treat nearly 40 different disorders including depression, fatigue, obesity, narcolepsy, drug addiction, and even the hiccups. It was also widely used by the US military to thwart fatigue and sleepiness in combat during both World Wars. By the 1960s amphetamine production surged as it was mass marketed as a weight loss aid. During this time of easy availability it was used by many college students to facilitate long study sessions in lieu of caffeine. Endurance athletes, particularly competitive cyclists, found amphetamines useful to enhance training and competition. Sadly their use in sports led to a number of unfortunate deaths related to cardiac toxicity. In the early 1970s, amphetamine production reached its all time high of over 10 billion tablets. Because of the widespread abuse of amphetamines Benzedrine was replaced with propylhexedrine as the active ingredient in the Benzedrex inhaler and Dexedrine became more restricted as it was classified as a Schedule II drug with high abuse potential and limited medical use. Dexedrine and other amphetamines are still prescribed to treat narcolepsy and some attention disorders.

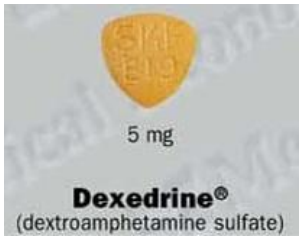


Figure 13: *Dexedrine, dextroamphetamine sulfate, is available in either tablet or capsule form.*

As amphetamine became less available, and users demanded an even more powerful drug, illicit amphetamine sales and the manufacture of methamphetamine surged. **Methamphetamine** was first synthesized from ephedrine in 1893, but its popularity in the US emerged in the 1980s as users quickly discovered its powerful euphoric effects. The name methamphetamine comes from its chemical name methyl-amphetamine (**desoxyephedrine**). Methamphetamine is easily produced by the chemical reduction of ephedrine (loss of the hydroxyl group shown in Figure 12). Clandestine laboratories perform this reduction by various methods requiring chemicals that are easily obtained. Methamphetamine differs structurally from amphetamine by the additional methyl group (CH_3) which increases its lipid solubility allowing it to cross the blood brain barrier within seconds of an injection. As the illustration in Figure 14 shows, pure methamphetamine is in a crystal form, thus the name **crystal meth**.

Figure 14*: Methamphetamine (desoxyepherdine) is derived from several precursor compounds including ephedrine and pseudoephedrine. This crystalline form is typically called crystal meth.*

Pharmacology of the Amphetamines

Amphetamines can be administered by various methods including the oral ingestion of pill forms, nasal inhalation (snorting), smoking, or by iv injection. Peak plasma levels are reached in about 2 to 3 hours after oral administration and within 5 minutes after an iv injection or smoking. Once administered amphetamine is rapidly distributed to body tissues including the brain. Because of its greater lipid solubility, methamphetamine crosses the blood brain barrier more quickly allowing larger concentrations of the drug to enter the brain. For this reason methamphetamine produces a greater "high" and users prefer it over other forms of amphetamine.

The metabolic half-life of the amphetamines varies between approximately 10 to 15 hours. Amphetamine is metabolized into p-OH-amphetamine and norephedrine, both of which are inactive. Methamphetamine is first metabolized into amphetamine before it is more completely metabolized and excreted by the kidneys.

*Mechanisms of Amphetamine Actio*n

Amphetamines, including methamphetamine, have perhaps some of the most complex and wide ranging synaptic effects of any psychoactive drug (see Figure 15).

They increase synaptic concentrations of both norepinephrine and dopamine by several different mechanisms. First of all, amphetamines block the **reuptake transporters** for norepinephrine as well as increase the amount of norepinephrine (NE) released into the synapse during neuronal firing. Both of these effects contribute to enhanced norepinephrine activity in both the brain and the peripheral nervous system.

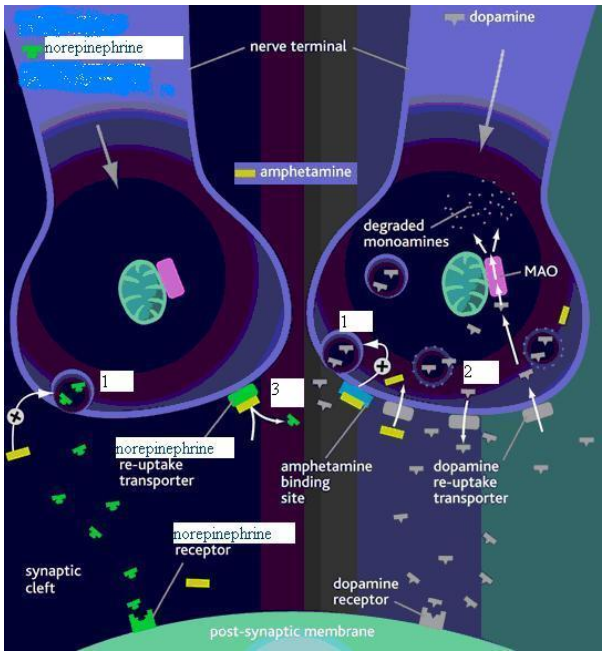


Figure 15: *Amphetamines (including methamphetamine) increase the availability of norepinephrine and dopamine in several different ways including: (1) by binding to the pre-synaptic membrane of dopaminergic and noradrenergic neurons it increases the release of both norepinephrine and dopamine from synaptic vesicles; (2) by causing the transporters for dopamine to act in reverse transporting vesicular dopamine back into the terminal and to transport this "free" dopamine into the synaptic cleft; and (3) by blocking the re uptake transporter for norepinephrine.*

Amphetamines contribute to increased dopamine activity by several different mechanisms. First, they bind to the vesicular transporter and cause dopamine to be released from its storage vesicles into the cytoplasm of the terminal button. This "free" dopamine is then transported into the synaptic cleft by amphetamine-induced reversal of

the dopamine transporter (DAT). Amphetamines also increase the amount of dopamine released from synaptic vesicles during neuronal signaling. These combined mechanisms enhance extra cellular concentrations of dopamine significantly.

The mechanisms by which the amphetamines contribute to behavioral stimulation, euphoria, and to cortical arousal appear to be complex as well. Dopamine agonism contributes to both euphoria and to increased cortical arousal via the **mesolimbic-mesocortical pathways** originating in the ventral tegmental area (VTA). Dopamine projects from the VTA to the nucleus accumbens as well as several other limbic structures including the amygdala and hypothalamus. It is believed that the euphoria caused by amphetamine is mediated in these regions of the brain. Dopamine neurons from the VTA also project to the frontal cortex. Amphetamines also increase dopamine activity and release in the **nigrostriatal system** which originates in the substantia nigra and projects to regions of the basal ganglia. The motor stimulating effects of amphetamines are mediated by increased dopamine activity in these regions. At high doses amphetamines can induce **stereotyped behavior** and hallucinations resembling behaviors observed in some schizophrenic patients. In fact, researchers have used this observation to induce psychotic states in animals with amphetamine as a method to investigate the effectiveness of novel antipsychotic medication. The psychotic symptoms caused by toxic doses of amphetamine, referred to as **amphetamine psychosis**, are believed to involve structures within the basal ganglia.

In summary, amphetamines cause a wide array of effects mediated by enhanced dopaminergic activity in all three of the major dopamine pathways in the brain. These

effects include enhanced or stimulated cognitive abilities, increases in motor activity, and states of euphoria and well-being.

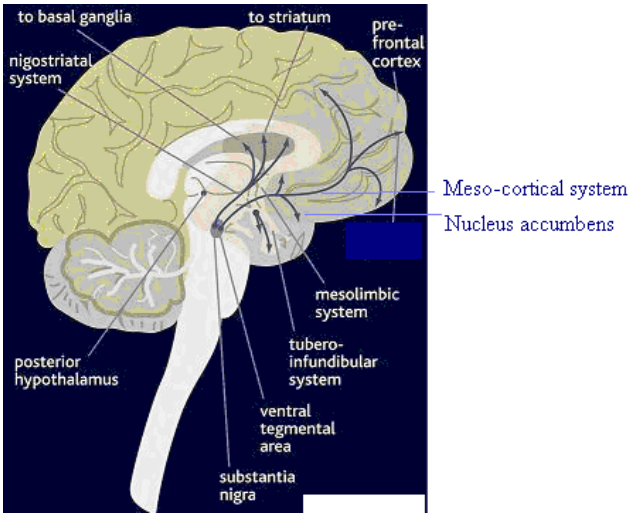


Figure 16: *Dopamine pathways originate in the substantia nigra and ventral tegmental area of the midbrain. The nigrostriatal system innervates the basal ganglia while the mesolimbic-cortical system projects to the nucleus accumbens and to the frontal cortex.*

As illustrated in Figures 16 and 17, amphetamines cause increased norepinephrine and dopamine activity which also contribute to cortical arousal via the **reticular activating system** originating in the brain stem. Increased activity in the reticular activating system increases cortical arousal, vigilance, and attention. These neurotransmitters also contribute to amphetamines anorectic (decreased appetite) effects. Amphetamines increase the expression of the appetite-suppressing peptide **CART** (**cocaine and amphetamine-regulated transcript**) in the **arcuate nucleus** of the hypothalamus. CART is believed to play a significant role in the hypothalamic regulation of feeding and satiety. Certainly CART is at least partially involved in the appetite suppressing effects of both cocaine and amphetamine.

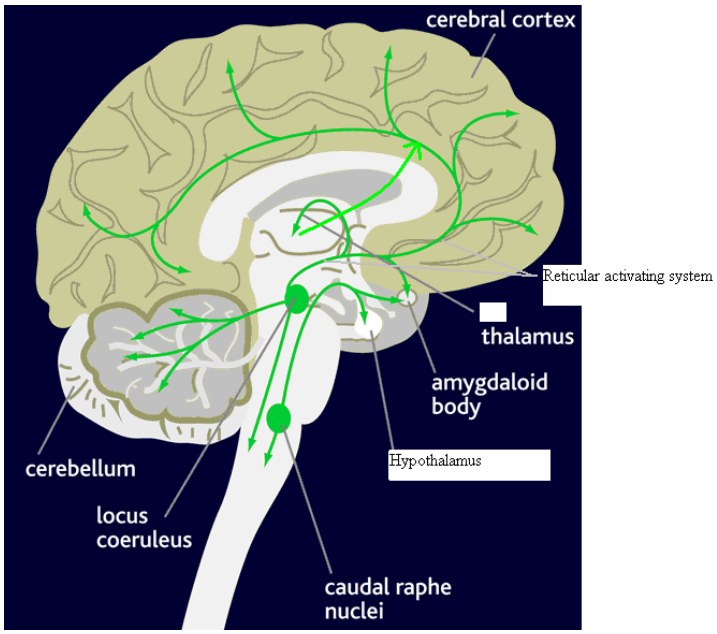


Figure 17*: Cell bodies of norepinephrine neurons are predominantly located in the locus coeruleus and project along the reticular activating system to the hypothalamus, the thalamus and to the frontal cortex.*

Other Amphetamine-related Compounds

A number of other compounds that are structurally related to the amphetamines also have powerful euphoric effects. Perhaps the best known of these is **ecstasy** or methylenedioxymethamphetamine (**MDMA)**. Another, but less familiar compound is 3,4 methylenedioxyamphetamine (**MDA**).

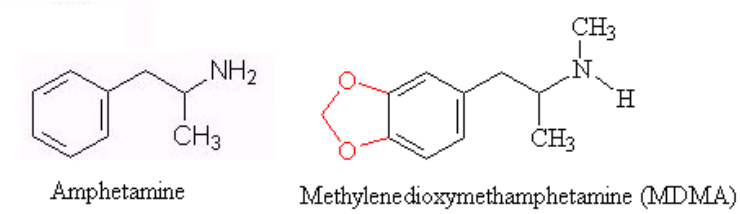


Figure 18: *Methylenedioxymethamphetamine (MDMA), also referred to as ecstasy, is structurally similar to amphetamine.*

Figure 19: *Tablets of Methylenedioxymethamphetamine (MDMA), used as a club drug, have been banned since 1985.*

MDMA, also referred to as ecstasy, first gained popularity in the 1970s as a drug used to assist psychotherapy. Therapists who promoted its use claimed it facilitated communication and allowed patients to more directly experience their inner self. MDMA quickly spread to recreational use before it was banned by the FDA in 1985. MDMA is now listed as a Schedule I drug with no accepted medical use and a high potential for abuse. The use of MDMA peaked in the early 2000s as its popularity as a "club drug" soared. By 2003 an estimated 15% of 18-25 year olds had used ecstasy. Since 2003 there has been a slight decline in MDMA use.

Users of MDMA report that it produces euphoria, increased self-perception, enhanced sensations, and that it promotes intimacy with others. Ecstasy also produces some very troubling side effects including increased heart rate and blood pressure, intense sweating, and teeth grinding so forceful broken teeth were not uncommon. To prevent tooth damage users often chew on baby pacifiers. Perhaps the most troubling effect of MDMA, however, is its powerfully neurotoxic effects.

In animal studies short-term MDMA administration is known to cause significant damage to cortical serotonergic and dopaminergic neurons (Hatzidimitriou et al., 1999; Mechan et al., 2006; Ricaurte et al., 2002). These degenerative effects appear to persist

for many years after acute MDMA use. By all indications the use of MDMA by humans is also associated with neurotoxicity. Two recent reviews of research studies that have examined the effects of MDMA use on cognitive functions both concluded that even low to moderate drug use was associated with decrements in a number of cognitive domains including attention, concentration, and memory (Kalechstein et al., 2007; Zakzanis et al., 2007).

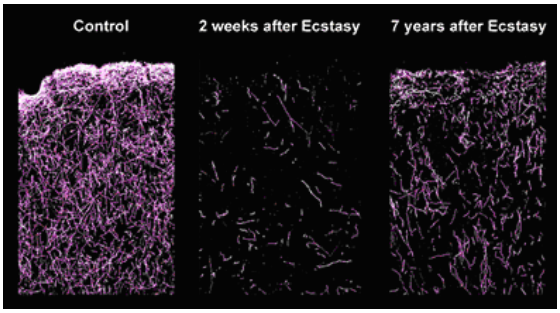


Figure 20*: Cortical serotonergic axons in a squirrel monkey after saline (control) or 5 mg/kg MDMA twice daily for 4 days. Animals were sacrificed and examined after 2 weeks or after 7 years. Some cortical regeneration can be seen after 7 years. From Hatzidimitriou et al., 1999.*

MDMA is a potent serotonin and dopamine agonist. It directly increases serotonin activity by both enhancing serotonin release during neuronal signaling and preventing its reuptake. MDMA appears to enhance dopamine activity in the nucleus accumbens by blocking DAT and perhaps indirectly by activating serotonergic neurons which regulate dopamine activity in the ventral tegmental area (Amato et al., 2007; Federici et al., 2007). MDMA is predominantly a serotonin agonist, but dopamine activity plays a significant role in its euphoric and behavior stimulating effects. Dopamine is also believed to mediate MDMAs reinforcing effects in animal self-administration studies (Daniela et al., 2006).

Psychedelic Drugs: LSD & Psilocybin

Of all of the psychotropic drugs **LSD** (**lysergic acid diethylamide**) causes perhaps the most astonishing psychological effects. Most notable are LSD's powerful hallucinogenic effects. Hallucinations, which are profound distortions of a person's perceptual experiences, can occur in any sense modality. The most striking hallucinations caused by LSD are visual. These hallucinations typically involve color and movement elaboration. For example, while observing clouds a person under the influence of LSD may see complex distortions in their color and movement. Sounds or music may be heard with greater intensity and complexity. For instance, because of sound exaggeration a person may describe hearing a piece of music for the first time when in fact they have heard it on many occasions. Some LSD users describe their hallucinations as **synesthesia** where sensations in one modality are experienced or mixed with another. For instance, visual hallucinations may occur to the sound of music. Users of LSD typically describe their perceptual experiences as pleasurable and amusing, but these hallucinations can be disturbing to some.

Lysergic acid diethylamide (LSD) was first synthesized in 1938 by Dr. Albert Hofmann (1906-2008) who was working as a chemist for the Swiss pharmaceutical company Sandoz laboratories. Hofmann was investigating the pharmacological properties of variety of alkaloids extracted from plants and the ergot fungus which grows on grain. Because of other research projects, Hofmann placed the LSD on a shelf only to return to it 5 years later.

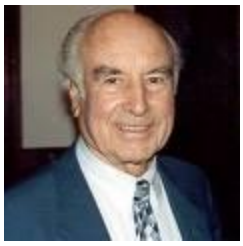


Figure 21: *Albert Hofmann (1906-2008). Discoverer of LSD and advocate of its responsible use.*

In 1943 Hofmann began investigating the properties of his previously synthesized LSD, known as LSD-25 because it was the 25th lysergic acid compound synthesized in his laboratory. Hofmann reported in his journal that after working with LSD-25 he became

> "*remarkably restless, combined with a slight dizziness*". He returned home where he further reported "*fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors*".

Hofmann believed that he must have absorbed a small amount of LSD through his skin. Several days later he ingested 250 ug of LSD to experiment with it further. Soon after ingesting this dose Hofmann began to get dizzy again. He found it difficult to speak but managed to get his assistant to escort him home on his bicycle.

> "*On the way home, my condition began to assume threatening forms. Everything in my field of vision wavered and was distorted as if seen in a curved mirror. I also had the sensation of being unable to move from the spot*."

Once home Hofmann found his surroundings both unfamiliar and frightening. He believed that there was no other known substance that evoked such profound psychic effects

"Everything in the room spun around, and the familiar objects and pieces of furniture assumed grotesque, threatening forms. They were in continuous motion, animated, as if driven by an inner restlessness".

Albert Hoffman continued taking LSD (usually on his birthday) for the remainder of his life. He remained an advocate of its responsible use and founded a nonprofit foundation dedicated to furthering the investigation of **psychedelic** substances.

Pharmacokinetics of LSD and psilocybin

LSD is rapidly absorbed after oral administration and peak plasma levels are reached within about 2 hours. LSD readily crosses the blood brain barrier and is quickly distributed to tissues throughout the body. The half-life of LSD ranges between 2 - 3 hours, but its effects may last as long as 12 hours. LSD is the most potent of all of the psychoactive drugs. Effective doses begin at approximately 25 ug (25 millionths of a gram) which is about 1000 times more potent than amphetamine or cocaine which have effective doses of approximately 25 mg (thousandths of a gram). Ironically, even though LSD is extremely potent there appears to be no confirmed lethal dose. In 1977 a case of possible overdose was reported where it was estimated upon autopsy that the user had ingested 320 mg (320,000 ug) of LSD. However, no cause of death was reported (Griggs et al., 1977). Other estimates for lethal overdose in humans range between 50,000 and 100,000 ug or between 2000 and 4000 doses.

Psilocybin is a psychedelic compound found in a variety of mushrooms in the *Psilocybe* genus. One common North American species is *Psilocybe semilanceata* which can be found in cattle or sheep pastures in the Pacific Northwest as well as in several northeastern states. Because the pharmacological properties of LSD and psilocybin are so similar, and because the majority of research conducted with psychedelic substances is conducted with LSD, we focus here on LSD.

Figure 22: *A popular way to deliver and administer LSD is on small stamps which contain 50 to 100 ug of LSD. These stamps are placed on the tongue where the drug is rapidly absorbed.*

Figure 23: *Psilocybin mushroom (Psilocybe semilanceata). A common species of psilocybin mushroom found in the Pacific Northwest and in the Northeastern United States.*

LSD toxicity and side effects

LSD is characterized by its remarkable hallucinogenic effects, but several noticeable side effects are also common. These include increased body temperature, heart

rate, and blood pressure, pupil dilation, dizziness, and occasional nausea. The psychological side effects can include confusion, acute panic, and noticeable distortions in both space and time. Occasionally LSD users report that their experience was disturbing or frightening and that their experience was a "bad trip". In addition, a few users report that they experience flashbacks of these disturbing experiences. While there is no known pharmacological mechanism that could cause flashback experiences, these unpleasant perceptual experiences more likely correspond to memories of these experiences rather than to some residual drug effect. Nevertheless, because a number of LSD users have reported flashbacks that have persisted long after drug use a separate category was created in the DSM for **Hallucinogen Persisting Perception Disorder.**

The DSM-IV criteria for *Hallucinogen Persisting Perception Disorder (HPPD)* require that the person has not recently used a hallucinogenic drug and shows no present signs of any drug intoxication. The following diagnostic criteria must be met:

A. *The re-experiencing, following cessation of use of a hallucinogen, of one or more of the perceptual symptoms that were experienced while intoxicated with the hallucinogen (e.g., geometric hallucinations, false perceptions of movement in the peripheral visual fields, flashes of color, intensified colors, trails of images of moving objects, positive afterimages, halos around objects).*

B. *The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.*

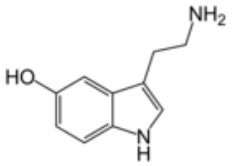
C. *The symptoms are not due to a general medical condition (e.g., anatomical lesions and infections of the brain, visual epilepsies) and are not better accounted for by another mental disorder.*

In a recent review of the literature on hallucinogen persisting perception disorder (flashbacks) it was concluded that while the disorder is likely to be genuine and can persist for months after LSD use, it is an uncommon occurrence with no known

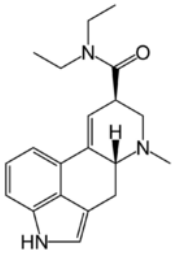
pathology. In addition, there is no consensus on how, or whether, HPPD should be treated (Halpern et al., 2002).

Pharmacodynamics of LSD and psilocybin

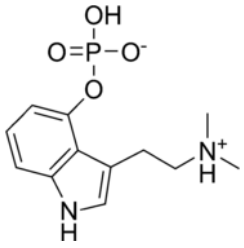
Lysergic acid diethylamide and psilocybin are partial serotonin (5-HT) agonists that bind with high affinity to a number of 5-HT receptor subtypes. If you recall from Chapter 2, **partial agonists** are drugs that have an affinity for a receptor site, but may exert less of an effect on the receptor than the endogenous ligand—in this case serotonin. The affinity of LSD and psilocybin for 5-HT receptors is believed to be a consequence of their similar molecular structure. All three of these substances share a common indole structure which is illustrated in Figure 23.



Serotonin (5-HT)



Lysergic acid diethylamide (LSD)



Psilocybin

Figure 24: *Lysergic acid diethylamide (LSD) and psilocybin share a common indole molecular structure with serotonin.*

Research with laboratory animals suggests that the hallucinogenic effects of LSD are mediated by the 5-HT_{2A} receptor subtype specifically. For example, drugs that block 5-HT_{2A} receptors also disrupt the ability of laboratory animals to discriminate between LSD and saline administrations (Appel et al., 2004). Blocking other serotonin receptors does not disrupt the discriminative properties of LSD. Animals lacking the serotonin transporter gene (SERT knockout animals) also fail to discriminate LSD from saline providing further support for the role of 5-HT_{2A} receptors in LSD's effects (Krall et al., 2008).

Understanding the action of LSD or psilocybin on serotonin receptors only partially explains their profound perceptual effects. What is clearly needed is a better understanding of how serotoninergic systems in the brainstem and the cortex modulate sensory information and perception. Several lines of research are beginning to elucidate how hallucinations may be caused. One approach is to evaluate how serotonin systems regulate sensory information projected from the brainstem to the thalamus and then to cortical sensory areas. Possibly, LSD disrupts the normal filtering of extraneous sensory information resulting in over stimulation of cortical sensory areas. LSD does increase the activity of sensory neurons to stimulation (Aghajanian et al., 1999). Additionally, LSD may alter the activity of several cortical areas including the medial prefrontal cortex and the anterior cingulate by agonizing 5-HT_{2A} receptors there. To demonstrate this, researchers have investigated the increased activity of cortical neurons in response to LSD administration (Gresch et al., 2002). More recent research has shown that LSD effects are mediated by specific pathways within the somatosensory cortex that express the 5-HT_{2A} receptor. Activating these signaling pathways may be sufficient to induce

hallucinations independently of sensory input via the thalamo-cortical pathways (González-Maeso et al., 2007).

In summary, LSD and psilocybin hallucinogenic effects are believed to be mediated by partial agonism of 5-HT_{2A} receptors in the brain stem and in several cortical areas including the medial prefrontal cortex, the anterior cingulate, and the somatosensory cortex. How alterations in 5-HT_{2A} activity in these brain regions cause hallucinations remains unknown, but several possibilities have been proposed. First, 5-HT_{2A} agonism in the brainstem appears to disrupt normal filtering of sensory information to the thalamus and cortex resulting in sensory overload. And secondly, increased cortical activity by 5-HT_{2A} receptor agonism independently of sensory stimulation may cause hallucinations. Research on both the neurophysiological and the behavioral effects of hallucinogens is typically done with laboratory animals. Whether the patterns of neuronal signaling induced by these substances in animals resemble the hallucinations reported by humans may never be known.

Marijuana (cannabinoids)

Marijuana is the common name for the hemp plant ***Cannabis sativa***. Archeological evidence for the use of cannabis by the Chinese dates back about 10 thousand years BC. From China cannabis apparently spread to India and other regions of the Middle East where its resin, known as hashish, was and still is widely used. From Egypt cannabis use continued to spread throughout Europe and finally to the United States. During the colonial period the hemp plant was considered a valuable agricultural commodity and used primarily for the production of rope. Whether the colonists were

aware of the intoxicating effects of cannabis is still controversial. Certainly by the mid 1800s cannabis was being used for its pharmacological effects in the United States. In the mid 1800s a number of popular European writers were describing their experiences with cannabis including the French authors Victor Hugo and Pierre Gautier, who established the then famous Club des Hashischins in Paris. In the early 1900s cannabis was being touted for its medicinal properties in Western medicine and an assortment of cannabis products was available. In the 1930s at least 28 different cannabis products were available to American physicians including a variety of pills, syrups, and even drug mixtures. Further investigations into the pharmacological properties and uses of cannabis were cut short however by the **Marihuana Tax Act** of 1937 which essentially banned cannabis altogether by an elaborate code of costly tax provisions. Legal historians have argued that had it not been for numerous unfounded claims that cannabis caused insanity, murder, and death the Act may not have passed. Cannabis was further regulated by the **Controlled Substance Act** of 1970 which listed cannabis as a Schedule I drug. Since 1970 a number of states have attempted to decriminalize marijuana use, but all legal efforts to reschedule it for medicinal purposes have failed. A few states, however, do allow patients with specific medical conditions to grow or purchase small amounts of marijuana for medicinal use.

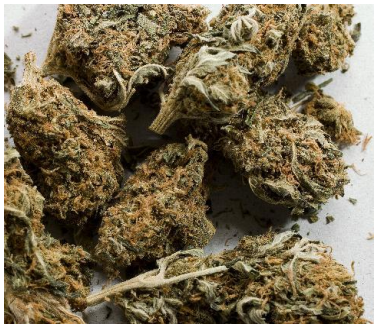


Figure 25: *Marijuana plant (top) and dried mature flower (bottom).*

Pharmacokinetics of Marijuana (Δ^9*- tetrahydrocannabinol)*

With the isolation of the active compound in marijuana by two Israeli chemists in 1964, and its synthesis a year later, the pharmacological properties of cannabis were quickly pursued (Gaoni & Mechoulam, 1964; Mechoulam & Gaoni, 1965). Prior to the isolation of Δ^9**- tetrahydrocannabinol** by Gaoni and Mechoulam it had been assumed that the psychoactive properties of cannabis were due to a combination of cannabinols which had been first extracted from marijuana in 1846 by the Smith brothers in Edinburgh Scotland. The Smiths were pioneers of modern pharmacology who produced a variety of plant extracts for medicinal purposes. Using traditional methods of their time, they tested their cannabis extract on themselves and reported that:

> *two thirds of a grain of this resin acts upon ourselves as a powerful narcotic, and one grain produces complete intoxication.*
>
> (From Iversen, 2000; 1 grain is approximately 65 mg).

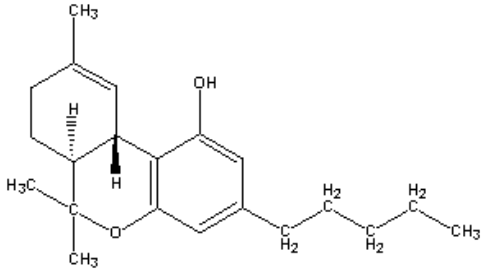


Figure 26*: Molecular structure of* Δ^9*- tetrahydrocannabinol (THC)*

Smoking marijuana is perhaps the most effective method of administration. Upon heating, the Δ^9- tetrahydrocannabinol (THC) in marijuana is vaporized and readily passes through the surface of the lungs into the blood. Within seconds of inhalation THC passes through the blood brain barrier and enters the brain. Peak plasma levels are typically reached within a few minutes of smoking. While plasma concentrations vary depending on the amount administered, typical doses in experienced users result in concentrations between 100-200 ng/mL of plasma. The THC concentration of marijuana is highly variable depending upon the variety of cannabis and how it is grown. Concentrations of THC in the dried flowering top of the plant average about 8.5% but can range from about 3% to as high as 25% for some varieties that have been developed through selective breeding. If a typical marijuana cigarette contains about 0.5 g of plant material with a THC content of about 8.5% it would contain approximately 42.5 mg of THC. The amount of this dose that is actually inhaled may only be as high as 10-20% with the remaining going up as side stream smoke or exhaled before complete absorption. Thus, the bioavailability of THC in a cigarette may be only about 5 mg.

After administration TCH is rapidly metabolized into the active metabolite 11-hydroxy-THC in the liver and then into the inactive metabolite 11-nor-9-carboxy-THC before excretion. Relatively small amounts of THC are excreted unchanged. The subjective effects of THC peak at about the same time as plasma levels and persist for about 1-2 hours or when plasma levels decline below about 5.0 ng/mL. The elimination half-life of THC ranges between 24 and 72 hours.

Orally ingested marijuana is absorbed much more slowly and incompletely and can depend heavily on what else is available in the stomach and digestive system since THC can be absorbed by dietary fats. In addition, orally ingested THC must first pass through the liver where much of it is metabolized by liver enzymes. Peak plasma levels are reached between 1 and 4 hours after consumption. Because THC and its metabolites remain in the body for such long periods sensitive drug tests can detect a single use for up to 2 weeks after exposure. Frequent users of marijuana may have detectable levels of metabolites for 3 to 4 weeks after abstinence as the THC that had accumulated in tissues is gradually metabolized.

Pharmacodynamics of Marijuana (Δ^9- tetrahydrocannabinol)

Before THC was isolated it was assumed that cannabis acted on nerve cells in some nonspecific way that interrupted normal cell functioning. For example, an active substance might enter and distort the cell's membrane and thereby alter cell firing. We'll see later on that alcohol can exert these kinds of nonspecific effects. After the discovery of THC, however, it became clear that it must interact directly with neuronal signaling systems. One clue to this hypothesis was that doses of THC that produce noticeable

effects are extremely small. If an average marijuana cigarette delivers about 5 mg of THC, only a very small fraction of this amount actually enters the brain. To exert its effects, therefore, it is presumed that THC must be acting directly on cell receptors rather than by some unknown nonspecific effect such as altering the conformation of cell membranes.

In 1988 researchers using a radioactive labeling technique identified **cannabinoid receptors** in the brains of laboratory rats. In their experiments radioactive tritium was attached to the synthetic cannabinoid compound CP-55,940 (Devane et al., 1988). By labeling cannabinoid receptors with a radioactive marker, scientists were now able to locate the distribution of these receptors throughout the brain. Numerous cannabinoid receptors (CB_1 receptors) are now known to be located in the basal ganglia, cerebellum, hippocampus, amygdala, thalamus, and the cortex. The distribution of these receptors will at least partially account for many of marijuana's behavioral effects. A second type of cannabinoid receptor has since been found outside of the brain in lymphatic tissues of the immune system. These receptors are classified as CB_2 receptors to distinguish them from the CB_1 receptors located in the brain.

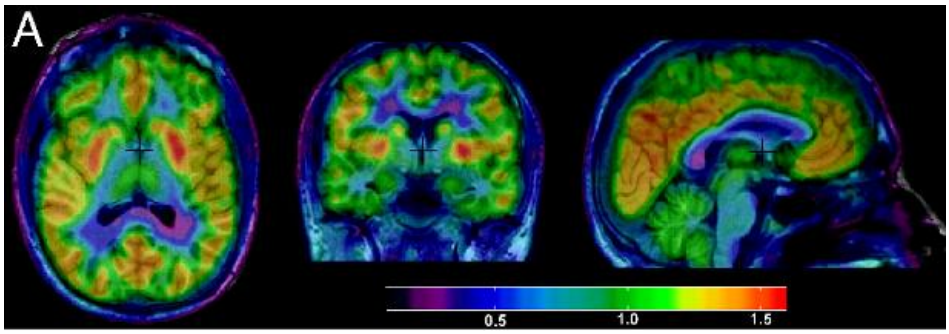


Figure 27: PET images of a brain following the injection of a radioactive CB_1 receptor ligand. High densities of cannabinoid receptors are expressed in the cerebral cortex, cerebellum, caudate nucleus, putamen, globus pallidus, substantia nigra, and in the hippocampus (Burns et al., 2007).

Cannabinoid CB_1 receptors are located on the presynaptic terminals of several different types of neurons. All of these receptors are metabotropic G-protein coupled receptors that regulate the formation of cAMP. In fact, it is believed that CB_1 receptors are the most widely expressed G-protein coupled receptors in the brain. Activation of the G-protein by THC inhibits cAMP formation, inhibits voltage-dependent Ca^{++} channels, and it facilitates K+ efflux, all of which contribute to neural inhibition. In the hippocampus THC binds to CB_1 receptors on GABA neurons which exert inhibitory control over glutamate activity. The activation of these CB_1 receptors in the hippocampus disinhibits glutamate activity in hippocampal pyramidal cells allowing them to fire more readily. Similarly, in the ventral tegmental area THC binds to CB_1 receptors on GABA neurons which exert inhibitory control over dopamine activity (Szabo et al., 2002). This form of neuronal suppression appears to be a common type of short-term neuronal plasticity where depolarization of a neuron causes a decrease in GABA-mediated neural inhibition.

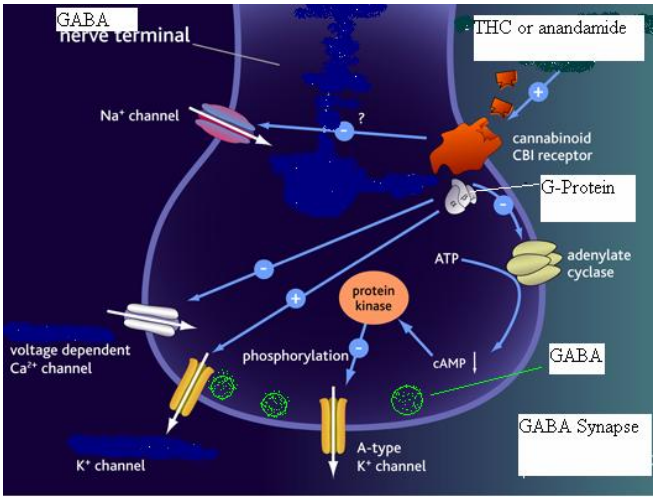


Figure 28: CB_1 G-Protein coupled receptors *on GABA pre synaptic nerve terminal. The binding of THC or anandamide to the* CB_1 *receptor inhibits GABA release by preventing* Ca^{++} *influx.*

Following the discovery of cannabinoid receptors in 1988, the search for endogenous ligands intensified. In 1992 William Devane (the discoverer of the cannabinoid receptor) and his colleagues in Israel also isolated an endogenous cannabinoid, arachidonoyl ethanolamine. They named this substance **anandamide** after the Sanskrit word *ananda* which means bliss. Anandamide is enzymatically synthesized on demand by neurons from the precursor fatty acid, arachidonic acid. It is now recognized that anandamide plays an important role in regulating neural activity that mediates memory formation, appetite, pain signaling, motor activity, and reward. Other endogenous ligands for the cannabinoid receptor have yet to be found. The euphoric effects of marijuana are believed to be mediated in part by disinhibition of dopamine activity in the mesolimbic system (Fadda et al., 2006; Lecca et al., 2006; Solinas et al., 2008). Whether cannabis use is sufficient to cause the kinds of adaptations to dopaminergic neurons that underlie addiction, remains unclear.

Medicinal uses for cannabinoid compounds

In the past decade a number of states have attempted to pass legislation to allow marijuana for medicinal uses. Presently only about a dozen states permit physicians to prescribe marijuana and even in those states it may be difficult to get a prescription. A number of unsuccessful attempts have also been made to reclassify marijuana as a Schedule II drug.

Drug manufacturers have created several synthetic THC drugs which are available by prescription. Dronabinol (Marinol) is a synthetic THC that is extracted from marijuana. Originally listed as a Schedule II drug, Marinol was recently rescheduled as a Schedule III drug. Marinol has been approved by the FDA to treat nausea and vomiting associated with cancer chemo and radiation therapy as well as appetite loss in patients with AIDS. Advocates for the medicinal use of marijuana claim, however, that Marinol is not as effective as marijuana, perhaps because synthetic drugs lack the nearly 60 other cannabinoids that are present in marijuana. In addition, users of Marinol often complain about its delayed onset and its excessive intoxicating effects that are much more difficult to regulate than smoked marijuana.

Nabilone (Cesamet) is an entirely synthetic THC that was originally approved by the FDA in 1985, but marketing actually began in 2006. It was approved to treat nausea and vomiting related to cancer therapy as well as to treat anorexia and weight loss associated with AIDS. Nabilone is presently a Schedule II drug.

A number of other medical conditions may also respond well to marijuana treatment. These include the vision-threatening increase in ocular pressure associated with glaucoma, as an analgesic for chronic and phantom limb pain, to treat withdrawal

symptoms associated with opiate and alcohol addictions, and for treating muscle spasms in patients with multiple sclerosis, Huntington's disease, and Parkinson's disease. Marijuana may also be useful in treating bronchial constriction in asthmatics and in treating certain kinds of cancer by inhibiting cell proliferation and metastasis (Kogan, 2005; Preet et al., 2008). Clearly more research on the potential therapeutic benefits of marijuana is needed.

Pharmacological Effects of marijuana, dronabinol, and nabilone (THC)

Memory and cognition

Marijuana and synthetic THC compounds exert significant effects on both the central and peripheral nervous systems. The central effects of THC include mild euphoria, anxiolysis, and distortions in the perception of time. In some users, THC can cause confusion and a heightened sense of anxiety, but these effects tend to dissipate after repeated administration or use. In addition, THC impairs both cognitive and motor functioning—effects that do not typically persist beyond the period of intoxication. The deleterious effects of marijuana on memory have long been known and recent research has revealed that these effects are mediated, at least in part, by cannabinoid CB_1 receptors in the hippocampus. Cannabinoids act by suppressing glutamate activity and **long-term potentiation (LTP)** in hippocampal neurons (Hoffman et al., 2007; Kang-Park et al., 2007; Nowicky et al., 1987; Ranganathan et al., 2006).

Motor control and coordination

Cannabinoids are also known to disrupt motor control and performance. These effects appear to be mediated by two distinct mechanisms. First, there is an abundance of cannabinoid receptors on glutamate neurons within the basal ganglia. High doses of THC inhibit the release of glutamate in afferent neurons in the basal ganglia causing disrupted movement and even cataplexy. Animals administered high doses of THC exhibit immobility as well as symptoms characteristic of Parkinson's disease (Gerdeman et al., 2001). In addition, cannabinoids disrupt normal cerebellar control of movement independently of central dopamine motor pathways (DeSanty et al., 2001; Patel et al., 2001). Taken together, cannabinoids have the potential to disrupt movement and coordination by activating CB_1 receptors in both the cerebellum and in the nigrostriatal dopamine system. Paradoxically, activation of these cannabinoid receptors seems to have therapeutic effects for individuals with degenerative motor diseases including multiple sclerosis, Parkinson's, and Huntington's disease. Cannabinoids may also offer protection from further neurodegeneration associated with these diseases by inhibiting the cytotoxic effects of excessive Ca^{++} influx into neurons in the motor pathways (Battista et al., 2006; Sagredo et al., 2007).

Figure 29*: Rota-rod treadmill test for motor coordination. Rats or mice are placed on a rotating rod. Time spent on the rod is a measure of motor coordination.*

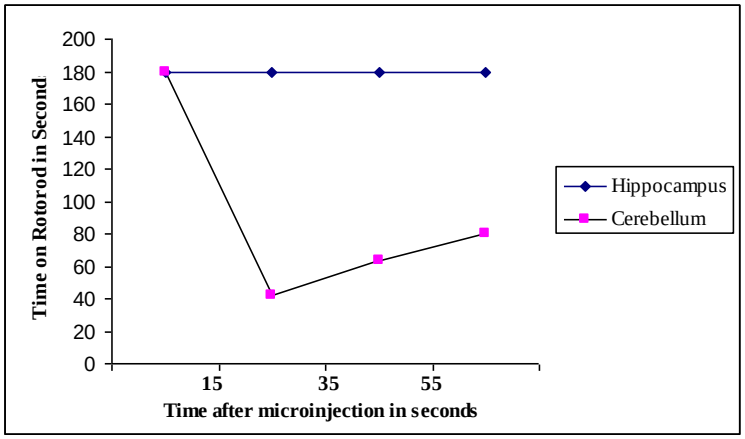


Figure 30: *Time mice spent on a rota-rod as a measure of motor coordination after a microinjection of the CB_1 agonist CP55,940 into either the hippocampus (control) or the cerebellum. Cerebellar injections of the CB_1 agonist sharply disrupted performance (data from DeSanty, 2001).*

Antiemetic effects: nausea and vomiting

Chemo and radiation therapy-induced nausea remains to be a significant problem for most patients undergoing treatment for cancer. While several **antiemetic** (anti nausea) drugs including benzodiazepines are often useful, a significant number of

patients prefer marijuana over the alternatives. Cannabinoids may not only be more effective than benzodiazepines for nausea, the side effects cannabinoids are also more tolerable to many patients. Nausea and vomiting are triggered as toxic drugs and cellular debris stimulate receptors in the **area postrema** of the brainstem. Cannabinoids appear to act directly on CB_1 receptors in the area postrema inhibiting the vomiting reflex (Sharkey et al., 2007; Slatkin et al., 2007; Van Sickle et al., 2001).

Cannabinoids also have significant peripheral effects including effects on the cardiovascular and immune systems. Additionally, cannabinoids exert a significant effect on the intraocular pressure associated with glaucoma.

Cardiovascular effects

The cannabinoids have notable effects on both heart rate and blood pressure. While initial use may cause both an increase in blood pressure and heart rate in some users, repeated use typically produces a significant decrease in blood pressure as a result of vasodilatation. This vasodialating effect is mediated peripherally through CB_1 receptors located on the heart and blood vessels. As blood pressure drops, heart rate increases moderately to compensate for a drop in blood flow. This increase in heart rate may be problematic for some with severe cardiovascular disease, but there is no evidence that cannabis use is associated with adverse cardiovascular events. In fact, cannabinoids may protect the heart against ischemia, a restriction in blood supply to the heart which can lead to a heart attack (Lépicier et al., 2006, 2007).

Immune system effects

As noted earlier, cannabinoids interact with both CB_1 and CB_2 receptor types. While CB1 receptors are expressed on both central and peripheral neurons, CB_2 receptors appear to be localized almost exclusively on cells of the immune system. The role of these cannabinoid receptors in immunoregulation remains obscure. Recent research has revealed, however, that cannabinoids, and CB_2 agonists specifically, inhibit immune responses and inflammation (Lombard et al., 2007; McKallip et al., 2002). The development of specific CB_2 agonists, therefore, may prove useful in treating a variety of inflammatory and autoimmune disorders. As of yet, the immunosuppressive properties of cannabis have not been demonstrated to be a significant concern for patients or users. There is no evidence that cannabis use is associated with an increased risk of infectious disease or the progression of cancer.

Tolerance and Dependence

In laboratory animals repeated administration of high doses of THC can produce tolerance to the cardiovascular and the behavioral responses to THC. For example, in a recent study with mice, researchers administered THC twice a day for 7 days on an escalating dose schedule beginning with 10 mg/kg increasing to 60 mg/kg. Animals on the increasing dose schedule developed tolerance to THC's locomotor and analgesic effects, while mice treated with 10 mg/kg twice each day did not. The mechanism underlying tolerance in these animals was a decrease in cannabinoid receptor activation in several brain regions including the hippocampus, cingulate cortex, periaqueductal gray area, the caudate nucleus, nucleus accumbens, and in the cerebellum (McKinney et al.,

2008). Other researchers have shown that cannabinoid receptor internalization may mediate this decrease in CB_1 receptor activation during tolerance (Wu et al., 2008). Changes in the rate of THC metabolism may also contribute to cannabis tolerance, but this alone would not be sufficient to account for tolerance to such high THC doses.

It is important to consider that while tolerance to THC has been demonstrated in humans and in animals that have been given extremely high doses of THC, tolerance may not occur to the doses most users and patients receive. A typical dose of Marinol, for example, would be approximately 5-20 mg/day for a patient being treated for nausea or glaucoma, and as stated above, a typical marijuana cigarette may contain about 5mg of THC. The doses required to demonstrate tolerance in mice would be equivalent to approximately 300 to 500 mg of THC for a person.

Chronic use has been reported to produce dependence in some cannabis users and abstinence can cause symptoms of withdrawal. These symptoms may include cravings, depressed mood, aggressiveness, and irritability—all symptoms associated with other drug dependencies including nicotine and caffeine. Because not all users experience withdrawals upon abstinence, whether or not cannabis causes dependence or addiction remains quite controversial. Proponents of marijuana use argue that it does not cause dependence nor does it contribute to addiction, while those opposing marijuana use argue that it does. Research with animals may at least partially resolve this controversy. One way researchers investigate a drug's abuse potential is to determine whether animals will administer the drug or substance to themselves. Typically such **self-administration** experiments involve training animals to press levers to receive small injections of a drug.

Self-Administration of THC

Drugs that have a high abuse potential such as cocaine, heroin, amphetamine, and nicotine easily maintain lever pressing by animals when these drugs are injected as reinforcers. In a self-administration experiment animals are trained to lever press for drug administration intravenously or directly into the brain via a cannula, upon each completion of the schedule requirement. For example, on a fixed ratio 10 (FR10) schedule a small amount of drug would be administered after each 10^{th} lever press response. After each drug administration there is typically brief delay before lever presses are counted for a successive trial. Over the course of an experimental session an animal may earn 20-30 microinjections of a particular drug. In one such study researchers trained squirrel monkeys to self-administer 4.0 ug/kg of THC per injection on a fixed ratio 10 schedule. Over the course of a one hour experimental session animals received between 40 and 50 injections of THC. After 5 one-hour sessions the reinforcer was switched from THC to the saline vehicle solution for another 5 sessions and then again to THC for the final 5 sessions (Justinova et al., 2003). The results of this experiment are presented in Figure 30. Clearly THC maintained high levels of self-administration in this experiment suggesting that TCH does have abuse potential.

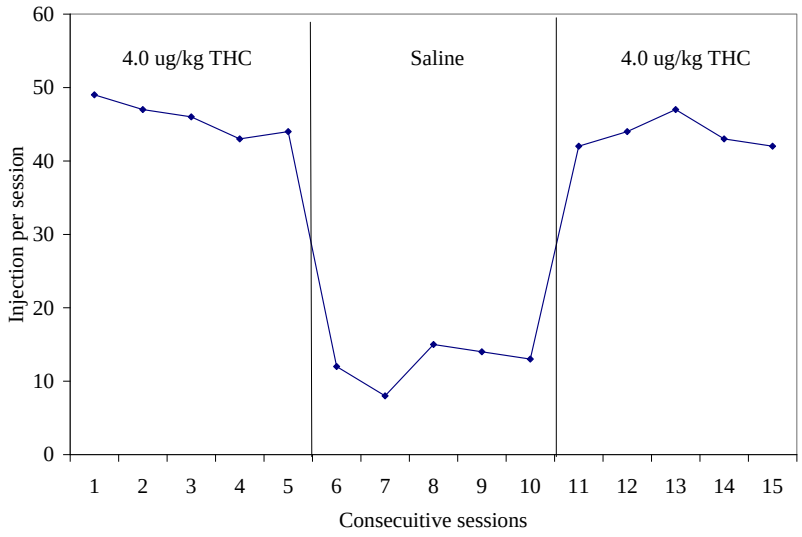


Figure 31: *Number of THC or saline vehicle injections per training session on an FR 10 schedule for squirrel monkeys self-administering THC. THC maintained high rates of self-administration when compared to the saline vehicle solution. (data from Justinova et al., 2003).*

To illustrate how complicated interpreting the research on the abuse potential of cannabis can be, let us consider an alternative method to evaluate a drug's abuse potential. It is widely accepted that addictive drugs produce sensitization to dopamine neural circuits in the mesolimbic reward system. These adaptations can be observed as behavioral sensitization and increased locomotor activity. In a recent experiment, the behavioral sensitizing effects of THC after repeated administration in mice were compared to those following methamphetamine administrations. As seen in Figure 31, methamphetamine produced behavioral sensitization while THC did not (Varvel et al., 2007). Whether the lack of behavioral sensitization is a consequence of THC's known motor depressing effects in the basal ganglia is not known.

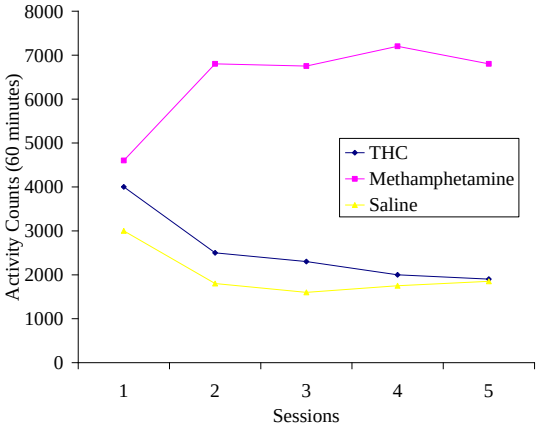


Figure 32: *Behavioral sensitization as measured by activity in mice observed following methamphetamine treatment but not after THC or saline treatment. (data from Varvel et al., 2007).*

In summary, cannabinoids can, under certain conditions, produce tolerance and dependence in both animals and humans. Tolerance appears to be mediated by receptor internalization and a subsequent decrease in receptor activity. The controversy about the abuse and addictive potential of cannabis and the synthetic THC compounds remains unresolved at the time of this writing. It has been estimated that about 4% of regular cannabis users develop a substance abuse disorder as defined by the DSM IV (Chen et al., 2005), a number is far lower than the frequency of dependency to other drugs of abuse. If cannabis use can lead to dependence, this risk is certainly much lower than it is for other abused drugs.

Glossary of Terms (bold)

drug schedule a drugs classification based on its potential for abuse as described by the Controlled Substance Act of 1970. Drugs with the highest abuse potential and lowest medicinal value are Schedule I drugs. There are 5 drug schedules (I-V).

Controlled Substance Act enacted in 1970 to control the manufacture, distribution, and use of certain drugs with abuse potential.

Drug Enforcement Administration an agency within the Department of Justice that oversees and enforces the **Controlled Substance Act.**

cocaine a powerful stimulant drug extracted from the coca plant (*Erythroxylum coca*).

Harrison Narcotic Tax Act enacted in 1914 to control the manufacture, distribution, and use of certain drugs with abuse potential. Superseded by the Controlled Substance Act of 1970.

methylbenzoylecgonine a compound produced by dissolving cocaine hydrochloride in ammonia. Also known as crack cocaine.

crack a cocaine produce that is produced by dissolving cocaine hydrochloride in ammonia or a solution of sodium bicarbonate.

benzoylecgonine a principle metabolite of cocaine

ecgonine a principle metabolite of cocaine

cocaethylene a compound that results from mixing the administrations of cocaine and alcohol.

dopamine transporter (DAT) a protein that selectively transports dopamine from the synaptic gap back into the terminal button.

mesolimbic system a pathway of dopaminergic neurons originating in the ventral tegmentum projecting to the nucleus accumbens. See also reward system and mesolimbic cortical system.

place preference conditioning an experimental procedure where animals are tested for their preference for an area in an experimental apparatus where drugs had been administered over other areas within the apparatus. A form of Pavlovian conditioning where a place becomes associated with drug effects.

ventral tegmental area an area of the midbrain which is the origin of dopaminergic cell bodies that comprise the mesolimbic system.

nucleus accumbens a structure of the mesolimbic system that receives dopaminergic input from the ventral tegmental area.

knockout animals an experimental animal that has been genetically altered to not express certain genes.

anesthetic a class of drugs used for anesthesia. Anesthetics produce a lack of awareness of body sensations and are used to sedate patients for surgery.

local anesthetic a drug that blocks the conduction of nerve signals in a localized area for surgery.

analgesic a class of drug that blocks ascending pain signals in the spinal cord and brain stem.

ephedra a mild stimulant that is extracted from the *ephedra sinica* plant.

dextroamphetamine (Dexadrine) an amphetamine compound used to treat narcolepsy, attention disorders, and obesity.

Methamphetamine (desoxyephedrine) an amphetamine compound that can be produced by the reduction of ephedrine.

desoxyephedrine See methamphetamine

crystal meth a crystalline form of methamphetamine.

reuptake transporters proteins embedded on the presynaptic terminal of neurons that transport neurotransmitter substances into the terminal button.

mesolimbic-mesocortical pathways neural pathway originating in the ventral tegmental area of the midbrain and project to the nucleus accumbens and to the prefrontal cortex.

nigrostriatal system a system of brain structures and neurons originating in the substantia nigra projecting to the striatum of the basal ganglia.

stereotyped behavior rigid repetitive movements observed in experimental animals after the administration of psychomotor stimulants such as cocaine or amphetamine.

amphetamine psychosis a psychotic state induced by the stimulants amphetamine and cocaine. Symptoms include paranoid delusions and hallucinations.

reticular activating system a system of neurons originating in the brainstem projecting to the thalamus. Involved in behavioral arousal and is crucial for maintaining the state of consciousness.

cocaine and amphetamine-regulated transcript (CART) a peptide neurotransmitter found in the arcuate nucleus of the hypothalamus. Believed to be involved in feeding.

CART See cocaine and amphetamine-regulated transcript.

arcuate nucleus a structure within the hypothalamus implicated in feeding regulation.

MDMA (methylenedioxymethamphetamine) an compound structurally related to amphetamine with euphoric effects. Also known as ecstasy.

MDA (3,4 methylenedioxyamphetamine) a compound structurally related to amphetamine and similar to MDMA. Produces a state of euphoria.

ecstasy see MDMA

LSD (**lysergic acid diethylamide)** a potent psychedelic drug that produces visual hallucinations. Discovered by Dr. Albert Hoffman.

synesthesia a perceptual phenomenon where sensations in one modality are experienced or mixed with another.

psychedelic a class of drug that causes disturbances in perception.

psilocybin a psychedelic compound found in a variety of mushrooms in the *Psilocybe* genus.

Hallucinogen Persisting Perception Disorder A DSM-IV-TR disorder characterized by the re-experience of hallucinogenic effects caused by psychedelic drugs long after drug intoxication.

partial agonist a drug that has an affinity for a receptor site, but may exert less of an effect on the receptor than the endogenous ligand

marijuana the common name for the hemp plant *Cannabis sativa*.

Cannabis sativa a variety of hemp plant commonly known as marijuana.

Marihuana Tax Act enacted in 1937 to regulate the distribution and use of marijuana by taxation.

Δ^{9}**- tetrahydrocannabinol (THC)** the psychoactive compound in marijuana.

cannabinoid receptors a class of receptors specific for endogenous cannabinoids such as anandamide. There are two distinct forms of the cannabinoid receptor CB_1 and CB_2.

anandamide an endogenous ligand for the cannabinoid receptor.

long-term potentiation (LTP) a long-term change in the excitability of a neuron induced by high frequency stimulation of its receptor. LTP is most often investigated in NMDA receptors.

antiemetic a class of drug used to treat nausea.

area postrema an area of the brainstem that controls the vomiting reflex. The area postrema has a relatively weak blood brain barrier so it can detect toxins in the blood.