National Institute on Drug Abuse
Advancing Addiction Science

Impacts of Drugs on Neurotransmission

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The defining features of drug intoxication and addiction can be traced to disruptions in cell-to-cell signaling.

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Drugs of abuse alter the way people think, feel, and behave by disrupting neurotransmission, the process of communication between brain cells. Over the past few decades, studies have established that drug dependence and addiction are features of an organic brain disease caused by drugs' cumulative impacts on neurotransmission. Scientists continue to build on this essential understanding with experiments to further elucidate the physiological bases for drug abuse vulnerability as well as the full dimensions and progression of the disease. The findings provide powerful leads to new medications and behavioral treatments.

This second article in our *NIDA Notes Reference Series* discusses the central importance of studying drugs' effects on neurotransmission and describes some of the most common experimental methods used in this research. As with other articles in the series, we provide illustrative references from articles published in *NIDA Notes*.

What is Neurotransmission?

A person reads. The words on the page enter the brain through the eyes and are transformed into information that is relayed, from cell to cell, to regions that process visual input and attach meaning and memory. When inside cells, the information takes the form of an electrical signal. To

cross the tiny intercellular gap that separates one cell from the next, the information takes the form of a chemical signal. The specialized chemicals that carry the signals across the intercellular gaps, or synapses, are called neurotransmitters.

The ebb and flow of neurotransmitters—neurotransmission—is thus an essential feature of the brain's response to experience and the environment. To grasp the basic idea of neurotransmission, compare the brain to a computer. A computer consists of basic units (semiconductors) that are organized into circuits; it processes information by relaying electric current from unit to unit; the amount of current and its route through the circuitry determine the final output. The brain's corresponding basic units are the neurons—100 billion of them; the brain relays information from neuron to neuron using electricity and neurotransmitters; the volume of these signals and their routes through the organ determine what we perceive, think, feel, and do.

Of course, the brain, a living organ, is much more complex and capable than any machine. Brain cells respond with greater versatility to more types of input than any semiconductor; they also can change, grow, and reconfigure their own circuits.

The Basic Research Questions

Neuroscientists seeking to understand why a drug is abused and the consequences of that abuse focus on two issues:

- Which neurotransmitter or neurotransmitters does it affect?
- How does it alter neurotransmission?

Neurotransmitter	Distribution in the Central Nervous System	Functions Affected	Drugs That Affect It
Dopamine	Midbrain, Ventral tegmental area (VTA), Cerebral cortex, Hypothalamus	Pleasure and reward Movement, Attention, Memory	Cocaine, Methamphetamine, Amphetamine. In addition, virtually all drugs of abuse directly or indirectly augment dopamine in the reward pathway
Serotonin	Midbrain, VTA, Cerebral cortex, Hypothalamus	Mood, Sleep, Sexual desire, Appetite	MDMA (ecstasy), LSD, Cocaine

Neurotransmitter	Distribution in the Central Nervous System	Functions Affected	Drugs That Affect It
Norepinephrine	Midbrain, VTA, Cerebral cortex, Hypothalamus	Sensory processing, Movement, Sleep, Mood, Memory, Anxiety	Cocaine, Methamphetamine, Amphetamine
Endogenous opioids (endorphin and enkephalin)	Widely distributed in brain but regions vary in type of receptors, Spinal cord	Analgesia, Sedation, Rate of bodily functions, Mood	Heroin, Morphine, Prescription painkillers (Oxycodone)
Acetylcholine	Hippocampus, Cerebral cortex, Thalamus, Basal ganglia, Cerebellum	Memory, Arousal, Attention, Mood	Nicotine
Endogenous cannabinoids (anandamide)	Cerebral cortex, Hippocampus, Thalamus, Basal ganglia	Movement, Cognition and memory	Marijuana
Glutamate	Widely distributed in brain	Neuron activity (increased rate), Learning, Cognition, Memory	Ketamine, Phencyclidine, Alcohol
Gamma-aminobutyric acid (GABA)	Widely distributed in brain	Neuron activity (slowed), Anxiety, Memory, Anesthesia	Sedatives, Tranquilizers, Alcohol

Which Neurotransmitter or Neurotransmitters Does the Drug Affect?

A person's experiences when abusing a drug reflect the functional roles of the particular neurotransmitter whose activity it disrupts. Each individual neuron manufactures one or more neurotransmitters: dopamine, serotonin, acetylcholine, or any one of a dozen others that scientists have discovered to date. Each neurotransmitter is associated with particular effects depending on its distribution among the brain's various functional areas. Dopamine, for example, is highly concentrated in regions that regulate motivation and feelings of reward, accounting for its importance in compulsive behaviors such as drug abuse. A neurotransmitter's impact also depends on whether it stimulates or dampens activity in its target neurons.

Some drugs primarily disrupt one neurotransmitter or class of neurotransmitters. For example, opioid drug abusers experience changes that are similar to—but more pronounced than—those that accompany normal fluctuations in the brain's natural opioid-like neurotransmitters, endorphin and enkephalin: increased analgesia, decreased alertness, and slowed respiration (see table). Other drugs interact with more than one type of neurotransmitter. Cocaine, for example, attaches to structures that regulate dopamine, thereby producing euphoria; however, cocaine also produces changes in norepinephrine and glutamate, which are the sources of its stimulant effects.

Because a neurotransmitter often stimulates or inhibits a cell that produces a different neurotransmitter, a drug that alters one can have secondary impacts on another. In fact, the key effect that all abused drugs appear to have in common—a dramatic increase in dopamine signaling in the nucleus accumbens (NAc), leading to euphoria and a desire to repeat the experience—is in many cases an indirect one. For example, nicotine stimulates dopamine-releasing cells directly by stimulating their acetylcholine receptors, and also indirectly by triggering higher levels of glutamate, a neurotransmitter that acts as an accelerator for neuron activity throughout the brain.[1]

How Does the Drug Alter Neurotransmission?

Neurotransmission is a cyclic process that transpires in several steps utilizing specialized components of the sending and receiving cells (*see inset box below*). Identifying the precise step that a drug disrupts, and how, provides crucial insight into its impact on abusers and is key to identifying medical and behavioral interventions to inhibit, counter, or reverse the disruption.

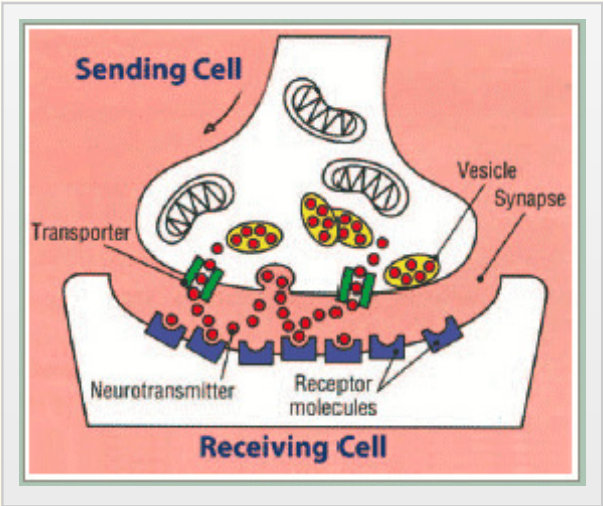
Some drugs mimic neurotransmitters. Opioid drugs such as heroin and OxyContin, for example, chemically resemble the brain's natural opioids sufficiently to engage and stimulate their specialized receptors. Since heroin stimulates many more receptors than the brain uses in the normal cycle of endorphin and enkephalin release and uptake, the result is a massive amplification of opioid activity. Marijuana and hashish mimic cannabinoid neurotransmitters, the most important of which is anandamide. Nicotine attaches to receptors for acetylcholine, the neurotransmitter for the cholinergic system.

Some drugs alter neurotransmission by interacting with molecular components of the sending and receiving process other than receptors. Cocaine, for example, attaches to the dopamine transporter, the molecular conduit that draws free-floating dopamine out of the synapse and back into the sending cell. As long as cocaine occupies the transporter, dopamine cannot reenter the cell by this route. It builds up in the synapse, stimulating receiving cell receptors more copiously and producing much greater dopamine impact on the receiving cells than occurs naturally. "Cocaine's Dopamine Connections" enumerates some of cocaine's interactions with the mechanisms of dopamine signaling, and how they motivate abuse and contribute to dependence and addiction.

Finally, some drugs alter neurotransmission by means other than increasing or decreasing the quantity of receptors stimulated. Benzodiazepines, such as diazepam or lorazepam, enhance receiving

cells' responses when the neurotransmitter gamma-aminobutyric acid (GABA) attaches to their receptors. Benzodiazepines' relaxation effects result from this increased sensitivity to GABA's inhibitory impact on cellular activity.

Getting the Message Across



The task in neurotransmission is to convey a signal from a sending cell to a receiving cell across an open space known as a synapse. All brain cells accomplish this in approximately the same way.

The sending cell manufactures neurotransmitter molecules and stores them in packets called vesicles. When stimulated appropriately, the cell generates an electric signal and causes some vesicles to migrate to the cell membrane, merge with it, open up, and release their contents into the synapse. Some molecules drift across the synapse and link up, lock-and-key fashion, with molecules called receptors on the surface of the receiving cell. Receptors bridge the receiving cell's membrane; they have one facet on the outside and one on the inside of the cell. When the neurotransmitter links up with the exterior facet, the interior facet precipitates an electrical response in the cell membrane or inside the cell. The result may be increased production of some cell product or—often—a repeat of the process just described, so that the message gets relayed in turn to the next cell in the circuit.

At this point, cell-to-cell communication is complete. The neurotransmitter molecules drop off the receptors. Loose again in the synapse, they meet three fates:

- Some attach to another receptor;
- Some encounter an enzyme, a chemical that breaks them apart; and
- Some reenter the sending cell via a special pathway through the axon membrane, called a transporter. Once back inside the cell, they are available for re-release in future neurotransmission episodes.

Normally, when drugs are not present, the cycle of release, breakup, and cell re-entry maintains the amount of neurotransmitter in the synapse, and hence neurotransmission, within certain limits. In most cases, when an abused drug enters the brain, it causes neurotransmission to increase or decrease dramatically beyond these limits.

What Changes Occur With Chronic Drug Abuse?

During the early phase of an individual's drug experimentation, neurotransmission normalizes as intoxication wears off and the substance leaves the brain. Eventually, however, drugs wreak changes in cellular structure and function that lead to long-lasting or permanent neurotransmission abnormalities. These alterations underlie drug tolerance, addiction, withdrawal, and other persistent consequences.

Some longer term changes begin as adjustments to compensate for drug-induced increases in neurotransmitter signaling intensities. For example, drug tolerance typically develops because sending cells reduce the amount of neurotransmitter they produce and release, or receiving cells withdraw receptors or otherwise dampen their responsiveness. Scientists have shown, for example, that cells withdraw opioid receptors into their interiors (where they cannot be stimulated) when exposed to some opioid drugs; when exposed to morphine, however, cells appear instead to make internal adjustments that produce the same effect—reduced responsiveness to opiate drugs and natural opioids.[2] Over time, this and related changes recalibrate the brain's responsiveness to opioid stimulation downward to a level where the organ needs the extra stimulation of the drug to function normally; without the drug, withdrawal occurs.

The drug-related mechanisms producing cumulative changes in neurotransmission sometimes are genetic in nature. While a drug cannot change a person's genes, drugs can prod some genes to increase their production of proteins, leading to changes in cell function or even actual reshaping of the physical structure of cells. For example, in rats, cocaine and amphetamine stimulate genes that produce the proteins used to build dendrites, branch-like cell structures that contain neurotransmitter receptors.[3] Brains normally sprout new dendrites as they register new learning; the accelerated dendrite formation stimulants induce may partially account for these drugs' unusual hold on an abuser's attention.

Some drugs are toxic to nerve cells, and the effect accumulates with repeated exposures. For example, the club drug methylenedioxymethamphetamine (MDMA, ecstasy) damages axons that release serotonin; the result is disruption of serotonin neurotransmission that likely underlies the long-lasting memory problems experienced by abusers.[4] Similarly, methamphetamine, over time, damages enough dopamine-sending cells to cause significant defects in thinking and motor skills; with abstinence, dopamine function can partially recover, but it is unclear whether cognitive and motor capabilities come back as well.[5]

Experimental Methods

To determine whether or how a drug affects a particular neurotransmitter, researchers typically will compare individuals who have a history of drug exposure with others who do not. If researchers are investigating links between a drug's impact on neurotransmission and a drug-related behavior or symptom, they may compare individuals who exhibit the behavior or symptom with others who do not. The subjects in these experiments may be animals or people. In the case of animals, drug exposure often takes place under laboratory conditions designed to mimic human drug consumption. Studies can be divided into those in which measurements are made in living animals or people and those in which animal brain tissue is removed and examined.

Brain Tissue Assays

With removed tissue, scientists may perform chemical assays to quantify the presence of a neurotransmitter, receptor, or other structure of interest. In a recent experiment, scientists assayed brain tissue from 35-day-old rat pups and found that those that had been exposed to nicotine *in utero* had fewer nicotine receptors in the reward system than unexposed rats.[6]

A second experimental method using removed brain tissue—*in vitro*, literally, *in glass*, a historical term referring to the containers for the tissue and solution—enables researchers to view a drug's effects on neurotransmission in action. Scientists place the tissue in a laboratory solution of nutrients that enables the cells to continue to carry out some of their living functions. The researchers may then, for example, add the drug being investigated to the solution and monitor whether the cells respond by increasing their release of neurotransmitters. Alternatively, they may measure cell membrane or electrical properties that stimulate or inhibit the release of neurotransmitters.

In both *in vitro* experiments and in living animals, the techniques for measuring neurotransmitter quantities and fluctuations include microdialysis and fast-scan cyclic voltammetry (FSCV). Microdialysis involves taking a series of samples of the intercellular fluid containing the neurotransmitter through a microscopic tube inserted into the tissue or living brain. FSCV, recently developed by NIDA-funded scientists, monitors neurotransmitter fluctuations at tenth-of-a-second intervals by measuring electrical changes related to neurotransmitter concentrations.[7]

Live Studies

Studies with living animals or people are essential for tying drugs' effects on neurotransmitters to behaviors or symptoms. A common design for experiments with either animals or people is to give study subjects a chemical that has a known effect on a particular neurotransmitter, and then observe the impact on their behavior. Typically, the chemical is either an agonist (promoter) or *antagonist* (blocker) of signaling by the neurotransmitter.

In a recent experiment, for example, a research team administered a glutamate agonist to rats and showed that the resulting increased levels of the neurotransmitter correlated with a reduction in the animals' cocaine seeking.[8] Another team using the same strategy implicated glutamate in nicotine withdrawal.[9] Such studies are a staple of testing compounds to identify medication classes with potential for treating abuse or addiction.

Researchers also genetically alter animals to have special characteristics, such as producing less or more than the normal amounts of a particular neurotransmitter, or lacking receptors for a neurotransmitter. Researchers expose such animals to a drug and observe whether the animals' display of some particular drug-related behavior—for example, pacing restlessly after being given a stimulant—increases or decreases.

Brain Scans

Brain imaging techniques enable neuroscientists to directly assess neurotransmission in people and living animals. With positron emission tomography (PET), researchers can compare groups of drug-abusing and nonabusing individuals, quantifying differences in their levels of a particular neurotransmitter molecule (e.g., dopamine) or neurotransmission component (e.g., a receptor or transporter). With PET, researchers also can correlate a drug's transit through the brain with fluctuations in a target neurotransmitter. They can elicit a drug-related behavior or symptom (e.g., craving) and relate neurotransmitter fluctuations to the rise and fall in its intensity.

One recent PET study, for example, showed that smokers have less of the neurotransmitter-degrading enzyme monoamine oxidase-B (MAO-B) throughout their bodies than nonsmokers.[10] The relative deficit of MAO-B may help explain why smokers are at higher risk for hypertension and other chronic diseases.

Researchers use both PET and functional magnetic resonance imaging (fMRI) to monitor metabolic activity in selected regions of the brain. Because each neurotransmitter has a unique distribution among the regions of the brain, information on locations of heightened or decreased activity provides clues to which neurotransmitter is affected under the conditions of the study.

Cocaine's Dopamine Connections

Research on cocaine illustrates that many dimensions may be involved in a single drug's interaction with the activity of a single neurotransmitter. Studies show that cocaine alters dopamine neurotransmission with effects on:

Reward

- Cocaine causes the pleasurable feelings that motivate drug abuse by raising dopamine concentrations in the synapses of the reward system.[a]
- Besides keeping dopamine in the synapses by blocking the transporters, cocaine can indirectly promote release of additional dopamine into the synapses by mobilizing a supply that the sending cells normally hold in reserve.[b]
- Cocaine's yield of pleasurable feelings arises largely through the activity of one particular set of dopamine receptors, called D3 receptors.[c]

Addiction

- Some studies indicate that the transition from casual cocaine abuse to addiction begins with the abuser's very first doses. For example, a single exposure to cocaine causes some cells in the brain's reward system to increase their responsiveness to subsequent stimulations.[d]
- In living animals with minimal exposure to cocaine, the drug alters the dopamine responsiveness for at least a week.[e]
- After chronic cocaine abuse dopamine ticks up in the reward system when the abuser encounters a cue associated with the drug.[f]
- Brains normally sprout new neurotransmitter receiving structures in the process of turning new experience into learning. Cocaine accelerates this process, which may help account for the drug's unusual hold on an addicted individual's attention.[g]

Vulnerability to Abuse

- A young person's marked taste for novelty may be an indication that dopamine activity in his or her brain's reward system is especially sensitive to cocaine.[h]
- An individual's attraction to cocaine's dopamine-stimulating effects also may relate to his or her social circumstances.[i]

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Summary

By altering neurotransmission, addictive drugs produce effects that make people want to continue to abuse them and induce health problems that can be longlasting and profound. The effects are drug-specific: Each drug disrupts particular neurotransmitters in particular ways. Some important effects, however, are shared by all: initial pleasurable feelings, and subsequent dependence and addiction, resulting from disruption of the dopamine neurotransmitter system.

Scientists use a wide variety of experimental tools and techniques to study drugs' effects on neurotransmission, and their consequences, in both animals and people. Their findings enhance our understanding of the experiences of drug abusers and the plight of addicts, point the way to new behavioral and medication treatments, and provide potential bases for prevention strategies and monitoring progress in treatment.

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