NS/202: Unit 4
Drug addiction, drug abuse and adverse drug reaction

Addiction is characterized by compulsive drug use, despite severe negative consequences

It follows a chronic course, with periods of abstinence followed by relapse. Vulnerability to relapse can persist even after years of abstinence, suggesting that long-lasting and perhaps permanent neurobiological changes underlie addiction.

There are tremendous individual differences in vulnerability, reflecting both **genetic and environmental influences**, and many people experiment with potentially addictive drugs without progressing to compulsive use.

Approximately **one in four of all deaths in the U.S.A**. are attributable to the use of alcohol, nicotine or illicit drugs.

Long-term drug exposure produces many physiological and behavioral changes that contribute to addiction.

Tolerance ***(a state in which an organism no longer responds to a drug)*** *is the need for increasing doses of a drug to* achieve the same effect.

Sensitization *refers to the enhancement* of drug responses as a result of repeated drug exposure. For a given drug, it is possible for certain effects to show tolerance and others to show sensitization.

Dependence *is an adapted physiological state of cells or* systems that develops to compensate for excessive stimulation by a drug. When drug intake stops, unmasking of this adapted state leads to a *withdrawal syndrome that may* have somatic (physical) components as well as affective and motivational components.

Many forces may drive compulsive drug use

The incentive-sensitization theory of addiction proposes that sensitization occurs in the neural systems that attribute incentive salience to drugs and drug-associated cues.

Drug 'wanting' sensitizes, even though drug 'liking' typically shows tolerance.

Drugs may produce dysregulation of cortical systems that normally exert inhibitory control over behavior, leading to **poor decision-making and impulsivity, which in turn drive compulsive pursuit of drugs.**

NEURONAL CIRCUITRY OF ADDICTION

Natural reinforcers and drugs of abuse use similar circuits

Drugs of abuse — like food, drink and sex — are reinforcing. That is, they 'stamp in' or 'reinforce' learned associations, such that behaviors associated with obtaining the reinforcer tend to be repeated.

However, a common mechanism underlying the reinforcing actions of most addictive drugs — and those of natural reinforcers — is **activation of mesocorticolimbic dopamine neurons.**

These neurons originate in the ventral tegmental area (VTA) of the midbrain and project to cortical and limbic target regions.

Elevation of dopamine levels in one of these target regions, the **nucleus accumbens, is particularly important for reinforcement.**

The **nucleus accumbens serves as an interface between limbic and cortical regions** important for motivation, and motor circuits responsible for execution of motivated behaviors.

Dopamine neurons in the substantia nigra, which project primarily to dorsal striatum, are also important, particularly in the learning and performance of habitual behaviors associated with addiction.

According to the incentive sensitization theory of addiction (above), dopamine signals the incentive salience attributed to drugs and drug associated cues, causing them to be 'wanted'.

Another influential theory holds that activation of dopamine neurons is important in learning and predicting the likelihood of reward when an animal is presented with reward-related stimuli.

While dopamine neurons are activated to a modest degree by natural rewards, drugs of abuse produce a much stronger elevation in dopamine levels that may not be subject to normal regulatory mechanisms.
For example**, dopamine released by natural rewards will be removed from the synapse by the dopamine transporter. However, cocaine works by blocking this transporter, so cocaine produces larger and more prolonged increases in dopamine levels.**

The neuronal circuitry underlying drug craving has been intensely studied to develop strategies for preventing relapse

Drug craving in human addicts, and the reinstatement of drug-seeking behavior in animal models of relapse, can be triggered by three types of stimuli:

a. *cues associated with prior drug use (such as drug paraphernalia),*

b. re-exposure to a low dose of drug and

c. exposure to stress

Animal studies have shown that these stimuli trigger reinstatement of drug-seeking through distinct but overlapping neuronal circuits.

For example,

the **basolateral amygdala** is critical for the ability of conditioned cues to maintain and reinstate drug-seeking behavior.

Cocaine-primed reinstatement requires **activation of glutamate projections** from the prefrontal cortex to the nucleus accumbens.

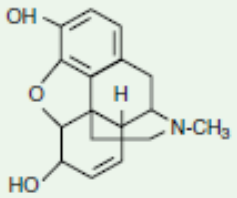
Stress-induced reinstatement involves brain **corticotrophin-releasing factor (CRF) and norepinephrine systems.**

Functional imaging studies in human addicts have found that cue-elicited craving is associated with **activation of the amygdala, the anterior cingulate cortex, the orbitofrontal cortex, and the dorsolateral prefrontal cortex.**

Activation of other regions has been reported less consistently. **The amygdala is critical for associative learning related to reward, while the three cortical areas are important for decision-making based on integration of cognitive and motivationally relevant information**. **Disruption of these circuits in addicts may be associated with alterations in dopamine transmission**

A. Opiates

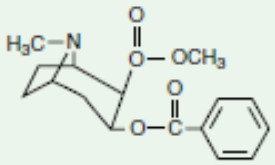
Morphine



Primary target: μ opioid receptor

B. Psychostimulants

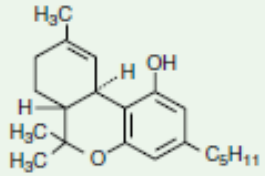
Cocaine



Primary target:
Monoamine transporters

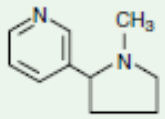
C. Cannabinoids

Δ^9-tetrahydrocannabinol



Primary target:
Cannabinoid CB1 receptor

D. Nicotine



Primary target:
Nicotinic acetylcholine receptor

E. Alcohol

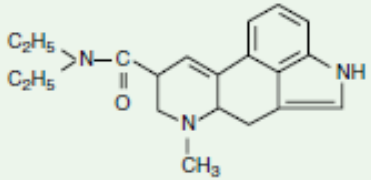
Ethanol

$H_3C - CH_2 - OH$

Primary target:
Ligand gated and voltage gated ion channels

F. Hallucinogens

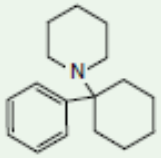
Lysergic acid diethylamine



Primary target:
Serotonin receptors

G. Dissociative Drugs

Phencyclidine



Primary target:
NMDA receptor

FIGURE 56-1 Major drug classes, structures of prototypical agonists and 'primary targets' implicated in drug class reward. See Figure 56-4 for structures of amphetamines.

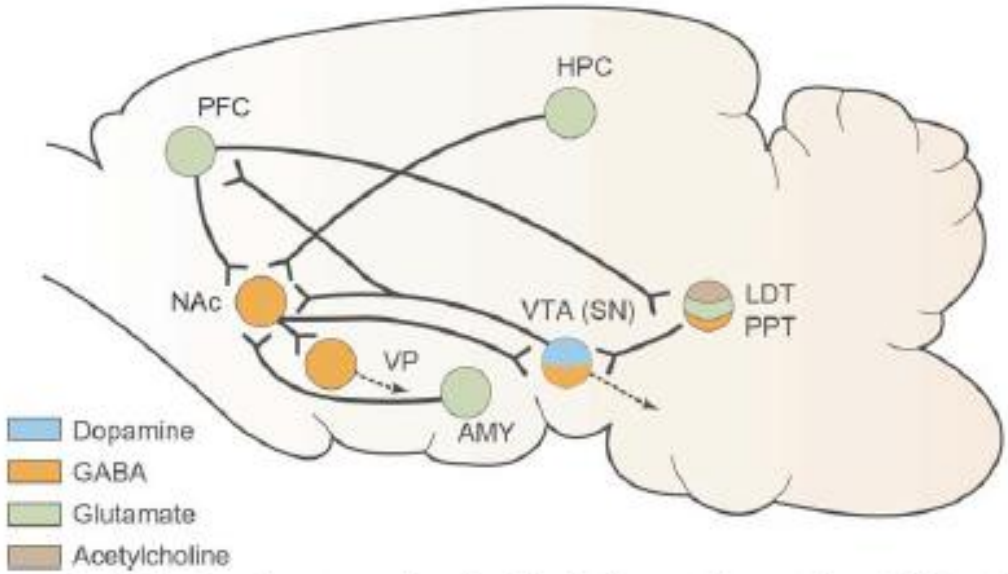


FIGURE 56-2 The mesocorticolimbic dopamine system and associated circuits. The ventral tegmental area (*VTA*) contains both dopamine and GABA neurons that innervate the nucleus accumbens (*NAc*), prefrontal cortex (*PFC*) and other forebrain targets not shown. Nucleus accumbens neurons, which use GABA as their transmitter, receive glutamate inputs from the PFC, amygdala (*AMY*), hippocampus (*HPC*), and thalamus (not shown). These glutamate inputs convey information important for goal-directed behaviors. NAc neurons integrate this information, and then transmit it to brain regions important for execution of these behaviors, including the ventral pallidum (*VP*), VTA and substantia nigra (*SN*), as well as other motor regions (*dashed arrows*). The prefrontal cortex influences this circuitry at many levels by sending descending glutamate projections to many targets, including the NAc, VTA, SN, pedunculopontine tegmental nucleus (*PPT*) and laterodorsal tegmental nucleus (*LDT*). The PPT and LDT send mixed cholinergic, glutamate and GABA projections to the VTA and SN, that exert an important regulatory influence on dopamine and GABA cells in the latter regions.

OPIATES

Opiates are drugs derived from opium, including morphine and heroin

There are three classical opioid receptor types, μ, δ, and κ 914
Chronic opiate treatment results in complex adaptations in opioid receptor signaling

Upregulation of the cAMP second-messenger pathway is a well-established molecular adaptation

Endogenous opioid systems are an integral part of the reward circuitry

OPIATES

Opiates are drugs derived from opium, including morphine and heroin

Opium, extracted from poppy plants, has been used for recreational and medicinal purposes for thousands of years.

Morphine was identified as the active pharmacological ingredient of opium in the early 1800s. Heroin was synthesized from morphine in the late 1800s in an attempt to develop a nonaddicting cough suppressant.

Opioid is a more inclusive term that includes opiates, as well as endogenous, or naturally occurring, opioid peptides. These include the **enkephalins, endorphins, dynorphins and endomorphins.**

Prolonged use leads to tolerance and dependence, and to craving and withdrawal symptoms when drug use is terminated. Withdrawal symptoms include **anxiety, nausea, insomnia, hot and cold flashes, muscle aches, perspiration, and diarrhea.**

Opiate actions in spinal cord and brain stem are important for analgesic effects, autonomic effects, and physical withdrawal symptoms.
Opiate effects on the **mesocorticolimbic system** are important for acute rewarding effects, some psychological withdrawal symptoms, and craving.

There are three classical opioid receptor types, μ, δ, and κ

The μ-opioid receptor is responsible for the reinforcing effects of heroin and morphine. Morphine is relatively selective for μ receptors.

Endorphins and enkephalins bind to μ and δ receptors, while dynorphin binds selectively to κ-opioid receptors.

The N/OFQ receptor, cloned in 1994, has high structural homology with classical opioid receptors, but very low affinity for conventional opioid ligands. Orphanin (nociceptin) is the endogenous ligand for the N/OFQ receptor, and may modulate opioid effects.

Opioid receptors generally mediate neuronal inhibition. They couple to Gi or Go, and produce inhibition of Ca2+ channels and opening of K+ channels. They also inhibit adenylyl cyclase. Through this and other downstream signaling pathways, opioid receptors modulate synaptic plasticity and gene expression.

In the VTA, opiates stimulate μ-opioid receptors on GABA neurons that synapse on dopamine neurons. This inhibits the GABA neurons, leading to disinhibition of the dopamine neurons and enhanced dopamine release in the nucleus accumbens and other target areas. **Opiates also exert dopamine independent** effects in the nucleus accumbens by activating μ-opioid receptors on nucleus accumbens neurons themselves. The relative contribution of these two mechanisms to the reinforcing effects of opiates remains unclear. There is increasing evidence that endogenous cannabinoid systems are also important in mediating the rewarding effects of opiates, and vice versa.

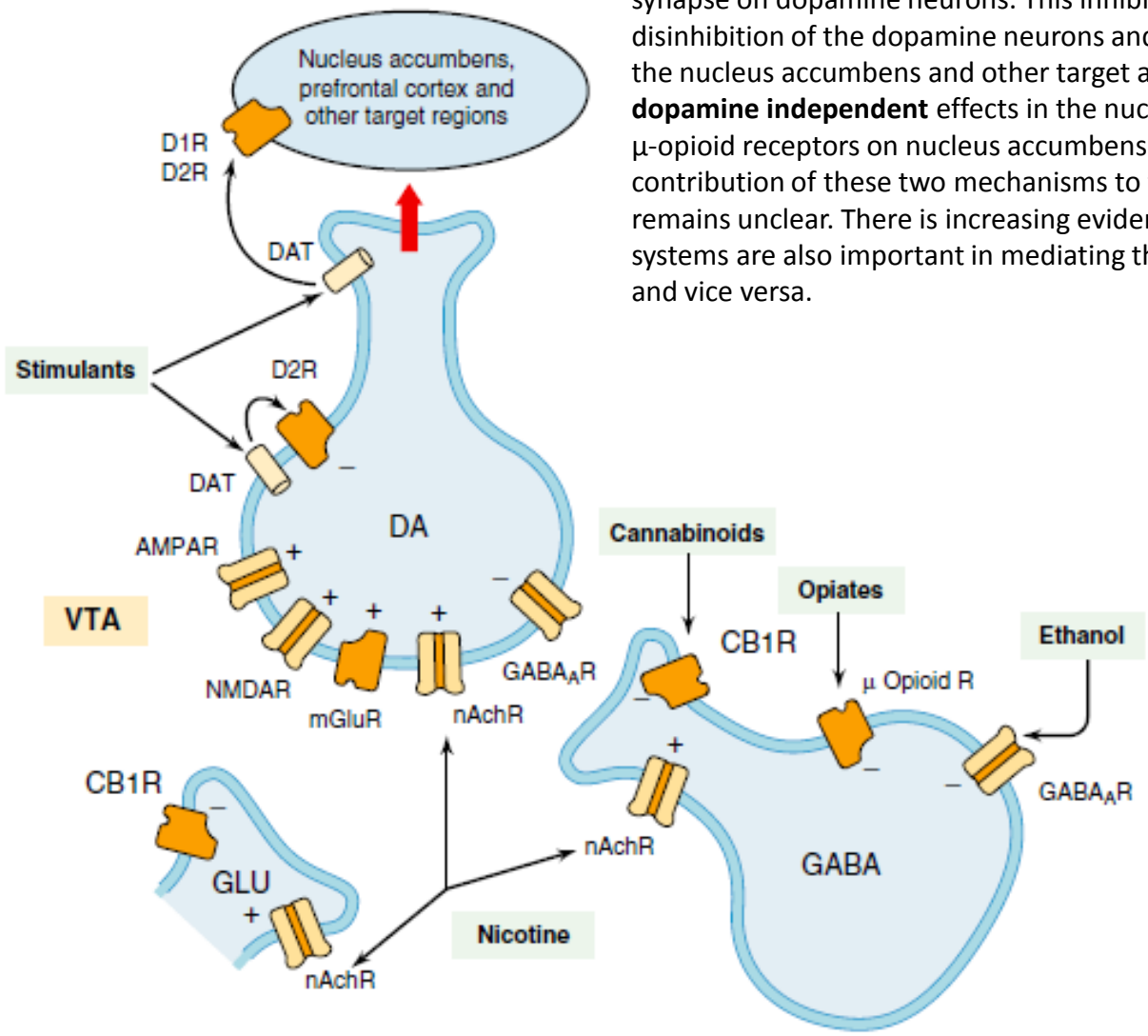


FIGURE 56-3 All reinforcing drugs increase dopamine transmission in the mesocorticolimbic dopamine system, but they use different mechanisms. Opiates, ethanol and cannabinoids decrease GABA transmission in the ventral tegmental area (*VTA*), thereby disinhibiting dopamine neurons. Psychomotor stimulants interact with the DA transporter (*DAT*) to elevate extracellular dopamine levels. Nicotine excites dopamine cells directly and promotes glutamate release from glutamate nerve terminals in the VTA.

Chronic opiate treatment results in complex adaptations in opioid receptor signaling

Much has been learned from studies on mechanisms of tolerance to the analgesic effects of opiates. This is a major clinical problem, as it means that **ever-escalating doses are required for the treatment of chronic pain.**

Different agonists direct opioid receptors towards different signaling and trafficking pathways. Understanding the **rules governing the function of ligand–receptor complexes may help in the development of opiates that are effective analgesics but have reduced liability to cause tolerance and dependence**.

Upregulation of the cAMP second-messenger pathway is a well-established molecular adaptation

It occurs in many brain regions after chronic administration of opiates and other drugs of abuse. The **locus coeruleus (LC; nucleus in the pons of brainstem involved with physiological responses to stress and panic) has been a useful model system for studying upregulation of the cAMP pathway.**

Located in the brain stem, the **LC is the largest cluster of norepinephrine containing neurons in the brain and normally participates in regulation of autonomic function and attentional states.**

Acutely, opiates suppress the activity of LC neurons via Gi-coupled receptors that inhibit adenylyl cyclase activity

Chronic opiate administration leads to compensatory upregulation of specific subtypes of adenylyl cyclase and specific subunits of protein kinase A. The transcription factor CREB plays a critical role in this adaptive response.

Upregulation of the cAMP pathway increases the excitability of LC neurons, enabling them to fire at normal rates despite the continued presence of opiates.

When opiates are withdrawn, upregulation of the cAMP pathway is no longer opposed by inhibitory effects of opiates, leading to a dramatic rebound activation of LC neurons that contributes to somatic withdrawal symptoms.

Of course, upregulation of the cAMP pathway is only one of many cellular mechanisms contributing to adaptive changes in the LC and other regions after chronic opiate administration.

The nucleus accumbens is another brain region in which the cAMP pathway is upregulated by chronic administration of opiates. This leads to **increased transcription of CREB-regulated proteins, including dynorphin, the endogenous ligand for the κ-opioid receptor.**

Dynorphin stimulates presynaptic κ-opioid receptors on dopamine nerve terminals, inhibiting dopamine release. In the presence of opiates, this effect of dynorphin may serve as a homeostatic adaptation that diminishes drug responsiveness by reducing activation of the dopaminergic system. However, once opiates are no longer present, decreased dopamine release may contribute to the anhedonia and dysphoria that characterize the early phase of opiate withdrawal.

There are two main treatments for the opiate withdrawal syndrome.
One **is replacement therapy with methadone or other μ agonists** that have a longer half-life than heroin or morphine, and produce mild stimulation rather than euphoria.

Withdrawal is also treated with the **α2 agonist clonidine, which inhibits LC neurons, thus counteracting autonomic effects of opiate withdrawal — such as nausea, vomiting, cramps, sweating, tachycardia and hypertension** — that are due in part to loss of opiate inhibition of LC neurons.

PSYCHOMOTOR STIMULANTS

This drug class includes cocaine and amphetamine derivatives

Transporters for dopamine (DAT), serotonin (SERT) and norepinephrine (NET) are the initial targets for psychomotor stimulants

Cocaine and amphetamines produce neuronal adaptations by repeatedly elevating monoamine levels

Dopamine receptor signaling through the PKA pathway mediates many effects of psychomotor stimulants

This drug class includes cocaine and amphetamine derivatives

Low-to-moderate doses lead to increased activity, talkativeness and feelings of euphoria and general wellbeing, along with decreases in fatigue and in food intake.

Repetitive motor activity (stereotyped behavior) is produced by higher doses, and very high doses can produce convulsions, hyperthermia, coma and death.

Stimulants have some therapeutic uses. For example, amphetamine is used to treat narcolepsy (excessive uncontrollable daytime sleepiness), and methylphenidate (Ritalin) is used in the treatment of children with attention deficit hyperactivity disorder. Because repeated administration of stimulants can produce sensitization of their reinforcing effects, there is concern that long-term childhood exposure to methylphenidate may increase vulnerability to drugs of abuse later in life.

Transporters for dopamine (DAT), serotonin (SERT) and norepinephrine (NET) are the initial targets for psychomotor stimulants

Psychomotor stimulants increase extra cellular levels of **monoamine neurotransmitters**.
Cocaine is a monoamine uptake inhibitor. The reinforcing effects of cocaine correlate best with its binding potency at the DAT.
These drugs interact with DAT, SERT and NET with varying relative affinities.

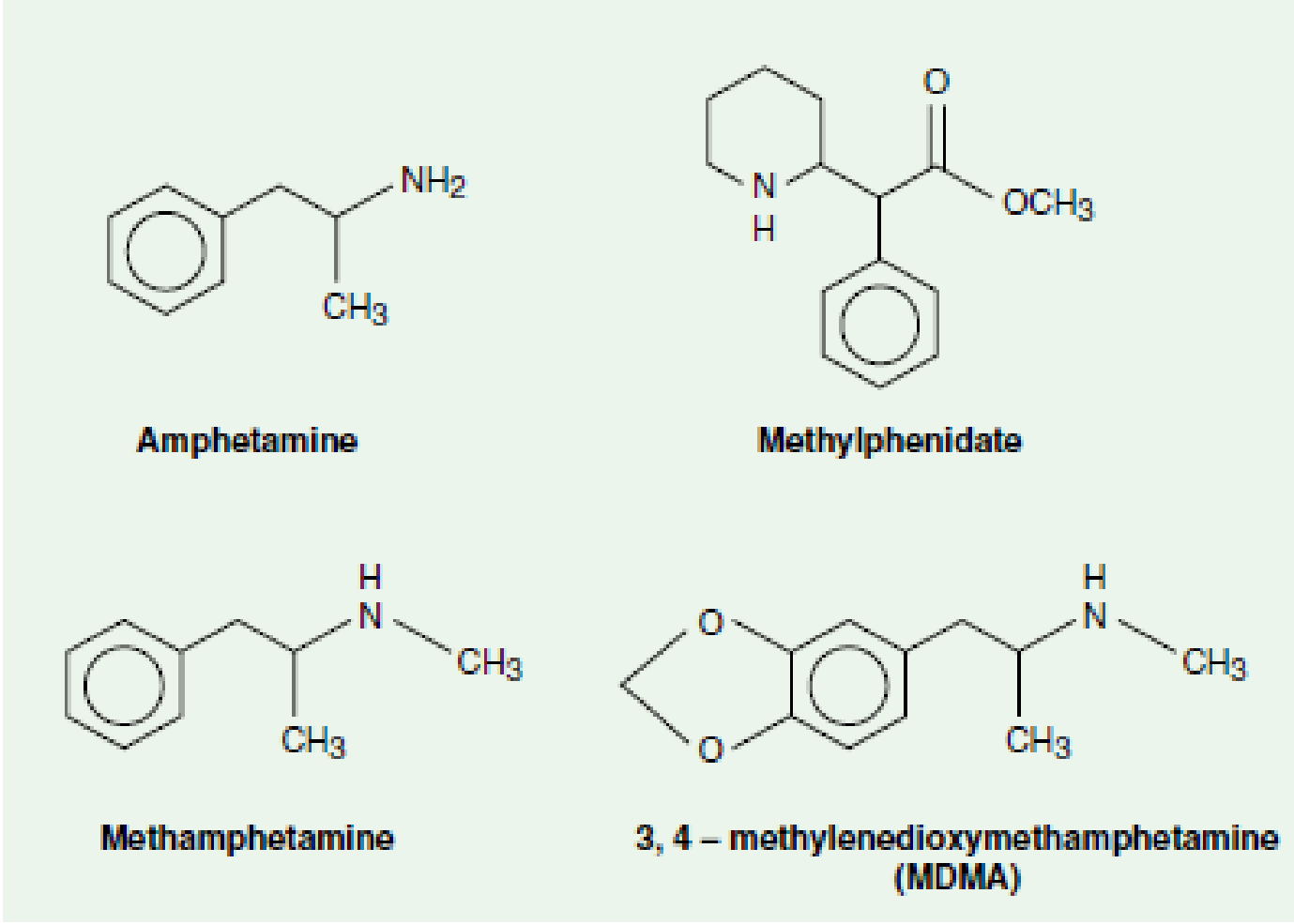


FIGURE 56-4 Amphetamine and other important stimulants.

In experimental animals, repeated exposure to high doses of some psychomotor stimulants **produces long-term decreases in markers for the integrity of dopamine and serotonin nerve terminals.**

This involves a **neurodegenerative process mediated by free radicals and oxidative stress. In rats, high-dose amphetamine preferentially damages dopamine terminals, methamphetamine damages serotonin and dopamine terminals, and 3,4-methylenedioxymethamphetamine (MDMA) preferentially damages serotonin neurons**.

There is emerging evidence that methamphetamine has **long-term effects on motor, cognitive and motivational function that are associated with reductions in DAT levels and brain metabolism; some effects recover and others persist, even after 12–17 months of abstinence .**

In MDMA users, there is some evidence for **mild impairments of memory and cognition**, but no strong evidence linking these impairments to neurotoxicity.

Cocaine and amphetamines produce neuronal adaptations by repeatedly elevating monoamine levels

The resulting overstimulation of monoamine receptors, located on target neurons postsynaptic to monoamine nerve terminals, leads to a complex cascade of downstream changes that **involves many brain regions and transmitter systems**. Many adaptations have been characterized that are associated with behavioral sensitization, an animal model of addiction.

During repeated drug administration, behavioral responses to psychomotor stimulants gradually **intensify or 'sensitize', including responses that provide an index of motivation for drug taking.**

The **dopamine system itself undergoes complex adaptations** during behavioral sensitization to psychomotor stimulants.
During the first few days after discontinuing drug administration, the firing rate of dopamine neurons increases due to transient changes in regulatory mechanisms in the VTA, including the development of LTP at excitatory synapses onto dopamine neurons. Adaptations in the VTA dissipate with longer withdrawal times, giving way to more persistent adaptations in the nucleus accumbens and other forebrain regions, some of which increase the responsiveness of the dopamine system to subsequent drug exposure
. For example, there are **alterations in Ca2+ signaling** within dopamine nerve terminals that allow **more dopamine to be released by depolarizing stimuli and psychomotor stimulants**. There are also alterations in **postsynaptic dopamine receptor signaling**.

Stimulant-induced changes in **glutamate transmission** have received considerable attention in recent years.

Focus on glutamate also reflects the fact that **postsynaptic neurons in most dopamine-innervated brain regions are co-regulated by convergent dopamine and glutamate** inputs, **with dopamine serving a neuromodulatory role.**
Glutamate transmission in the nucleus accumbens is the critical mediator of cocaine-seeking behavior in rats

Dopamine receptor signaling through the PKA pathway mediates many effects of psychomotor stimulants

Dopamine receptors can be divided into two major families, based on pharmacology and signal transduction mechanisms, the **D1-like receptors (D1 and D5) and the D2-like receptors (D2, D3 and D4).**

D1 receptors are positively coupled to adenylyl cyclase, while D2 receptors are negatively coupled to adenylyl cyclase.

In addition, both receptors influence other signaling mechanisms. Both serve as postsynaptic receptors in the nucleus accumbens, dorsal striatum, amygdala, prefrontal cortex and other dopamine innervated regions.

D2 receptors also serve as presynaptic autoreceptors.
Both D1 and D2 receptors mediate psychomotor stimulant actions, but D1 receptor signaling through the cAMP-dependent protein kinase (PKA) pathway may be more important for persistent drug effects.

Through this pathway, **dopamine regulates the phosphorylation state of many important proteins that influence neuronal excitability on different time scales.**
For example,
D1 receptors can exert rapid effects on neuronal excitability via PKA phosphorylation of ligand- and voltage-gated ion channels, including NMDA receptors, AMPA receptors, Na+ channels and Ca2+ channels. D1 receptors exert longer lasting effects by regulating transcription factors such as CREB

Repeated cocaine administration, like repeated morphine administration, leads to upregulation of the cAMP–CREB pathway in the nucleus accumbens.

It is important to keep in mind that repeated stimulant exposure produces adaptations in dopamine receptive neurons in addition to those related to D1 receptor–PKA signaling, and that convergent activation of PKA and Ca2+ signaling may be necessary for the recruitment of mechanisms that enable synaptic and structural plasticity.

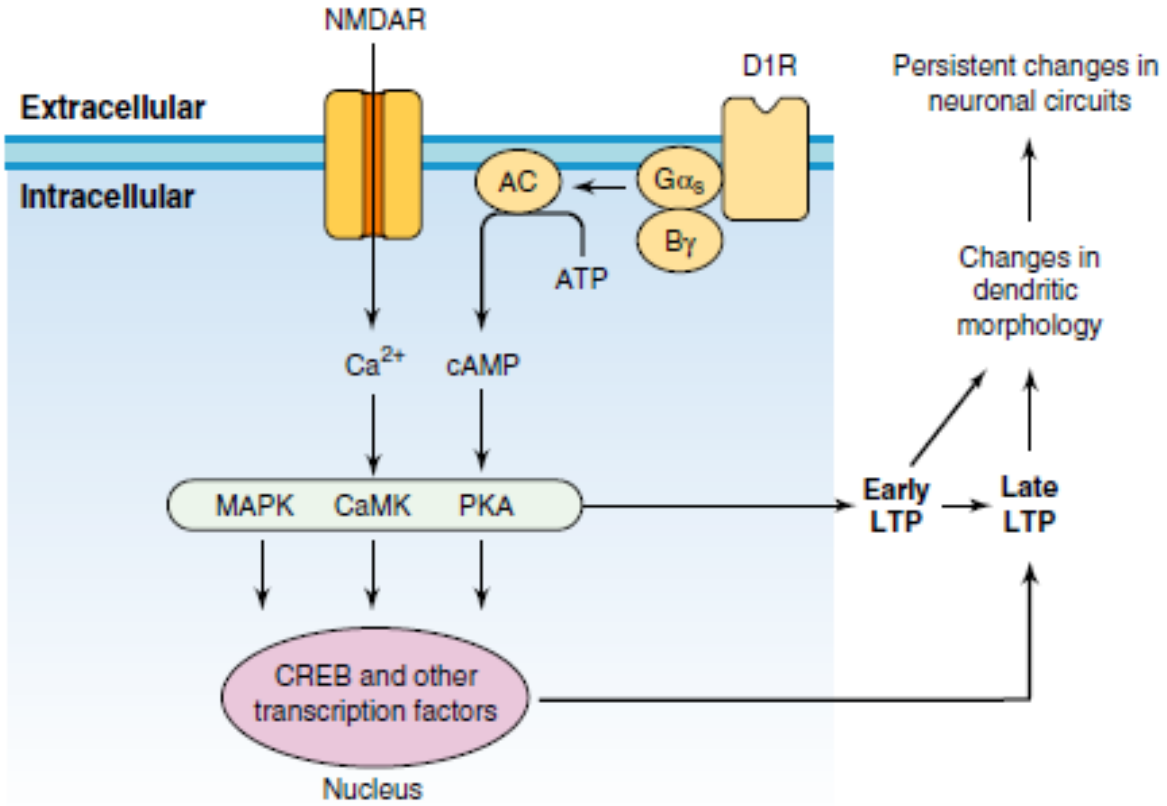


FIGURE 56-5 The D1 receptor–PKA signaling pathway influences neuronal excitability by regulating ion channels and receptors in the membrane (see text) and influences gene expression by activating transcription factors such as CREB. Note that some effects of this pathway are mediated indirectly by DARPP-32, a potent inhibitor of protein phosphatase-1 that is involved in many aspects of addiction (see Ch. 23). There is considerable cross-talk between the D1 receptor–PKA signaling pathway and other receptors located in dopamine-receptive neurons, for example, NMDA, AMPA, mGluR, D2 dopamine, serotonin, adenosine, opiate and $GABA_A$ receptors. The NMDA receptor plays an important role in activating Ca^{2+}-dependent signaling pathways. Convergent activation of cAMP and Ca^{2+} signaling pathways is necessary for some responses, e.g. CREB activation. The same cascades are critical for activity-dependent forms of plasticity such as LTP. During the early component of LTP, which requires activation of several protein kinases, synaptic strength is increased by mechanisms that include the synaptic insertion of new glutamate receptors. This is followed by a later more persistent component of LTP that requires protein synthesis. Over time, morphological changes occur in the postsynaptic density, perhaps related to the insertion of new glutamate receptors. Ultimately, dendritic spines and even presynaptic terminals undergo complex remodeling, leading to persistent changes in the activity of neuronal circuits. The ability of addictive drugs to influence the same signaling pathways that mediate LTP may explain their ability to produce persistent structural and functional changes in neuronal pathways related to motivation and reward (see Fig. 56-7).

CANNABINOIDS (MARIJUANA)

Marijuana and hashish are derivatives of the cannabis sativa plant

Cannabinoid effects in the CNS are mediated by the CB1 receptor

Endocannabinoids are endogenous ligands for the CB1 receptor

Endocannabinoids serve as retrograde messengers

There are many similarities between endogenous opioid and cannabinoid systems

CANNABINOIDS (MARIJUANA)

Marijuana and hashish are derivatives of the cannabis sativa plant.

Although cannabinoids have been used for centuries for recreational and therapeutic purposes, dramatic advances in cannabinoid neurobiology have occurred since 1990.

This is attributable to the cloning of cannabinoid receptors and the discovery of **endogenous cannabinoids, termed endocannabinoids.**

Marijuana's major effect in humans is **a mildly euphoric and relaxing 'high'**. Other effects **include increased appetite, and apparently reversible cognitive impairments related to attention and memory**. Less common effects are anxiety, paranoia and panic. The psychoactive component of cannabis is Δ9-tetrahydrocannabinol (THC).

Tolerance develops to most effects of marijuana, but it disappears rapidly. Very few people seek treatment for marijuana addiction, and withdrawal symptoms are rare.

However, a mild withdrawal syndrome has been observed in users who suddenly stop after heavy, daily marijuana use and in experimental animals treated chronically with THC and then administered a cannabinoid receptor antagonist

Cannabinoid withdrawal, like opioid withdrawal, is associated with upregulation of the cAMP pathway. But this occurs mainly in the cere bellum, accounting in part for much milder symptoms.

Cannabinoids also have therapeutic potential. Marijuana is used for the treatment of nausea produced by cancer chemotherapy, and wasting syndrome caused by AIDS.

Cannabinoid agonists and antagonists are being considered for use in a number of conditions, including movement disorders, eating disorders, and even for drug and alcohol addiction.

Cannabinoid effects in the CNS are mediated by the CB1 receptor

This Gi/Go-protein-coupled receptor was cloned in 1990. Its counterpart in the periphery, CB2, was cloned three years later. The brain may contain other undiscovered cannabinoid receptors.

CB1 is by far the most abundant G-protein-coupled receptor in the mammalian brain. It is highly expressed in the basal ganglia, cerebellum, hippocampus, cortex and brain stem.

Accordingly, cannabinoids modulate motor activity, motivation, learning, memory, and pain processing.

Many CB1 receptors are located presynaptically on GABA and glutamate nerve terminals, where they decrease GABA or glutamate release by inhibiting Ca2+ currents and altering K+ channel gating.

Presynaptic **CB1 receptors inhibit the release of other transmitters as well.**
CB1 receptors are also coupled to inhibition of adenylyl cyclase and activation of the MAP kinase/ERK pathway, as well as other protein kinase signaling cascades that regulate gene expression.

Cannabinoids share with other drugs of abuse the ability to increase the firing rate of VTA dopamine neurons and increase dopamine release in the nucleus accumbens.

Endocannabinoids are endogenous ligands for the CB1 receptor. The best established are anandamide (*N*-arachidonoylethanolamine) and 2-AG (2-arachidonoylglycerol). Others may also exist. Pathways involved in the formation and inactivation of anandamide and 2-AG are shown in Figure 56-6. Some steps in their formation are Ca^{2+}-dependent. This explains the ability of neuronal depolarization, which increases postsynaptic intracellular Ca^{2+} levels, to stimulate endocannabinoid formation and release. Some neurotransmitter receptors (e.g. the D2 dopamine receptor) also stimulate endocannabinoid formation, probably by modulating postsynaptic Ca^{2+} levels or signaling pathways (e.g. PLC) that regulate endocannabinoid formation.

Endocannabinoids are derived from lipids, making them different from classical and peptide transmitters in several important respects. The latter are stored in vesicles after their synthesis and released by exocytosis in response to action potential invasion of the nerve terminal. In contrast, endocannabinoids are produced 'on demand' when neuronal activity or occupation of membrane receptors leads to cleavage of membrane lipid precursors. Cannabinoid release is poorly understood, but it is not vesicular. Their hydrophobic nature raises questions about how they cross the extracellular space. It is possible that this is facilitated by extracellular lipid-binding 'carrier' proteins.

Endocannabinoids serve as retrograde messengers.

They are **released by postsynaptic neurons and act on presynaptic CB1 receptors on neighboring nerve terminals**. Retrograde signaling by endocannabinoids is essential for many forms of synaptic plasticity that are initiated by postsynaptic depolarization and increased postsynaptic intracellular Ca2+, but expressed as a presynaptic decrease in the probability of transmitter release.

Examples include some forms of long-term depression at GABA synapses in the hippocampus and the amygdala, and at glutamate synapses in the striatum and nucleus accumbens.

Marijuana may alter normal endocannabinoid mediated synaptic effects, perhaps leading to abnormal synaptic plasticity. This may be related to the short-term disruption of memory and learning associated with marijuana use, and to motivational and rewarding effects of marijuana.

There are many similarities between endogenous opioid and cannabinoid systems. Both CB1 and μ-opioid receptors are G_i/G_o-coupled receptors that share some signaling mechanisms and cellular effects, such as presynaptic inhibition. Both opioids and cannabinoids produce analgesic and rewarding effects. Finally, both systems are integral components of the reward circuitry and thus participate in responses to other drug classes. For example, in animals, blockade of endocannabinoid transmission attenuates reinstatement of cocaine- and heroin-seeking behavior and decreases motivation for alcohol consumption. It is likely that the mechanism involves CB1 receptor-mediated modulation of synaptic transmission and synaptic plasticity in reward-related brain regions such as the VTA, nucleus accumbens, dorsal striatum and amygdala. It is possible that drugs targeting endocannabinoid transmission may be useful in treating some aspects of addiction.

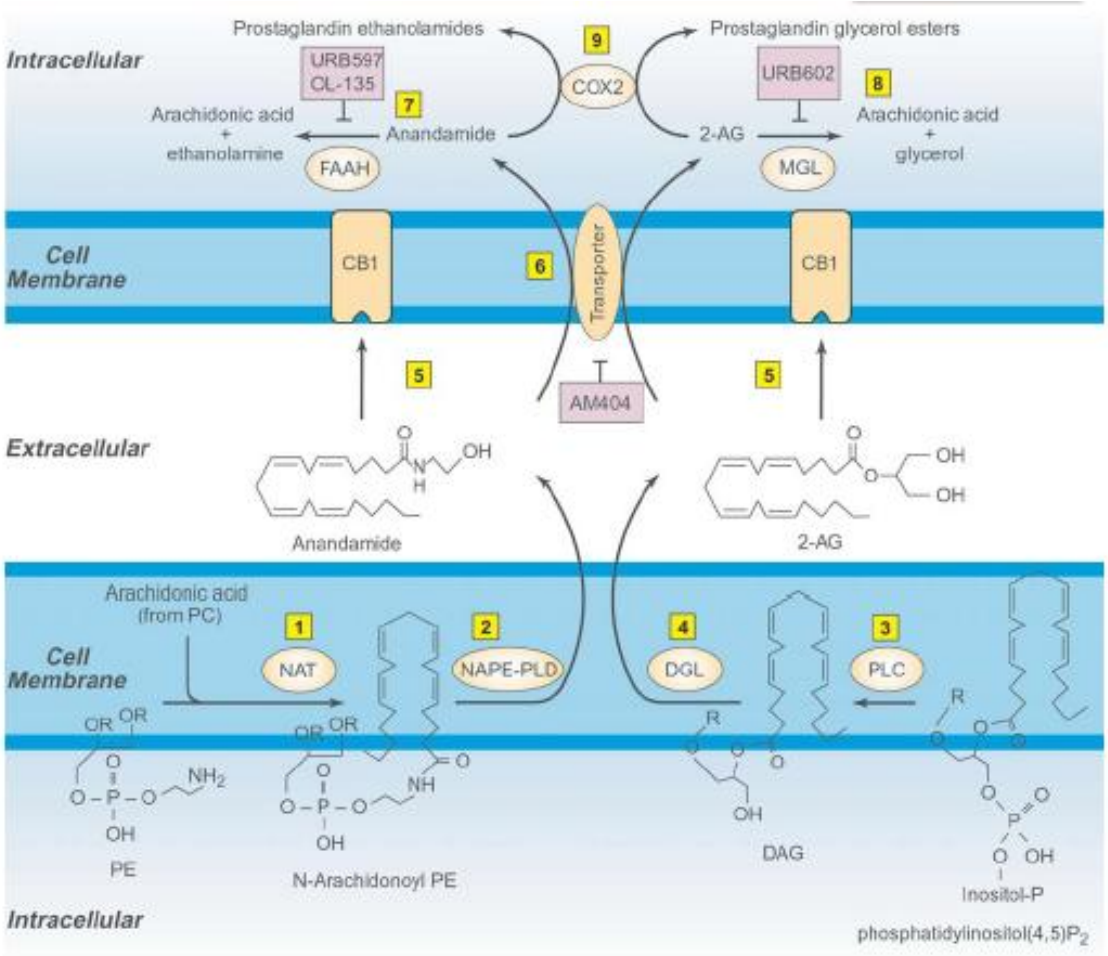


FIGURE 56-6 Formation and inactivation of the endocannabinoids anandamide and 2-AG. (**1**) *N*-arachidonoyl phosphatidylethanolamine (*N*-arachidonoyl PE), required for synthesis of anandamide, may be formed by *N*-acyl transferase (*NAT*), which transfers an arachidonate moiety, derived from the sn-1 position of phospholipids such as phosphatidylcholine (*PC*), to the primary amino group of PE. (**2**) Anandamide is generated from the hydrolysis of *N*-arachidonoyl PE, catalyzed by *N*-acylphosphatidylethanolamine-hydrolyzing phospholipase D (*NAPE-PLD*). (**3**) Phospholipase C (*PLC*) catalyzes the hydrolysis of phosphatidylinositol (4,5)-bisphosphate (PtdIns(4,5)P_2) to diacylglycerol (*DAG*) and inositol (1,4,5)-triphosphate. (**4**) DAG lipase (*DGL*) catalyzes the formation of 2-AG from DAG. An alternative pathway for 2-AG formation involves the formation of a 2-arachidonoyl-lysophospholipid such as lyso-PI (catalyzed by phospholipase A1) followed by its hydrolysis to 2-AG (catalyzed by lyso-PLC) (see Piomelli [36]). (**5**) Anandamide and 2-AG are agonists at the CB1 receptor. (**6**) Anandamide and 2-AG are removed from the extracellular space by carrier-mediated transport, which is inhibited by AM404. (**7**) Anandamide is hydrolyzed by a membrane-bound fatty acid amidohydrolase (*FAAH*), which is inhibited by URB597 and OL-135. (**8**) 2-AG is hydrolyzed by monoacylglycerol lipase (*MGL*). MGL is inhibited by URB602. (**9**) Anandamide and 2-AG are converted to prostaglandin ethanolamides and glycerol esters, respectively, by cyclooxygenase-2 (COX-2). Abbreviations: *AA*, arachidonic acid; *R*, fatty acid group.

NICOTINE

Nicotine is responsible for the highly addictive properties of tobacco products

Nicotine is an agonist at the nicotinic acetylcholine receptor (nAChR)

The ventral tegmental area (VTA) is a critical site for nicotine action

ETHANOL, SEDATIVES AND ANXIOLYTICS

Alcoholism is a chronic relapsing disorder

Ethanol interacts directly with ligand-gated and voltage-gated ion channels

Multiple neuronal systems contribute to the reinforcing effects of ethanol

There is a need for improved therapies for alcoholism

Barbiturates and benzodiazepines are used to treat anxiety

HALLUCINOGENS AND DISSOCIATIVE DRUGS

Hallucinogens produce an altered state of consciousness

Phencyclidine (PCP) is a dissociative drug1

ADDICTION AND NEURONAL PLASTICITY SHARE COMMON CELLULAR MECHANISMS

Addiction may result from inappropriate neuronal plasticity

Studies of behavioral sensitization have linked addiction to long-term potentiation (LTP)

Drugs of abuse have profound effects on transcription factors and gene expression

Persistent adaptations may involve changes in the structure of dendrites and dendritic spines

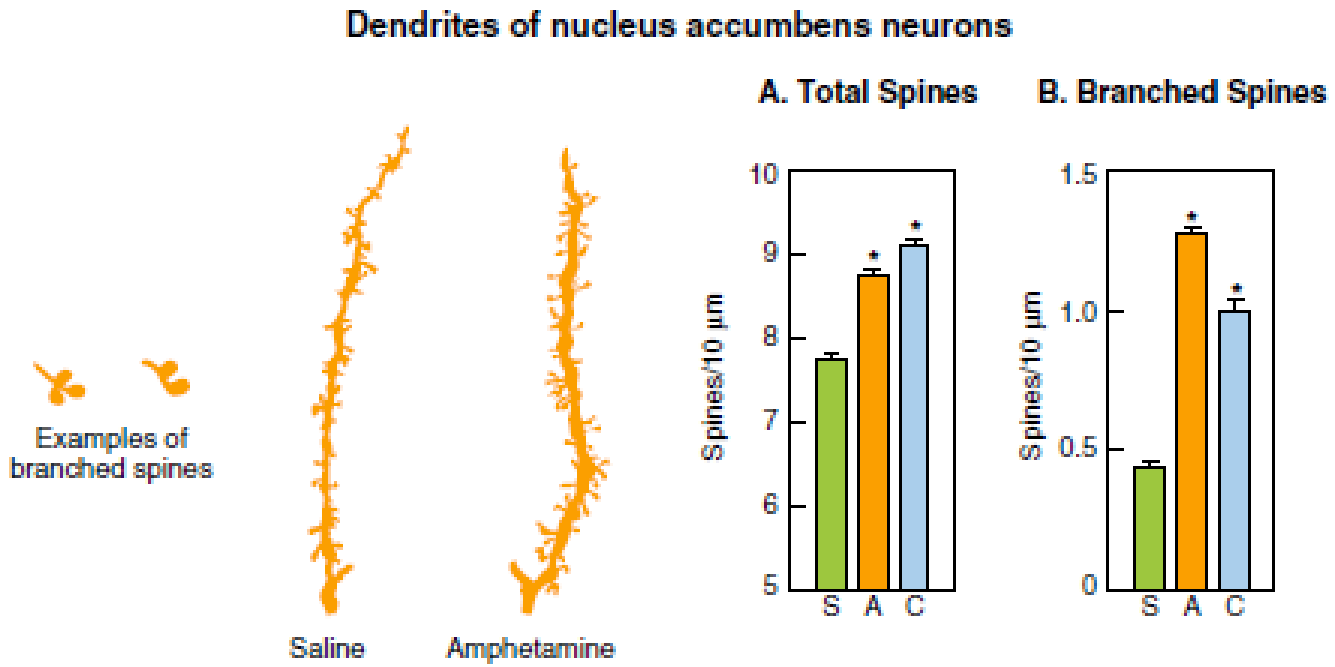


FIGURE 56-7 Repeated exposure to amphetamine or cocaine increases spine density and the number of branched spines in medium spiny neurons, the major cell type of the nucleus accumbens. Left: camera lucida drawings of representative dendritic segments. Rats received 20 injections of saline (*S*), amphetamine (*A*) or cocaine (*C*) over 4 weeks and were then left undisturbed for about 1 month prior to analysis. Adapted from Robinson, T. E. and Kolb, B., *Eur. J. Neurosci.* 11; 1598–1604, 1999.

Primary Site(s) of Major Drugs of Abuse

Heroin	**Depressant**	• **Acts primarily on endogenous opioid system** • **Also affects dopaminergic system**
Cocaine	**Stimulant**	• **Acts primarily on dopaminergic system, as well as on serotonergic and noradrenergic systems** • **Also affects opioid system**
Alcohol	**Stimulant & Depressant**	• **Undefined primary site of action** • **Affects dopaminergic, serotonergic and opioid systems**

Kreek, 1978, 1987, 2003