- Introduction to CNS pharmacology
- CNS stimulants

Lecture 1

College of Pharmacy

By:

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Organization of the nervous system

The nervous system is divided into two anatomical divisions:

- The central nervous system (CNS), which is composed of the **brain** and **spinal cord.**
- The peripheral nervous system, which includes **neurons located outside the brain and spinal cord** (any nerves that enter or leave the CNS).

The peripheral nervous system is subdivided into

- **The efferent division,** the neurons of which carry signals away from the brain and spinal cord to the peripheral tissues.
- **The afferent division,** the neurons of which bring information from the periphery to the CNS. (see, figure 1)

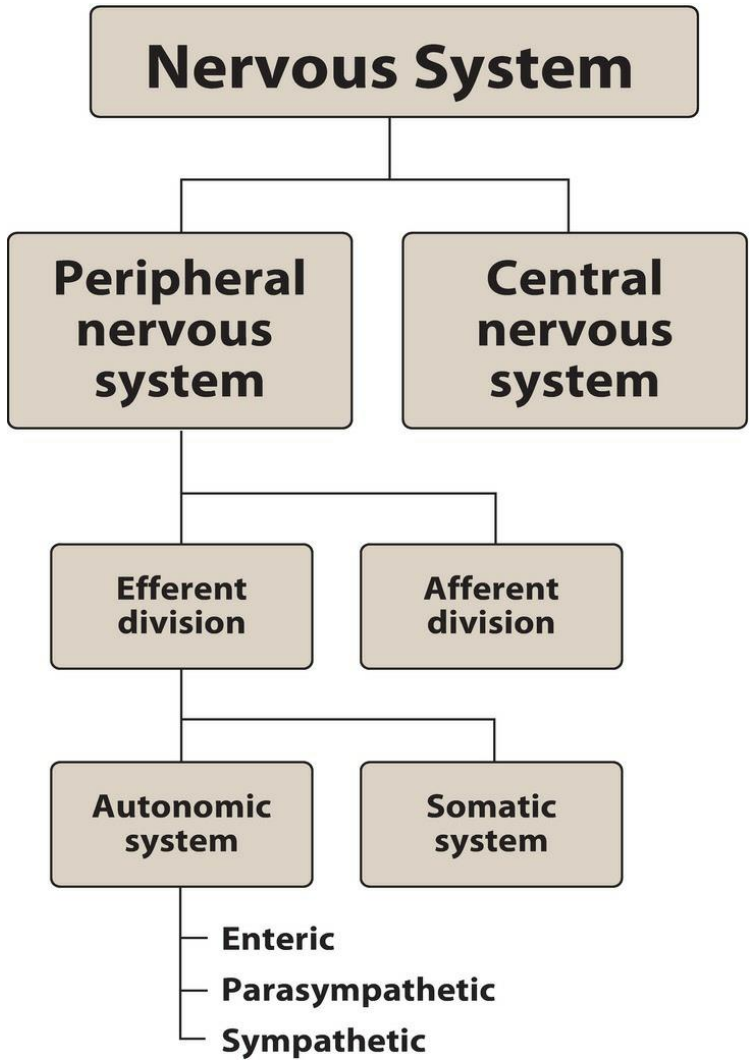


Figure 1: Organization of the nervous system

Functional divisions within the nervous system

The efferent portion of the peripheral nervous system is further divided into two major functional subdivisions:

- The somatic efferent neurons are involved in the voluntary control of functions such as contraction of the skeletal muscles essential for locomotion.

- The autonomic system regulates the everyday requirements of vital bodily functions without the conscious participation of the mind. Because of the involuntary nature of the ANS as well as its functions, it is also known as the visceral, vegetative, or involuntary nervous system. It is composed of efferent neurons that innervate smooth muscle of the viscera, cardiac muscle, vasculature, and the exocrine glands, thereby controlling digestion, cardiac output, blood flow, and glandular secretions.

Anatomy of the autonomic nervous system

- Efferent neurons: The autonomic nervous system carries nerve impulses from the CNS to the effector organs by two types of efferent neurons:

- **Preganglionic neuron,** and its cell body is located within the CNS. Preganglionic neurons emerge from the brainstem or spinal cord and make a synaptic connection in ganglia. These ganglia function as relay stations between a preganglionic neuron.
- A second nerve cell, **the postganglionic neuron**. The latter neuron has a cell body originating in the ganglion. It is generally nonmyelinated and terminates on effector organs, such as smooth muscles of the viscera, cardiac muscle, and the exocrine glands. (see, figure 2)

- Afferent neurons: The afferent neurons (fibers) of the autonomic nervous system are important in the reflex regulation of this system (for example, by sensing pressure in the carotid sinus and aortic arch) and signaling the CNS to influence the efferent branch of the system to respond.

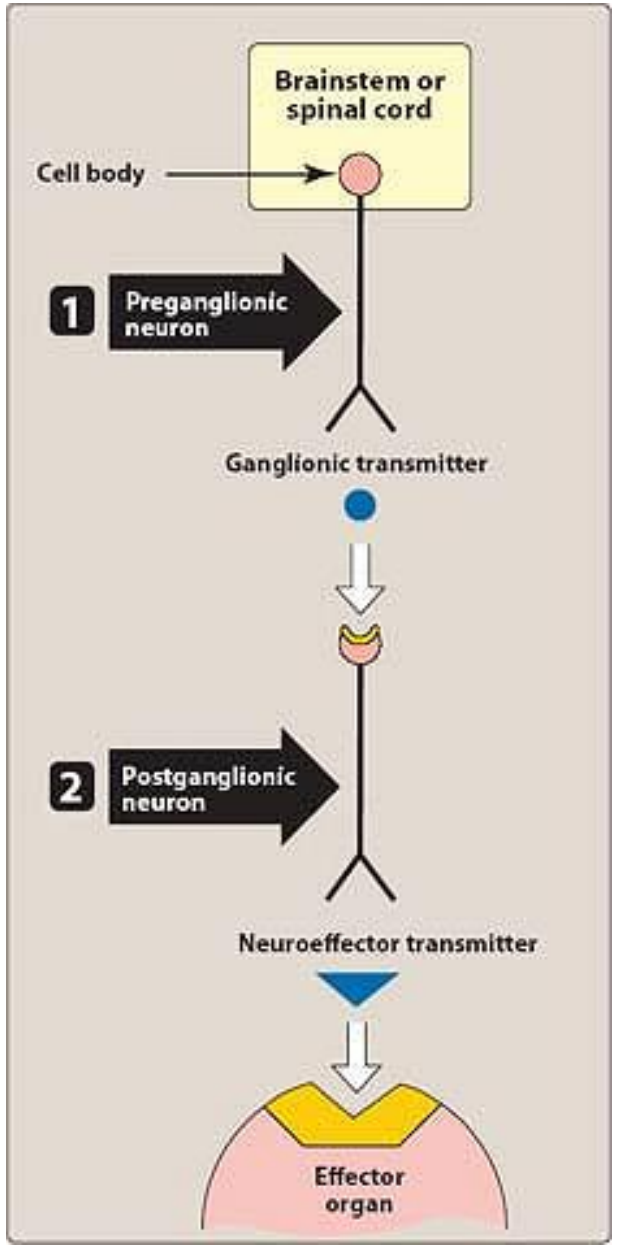


Figure 2: Efferent neurons of the autonomic nervous system

- Sympathetic neurons
- Parasympathetic neurons

	SYMPATHETIC	PARASYMPATHETIC
Sites of origin	Thoracic and lumbar region of the spinal cord (thoracolumbar)	Brain and sacral area of the spinal cord (craniosacral)
Length of fibers	Short preganglionic Long postganglionic	Long preganglionic Short postganglionic
Location of ganglia	Close to the spinal cord	Within or near effector organs
Preganglionic fiber branching	Extensive	Minimal
Distribution	Wide	Limited
Type of response	Diffuse	Discrete

Figure 3: Summary of differences between sympathetic and parasympathetic.

- Enteric neurons: The enteric nervous system is a collection of nerve fibers that innervate the gastrointestinal tract, pancreas, and gallbladder, and it constitutes the brain of the gut. This system functions independently of the CNS and controls the motility, exocrine and endocrine secretions, and microcirculation of the gastrointestinal tract. It is modulated by both the sympathetic and parasympathetic nervous systems.

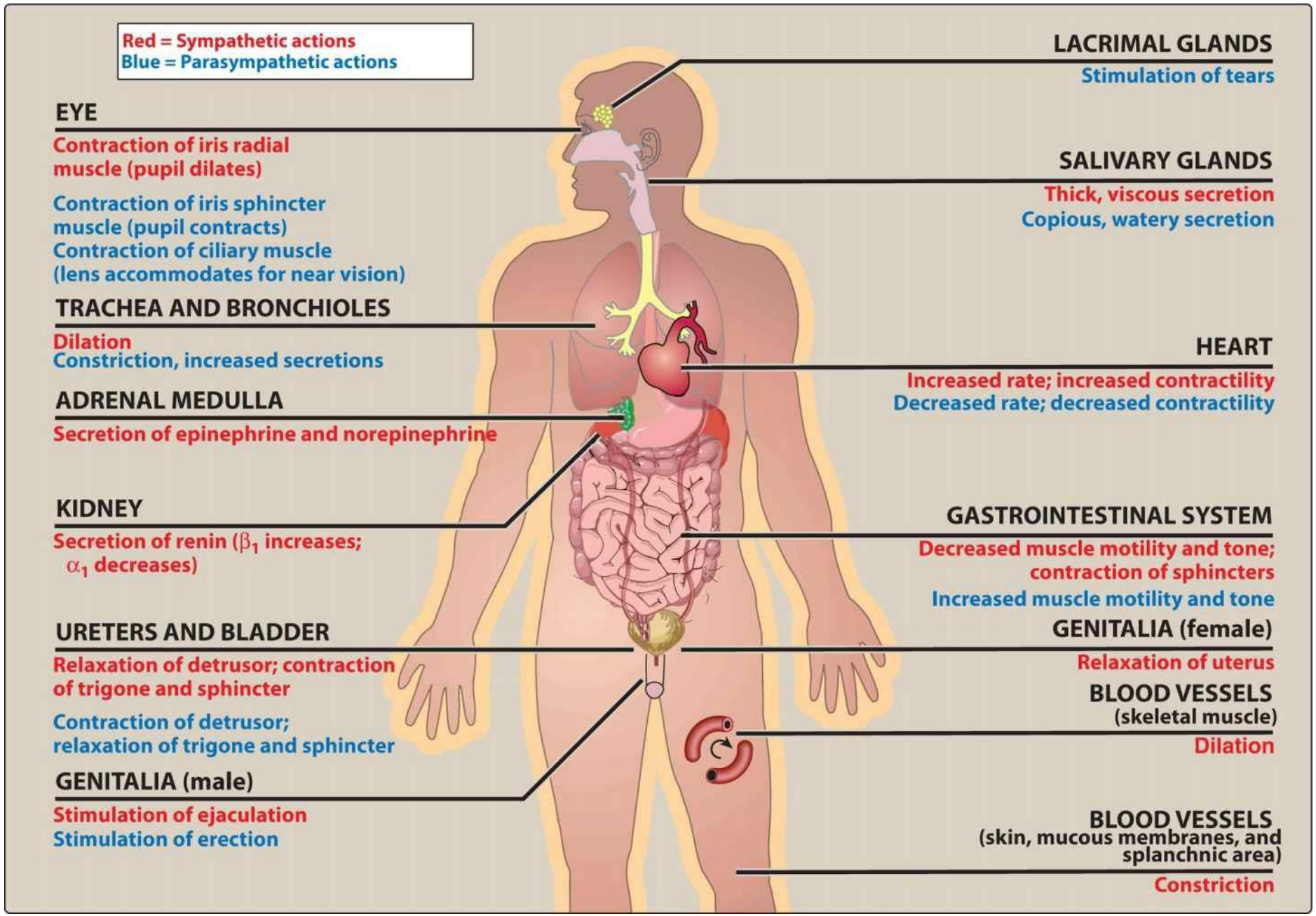
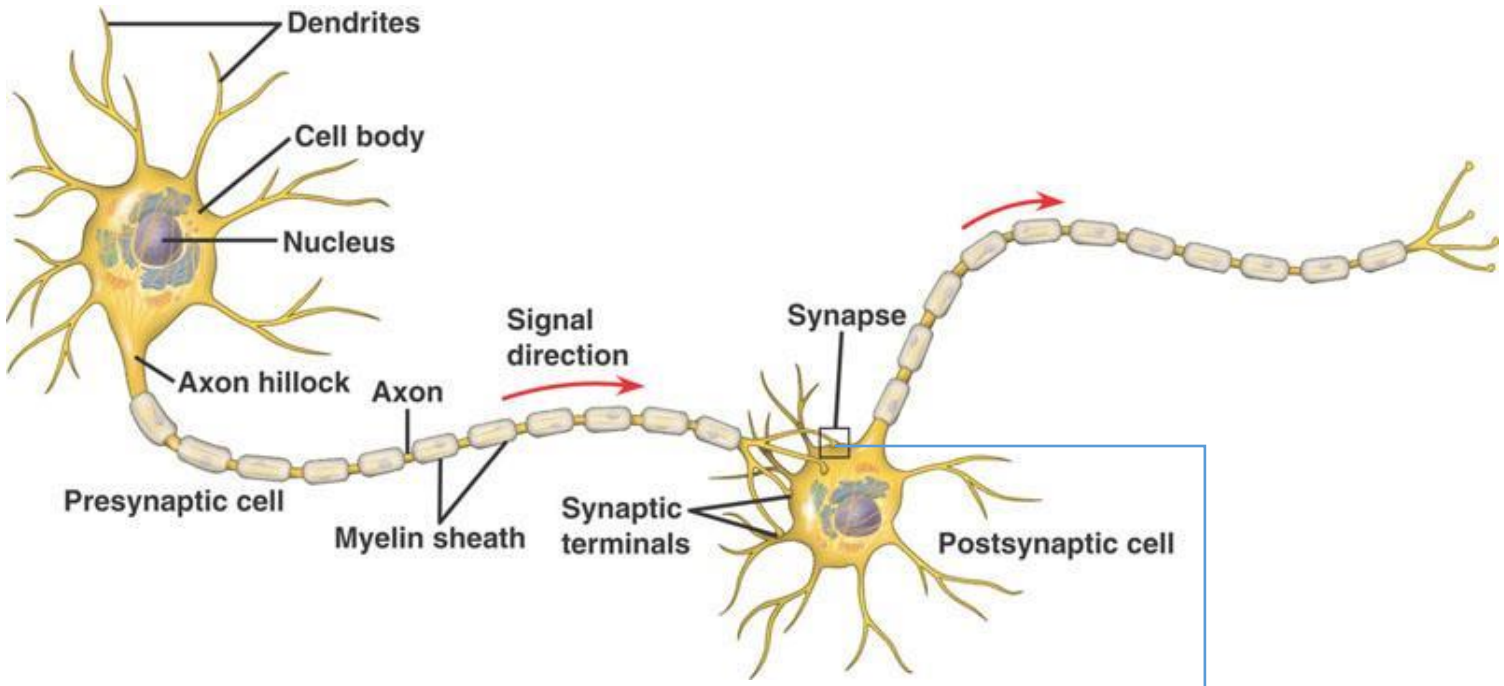


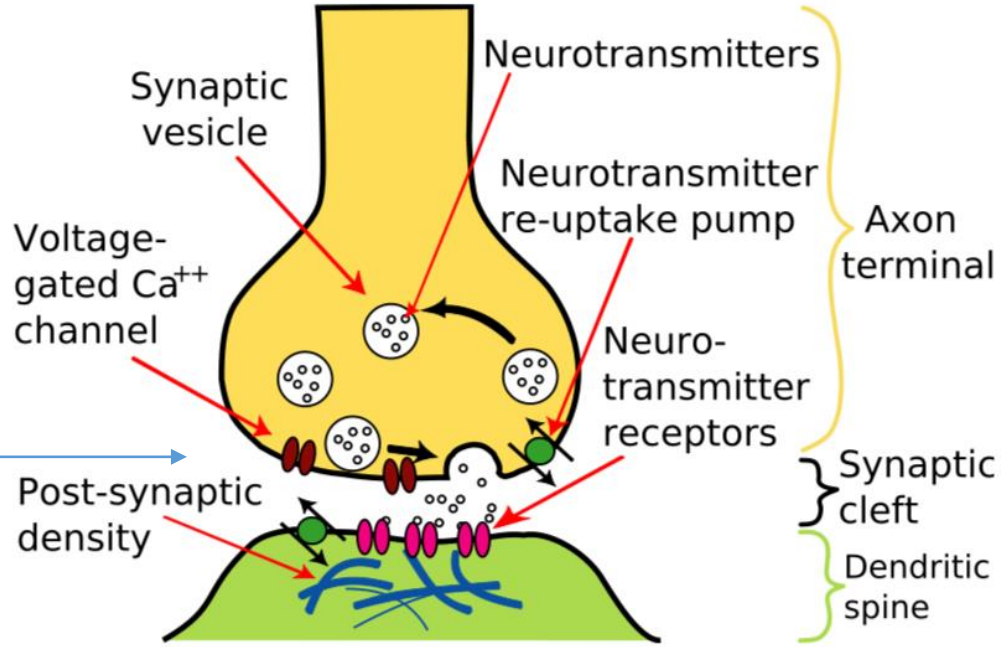
Figure 4: Actions of sympathetic and parasympathetic nervous systems on effector organs.

Neuron and Synapses



Neurons are electrically excitable cells that process and transmit information via an electrochemical process. There are many types of neurons in the CNS, and they are classified in multiple ways, such as by:

- Function
- Location
- The neurotransmitter they release.



Types of ion channels and neurotransmitter receptors in the CNS:

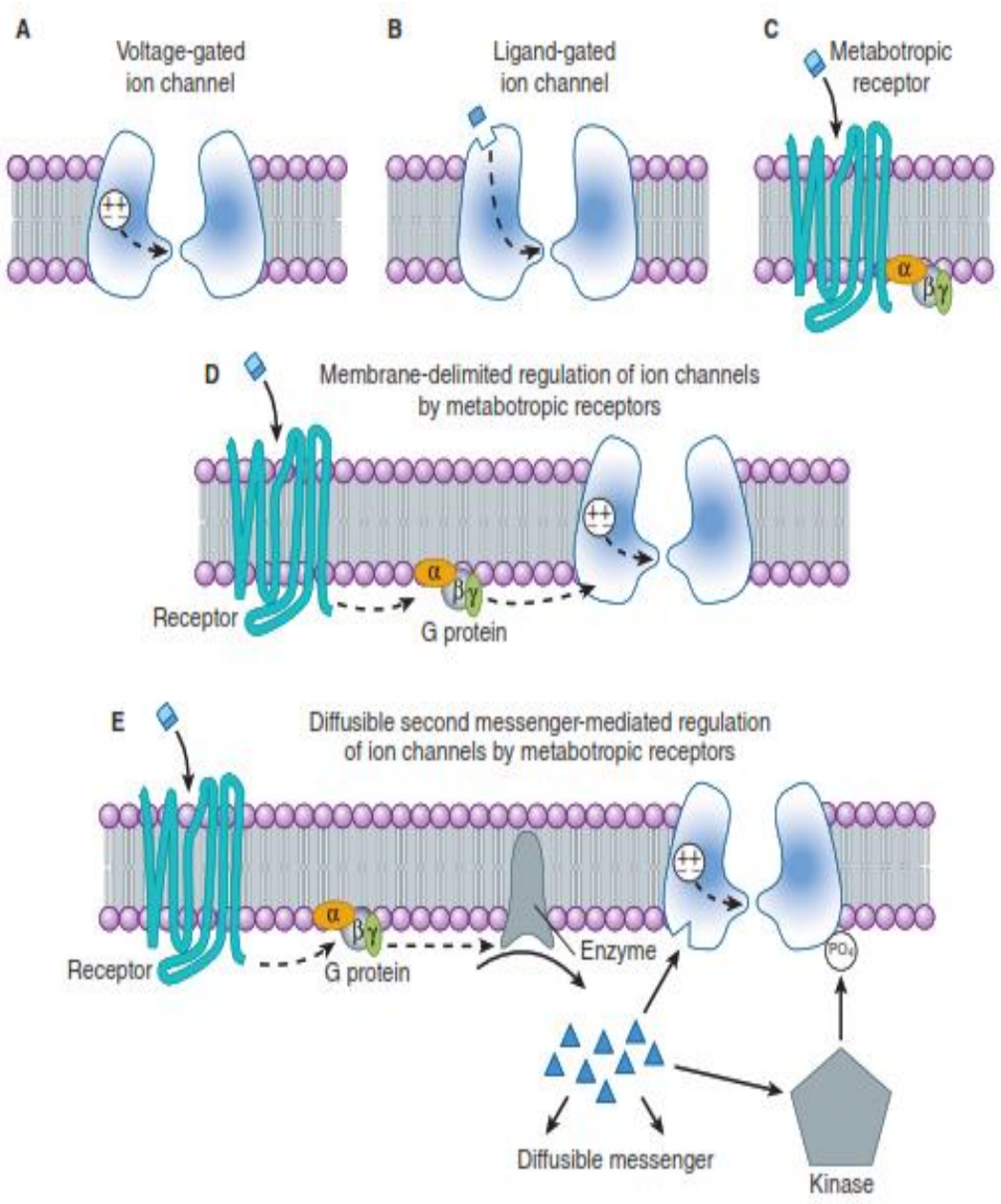
A- shows a voltage-gated channel in which a voltage sensor component of the protein controls the gating (broken arrow) of the channel.

B- shows a ligand-gated channel in which the binding of the neurotransmitter to the ionotropic channel receptor controls the gating (broken arrow) of the channel.

C- shows a G protein-coupled (metabotropic) receptor, which, when bound, activates a heterotrimeric G protein.

D and E- show two ways metabotropic receptors can regulate Ion channels. The activated G protein can interact directly to modulate an ion channel **(D)** or the G protein can activate an enzyme that generates a diffusible second messenger **(E),** eg, cAMP, which can interact with the ion channel or can activate a kinase that phosphorylates and modulates a channel.

Types of Ion Channels



Synaptic Potentials

- In the CNS, receptors in most synapses are coupled to ion channels. Binding of the neurotransmitter to the postsynaptic membrane receptors results in a rapid but transient opening of ion channels.
- Open channels allow specific ions inside and outside the cell membrane to flow down their concentration gradients. The resulting change in the ionic composition across the membrane of the neuron alters the postsynaptic potential, producing either **depolarization** or **hyperpolarization** of the postsynaptic membrane, depending on the **specific ions** and **the direction of their movement**.
- Neurotransmitters can be classified as either **excitatory** or **inhibitory**, depending on the nature of the action they elicit.

A. Excitatory pathways

Stimulation of excitatory neurons causes a movement of ions that results in a depolarization of the postsynaptic membrane. (see, figure 5)

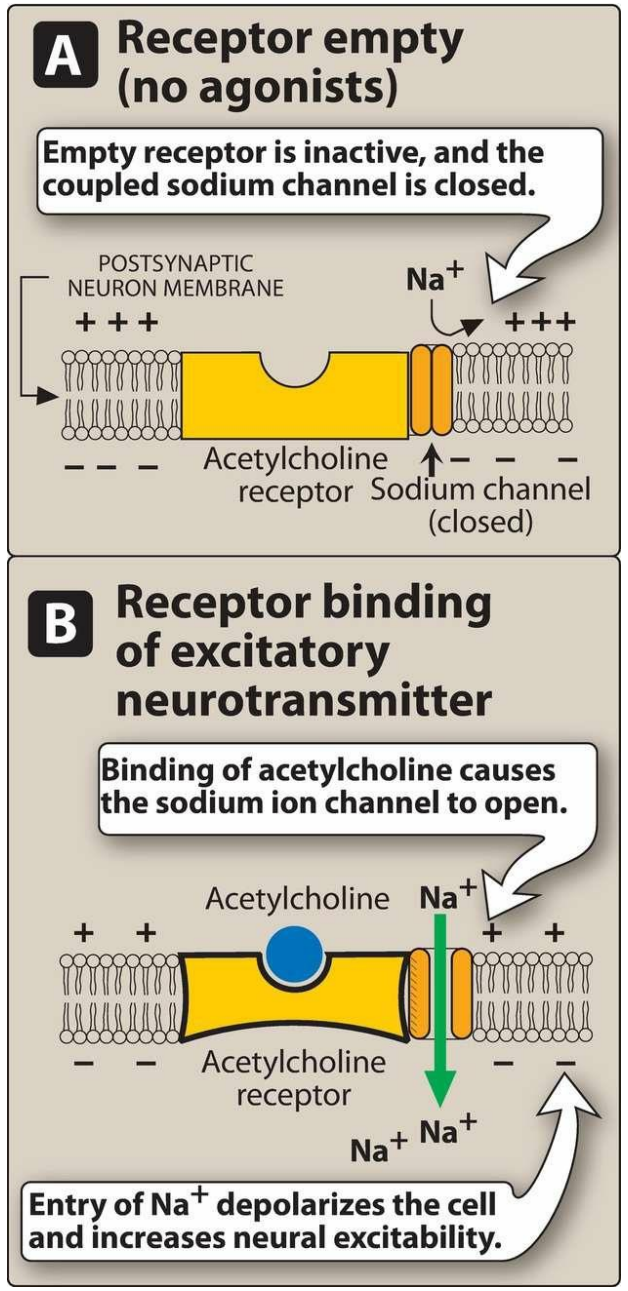


Figure 5: Binding of the excitatory neurotransmitter, acetylcholine, causes depolarization of the neuron.

B. Inhibitory pathways

Stimulation of inhibitory neurons causes movement of ions that results in a hyperpolarization of the postsynaptic membrane. (see, figure 6)

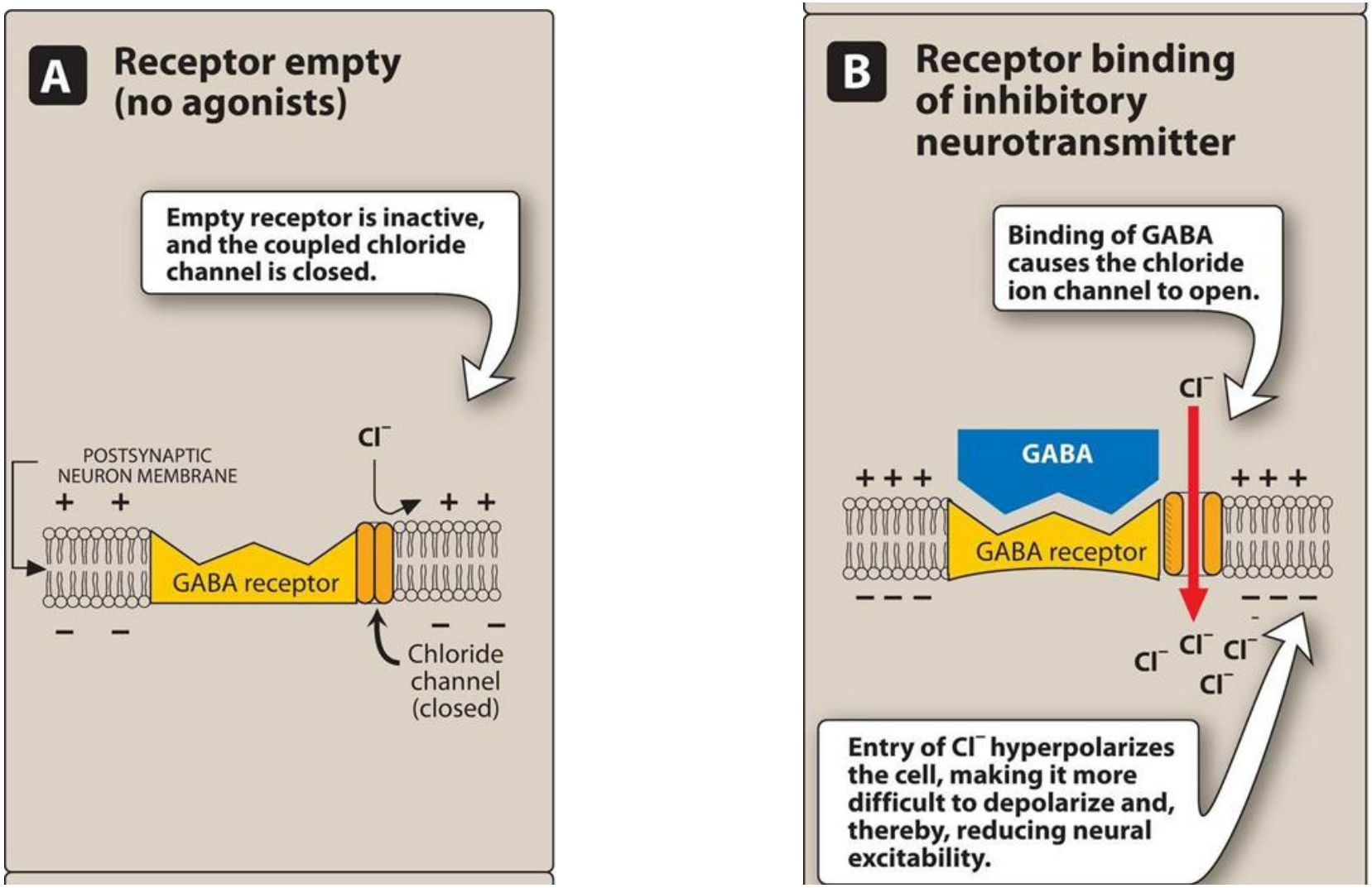


Figure 6: Binding of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA), causes hyperpolarization of the neuron.

Neurotransmitters

Communication between nerve cells and between nerve cells and effector organs occurs through the release of specific chemical signals, called **neurotransmitters**, from the nerve terminals. This release is triggered by the arrival of the action potential at the nerve ending, leading to depolarization. An increase in intracellular Ca^{2+} initiates fusion of synaptic vesicles with the presynaptic membrane and release of their contents. The neurotransmitters rapidly diffuse across the synaptic cleft or space (**synapse**) between neurons and combine with specific receptors on the postsynaptic (**target**) cell.

Types of neurotransmitters:

Although over fifty signal molecules in the nervous system have tentatively been identified, six signal compounds **norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, and γ-aminobutyric acid** are most commonly involved in the actions of therapeutically useful drugs. Each of these chemical signals binds to a specific family of receptors. (see, table 1)

Table 1: Summary of neurotransmitter pharmacology in the central nervous system.

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Acetylcholine	Cell bodies at all levels; long and short connections	Muscarinic (M_1): muscarine	Pirenzepine, atropine	Excitatory: ↓ in K^+ conductance; ↑ IP_3, DAG
		Muscarinic (M_2): muscarine, bethanechol	Atropine, methoctramine	Inhibitory: ↑ K^+ conductance; ↓ cAMP
	Motoneuron-Renshaw cell synapse	Nicotinic: nicotine	Dihydro-β-erythroidine, α-bungarotoxin	Excitatory: ↑ cation conductance
Dopamine	Cell bodies at all levels; short, medium, and long connections	D_1: dihydrexidine	Phenothiazines	Inhibitory (?): ↑ cAMP
		D_2: bromocriptine	Phenothiazines, butyrophenones	Inhibitory (presynaptic): ↓ Ca^{2+}; Inhibitory (postsynaptic): ↑ in K^+ conductance, ↓ cAMP
GABA	Supraspinal and spinal interneurons involved in pre- and postsynaptic inhibition	$GABA_A$: muscimol	Bicuculline, picrotoxin	Inhibitory: ↑ Cl^- conductance
		$GABA_B$: baclofen	2-OH saclofen	Inhibitory (presynaptic): ↓ Ca^{2+} conductance; Inhibitory (postsynaptic): ↑ K^+ conductance
Glutamate	Relay neurons at all levels and some interneurons	N-Methyl-D-aspartate (NMDA): NMDA	2-Amino-5-phosphonovalerate, dizocilpine	Excitatory: ↑ cation conductance, particularly Ca^{2+}
		AMPA: AMPA	NBQX	Excitatory: ↑ cation conductance
		Kainate: kainic acid, domoic acid	ACET	Excitatory: ↑ cation conductance
		Metabotropic: ACPD, quisqualate	MCPG	Inhibitory (presynaptic): ↓ Ca^{2+} conductance, ↓ cAMP; Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG

Glycine	Spinal interneurons and some brain stem interneurons	Taurine, β-alanine	Strychnine	Inhibitory: ↑ Cl^- conductance
5-Hydroxytryptamine (serotonin)	Cell bodies in mid-brain and pons project to all levels	$5\text{-}HT_{1A}$: eptapirone	Metergoline, spiperone	Inhibitory: ↑ K^+ conductance, ↓ cAMP
		$5\text{-}HT_{2A}$: LSD	Ketanserin	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		$5\text{-}HT_3$: 2-methyl-5-HT	Ondansetron	Excitatory: ↑ cation conductance
		$5\text{-}HT_4$: cisapride	Piboserod	Excitatory: ↓ K^+ conductance
Norepinephrine	Cell bodies in pons and brain stem project to all levels	α_1: phenylephrine	Prazosin	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		α_2: clonidine	Yohimbine	Inhibitory (presynaptic): ↓ Ca^{2+} conductance; Inhibitory: ↑ K^+ conductance, ↓ cAMP
		β_1: isoproterenol, dobutamine	Atenolol, practolol	Excitatory: ↓ K^+ conductance, ↑ cAMP
		β_2: albuterol	Butoxamine	Inhibitory: may involve ↑ in electrogenic sodium pump; ↑ cAMP
Histamine	Cells in ventral posterior hypothalamus	H_1: 2(*m*-fluorophenyl)-histamine	Mepyramine	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		H_2: dimaprit	Ranitidine	Excitatory: ↓ K^+ conductance, ↑ cAMP
		H_3: *R*-α-methyl-histamine	Thioperamide	Inhibitory autoreceptors

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Opioid peptides	Cell bodies at all levels; long and short connections	Mu: bendorphin	Naloxone	Inhibitory (presynaptic): ↓ Ca^{2+} conductance, ↓ cAMP
		Delta: enkephalin	Naloxone	Inhibitory (postsynaptic): ↑ K^+ conductance, ↓ cAMP
		Kappa: dynorphin, salvinorin A	Naloxone	Inhibitory (postsynaptic): ↑ K^+ conductance, ↓ cAMP
Orexins	Cell bodies in hypothalamus; project widely	OX_1: orexin A	Suvorexant	Excitatory, glutamate co-release
		OX_2: orexins A and B	Suvorexant	
Tachykinins	Primary sensory neurons, cell bodies at all levels; long and short connections	NK1: substance P methylester	Aprepitant	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		NK2: neurokinin A	Saredutant	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		NK3: neurokinin B	Osanetant	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
Endocannabinoids	Widely distributed	CB1: anandamide, 2-arachidonyglycerol	Rimonabant	Inhibitory (presynaptic): ↓ Ca^{2+} conductance, ↓ cAMP

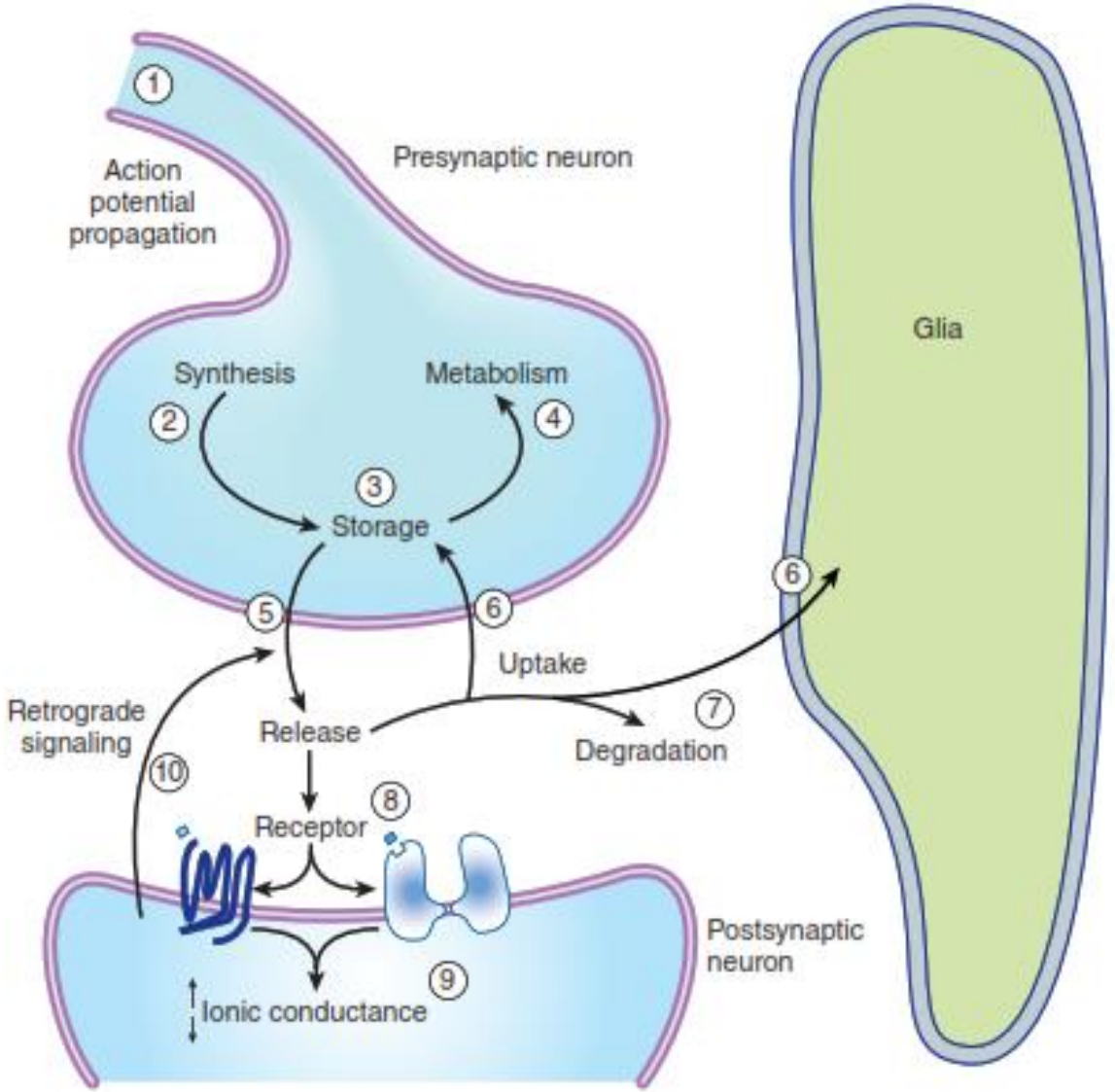
ACET, (S)-1-(2-amino-2-carboxyethyl)-3-(2-carboxy-5-phenylthiophene-3-yl-methyl)-5-methylpyrimidine-2,4-dione; ACPD, trans-1-amino-cyclopentyl-1,3-dicarboxylate; AMPA, DL-α-amino-3-hydroxy-5-methylisoxazole-4-propionate; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP3, inositol trisphosphate; LSD, lysergic acid diethylamide; MCPG, α-methyl-4-carboxyphenylglycine; NBQX, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(f) quinoxaline.

Second Messenger Systems in Intracellular Response

- Second-messenger molecules, produced in response to neurotransmitter binding to a receptor, translate the extracellular signal into a response that may be further propagated or amplified within the cell.
- Each component serves as a link in the communication between extracellular events and chemical changes within the cell.
- The two most widely recognized second messengers are the **adenylyl cyclase system** and the **calcium/phosphatidylinositol system**.

Sites of drug action

This figure represents the schematic drawing of steps at which drugs can alter synaptic transmission. (1) Action potential in presynaptic fiber; (2) synthesis of transmitter; (3) storage; (4) metabolism; (5) release; (6) reuptake into the nerve ending or uptake into a glial cell; (7) degradation; (8) receptor for the transmitter; (9) receptor-induced increase or decrease in ionic conductance; (10) retrograde signaling.



CNS Stimulants

There are two groups of drugs that act primarily to stimulate the central nervous system (CNS):

- **The psychomotor stimulants**, cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity.
- The second group, **the hallucinogens, or psychotomimetic drugs,** produce profound changes in thought patterns and mood, with little effect on the brainstem and spinal cord.

1- Psychomotor Stimulants

A- Methylxanthines

The methylxanthines include: **theophylline** which is found in tea, **theobromine**, found in cocoa; and **caffeine**. Caffeine, the most widely consumed stimulant in the world, is found in highest concentration in coffee, but it is also present in tea, cola drinks, chocolate candy, and cocoa.

Mechanism of action:

Several mechanisms have been proposed for the actions of methylxanthines, including:

- translocation of extracellular calcium
- increase in cyclic adenosine monophosphate and cyclic guanosine monophosphate caused by inhibition of phosphodiesterase
- blockade of adenosine receptors

Actions:

CNS:

- The caffeine contained in one to two cups of coffee (100-200 mg) causes a decrease in fatigue and increased mental alertness as a result of stimulating the cortex and other areas of the brain.
- Consumption of 1.5 g of caffeine (12-15 cups of coffee) produces anxiety and tremors.
- The spinal cord is stimulated only by very high doses (2-5 g) of caffeine.
- Tolerance can rapidly develop to the stimulating properties of caffeine; withdrawal consists of feelings of fatigue and sedation.

Cardiovascular system: A high dose of caffeine has positive inotropic and chronotropic effects on the heart.

Diuretic action: Caffeine has a mild diuretic action that increases urinary output of sodium, chloride, and potassium.

Gastric mucosa: Because all methylxanthines stimulate secretion of hydrochloric acid from the gastric mucosa, individuals with peptic ulcers should avoid beverages containing methylxanthines.

Therapeutic uses:

- Caffeine and its derivatives relax the smooth muscles of the bronchioles. Theophylline has been largely replaced by other agents, such as β2 agonists and corticosteroids, for the treatment of asthma.
- Caffeine is also used in combination with the analgesics acetaminophen and aspirin for the management of headaches in both prescription and over-the-counter products.

Pharmacokinetics:

- The methylxanthines are well absorbed orally.
- Caffeine distributes throughout the body, including the brain, cross the placenta to the fetus and are secreted into the mother's milk
- Metabolized in the liver, generally by the CYP1A2 pathway, and the metabolites are then excreted in the urine.

Adverse effects:

- Moderate doses of caffeine cause insomnia, anxiety, and agitation.
- A high dosage is required for toxicity, which is manifested by emesis and convulsions.
- The lethal dose is about 10 g of caffeine (about 100 cups of coffee), which induces cardiac arrhythmias; death from caffeine is thus highly unlikely. Lethargy, irritability, and headache occur in users who have routinely consumed more than 600 mg of caffeine per day (roughly six cups of coffee per day) and then suddenly stop.

B- Nicotine

Nicotine is the active ingredient in **tobacco**, it is second only to caffeine as the most widely used CNS stimulant and second only to alcohol as the most abused drug.

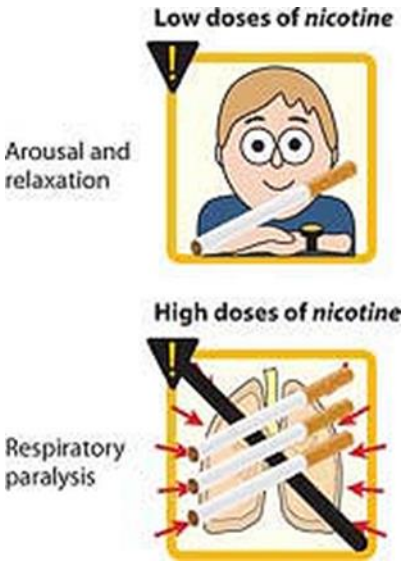
Mechanism of action:

- **In low doses**, nicotine causes ganglionic stimulation by depolarization.
- **At high doses**, nicotine causes ganglionic blockade.
- Nicotine receptors exist at a number of sites in the CNS, which participate in the stimulant attributes of the drug.

Actions:

CNS:

- Nicotine is highly lipid soluble and readily crosses the blood-brain barrier.
- Cigarette smoking or administration of **low doses of nicotine** produces some degree of euphoria and arousal as well as relaxation.
- It improves attention, learning, problem solving, and reaction time.
- **High doses of nicotine** result in central respiratory paralysis and severe hypotension caused by medullary paralysis.
- Nicotine is an appetite suppressant.



Peripheral effects:

The peripheral effects of nicotine are complex.

- **Stimulation of sympathetic ganglia** as well as the **adrenal medulla** increases blood pressure and heart rate. Thus, use of tobacco is particularly harmful in hypertensive patients. Many patients with peripheral vascular disease experience an exacerbation of symptoms with smoking. For example, nicotine-induced vasoconstriction can decrease coronary blood flow, adversely affecting a patient with angina.
- **Stimulation of parasympathetic ganglia** also increases motor activity of the bowel.
- At higher doses, blood pressure falls, and activity ceases in both the gastrointestinal tract and bladder musculature as a result of a nicotine-induced block of parasympathetic ganglia.

Pharmacokinetics:

- Because nicotine is highly lipid soluble, absorption readily occurs via the oral mucosa, lungs, gastrointestinal mucosa, and skin.
- Nicotine crosses the placental membrane and is secreted in the milk of lactating women.
- The acute lethal dose is 60 mg.
- More than 90 percent of the nicotine inhaled in smoke is absorbed. Clearance of nicotine involves metabolism in the lung and the liver and urinary excretion.
- **Tolerance** to the toxic effects of nicotine develops rapidly, often within days after beginning usage.

Adverse effects:

- The CNS effects of nicotine include irritability and tremors.
- Nicotine may also cause intestinal cramps, diarrhea, and increased heart rate and blood pressure.
- In addition, cigarette smoking increases the rate of metabolism for a number of drugs.

Withdrawal syndrome:

- Nicotine is an addictive substance, and **physical dependence** on nicotine develops rapidly and can be severe.
- **Withdrawal** is characterized by irritability, anxiety, restlessness, difficulty concentrating, headaches, and insomnia.
- Appetite is affected, and gastrointestinal pain often occurs.
- The **transdermal patch** and **chewing gum** containing nicotine have been shown to reduce nicotine withdrawal symptoms and to help smokers stop smoking. (figure 7)
- Other forms of nicotine replacement used for smoking cessation include the **inhaler, nasal spray**, and **lozenges**.
- **Bupropion**, an antidepressant, can reduce the craving for cigarettes, assist in smoking cessation, and attenuate symptoms of withdrawal.

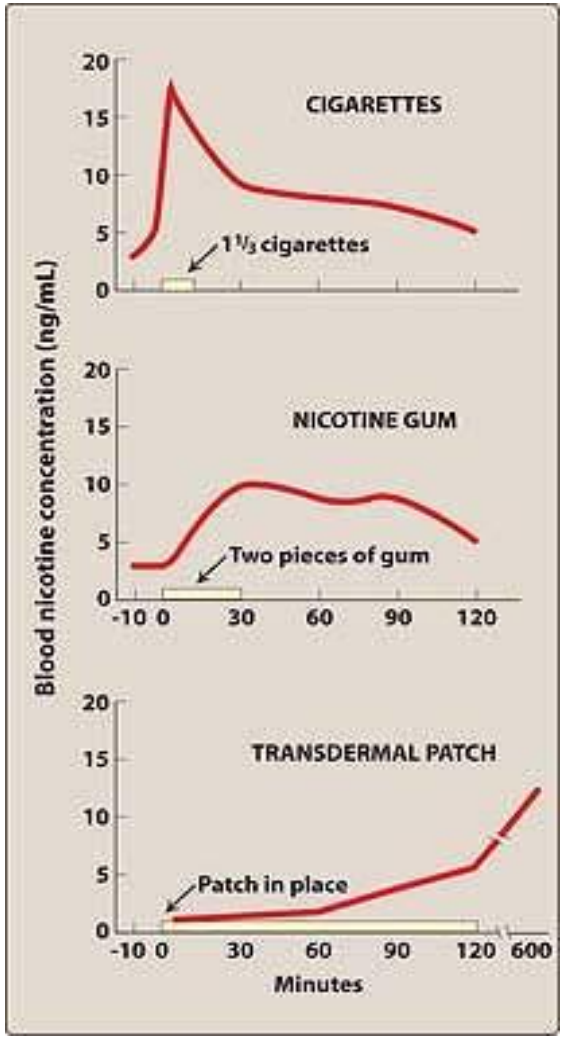


Figure 7: Blood concentrations of nicotine in individuals who smoked cigarettes, chewed nicotine gum, or received nicotine by transdermal patch.

- [*Smoking cessation programs that combine pharmacologic and behavioral therapy are the most successful in helping individuals to stop smoking.*]

C- Varenicline

- **Varenicline** is a **partial agonist** at neuronal nicotinic acetylcholine receptors in the CNS. Therefore, it produces less euphoric effects than those produced by nicotine itself (nicotine is a full agonist). Thus, it is useful as an adjunct in the management of smoking cessation in patients with nicotine withdrawal symptoms.
- Additionally, varenicline tends to attenuate the rewarding effects of nicotine if a person relapses and uses tobacco.
- Patients taking varenicline should be monitored for suicidal thoughts, vivid nightmares and mood changes.

D- Cocaine

Cocaine is a widely available and highly addictive drug.

Mechanism of action:

- The primary mechanism of action underlying the central and peripheral effects of cocaine is blockade of reuptake of the monoamines (norepinephrine, serotonin, and dopamine) into the presynaptic terminals.
- This blockade is caused by cocaine binding to the monoaminergic reuptake transporters and, thus, potentiates and prolongs the CNS and peripheral actions of these monoamines.
- In particular, the prolongation of dopaminergic effects in the brain's pleasure system (limbic system) produces the intense euphoria that cocaine initially causes.
- Chronic intake of cocaine depletes dopamine. This depletion triggers craving for cocaine. (see, figure 8)

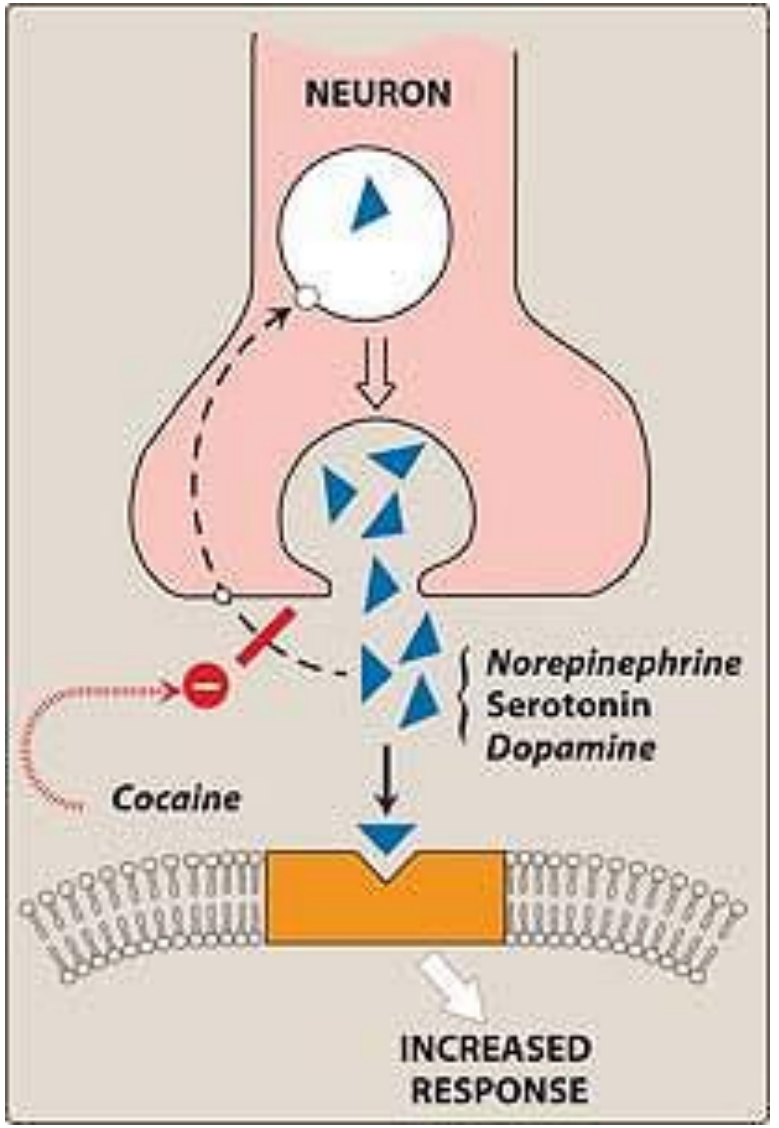


Figure 8: Mechanism of action of Cocaine

Actions:

CNS:

- The behavioral effects of cocaine result from powerful stimulation of the cortex and brainstem.
- Cocaine acutely increases mental awareness and produces a feeling of well-being and euphoria similar to that caused by amphetamine. Like amphetamine, cocaine can produce hallucinations and delusions of paranoia or grandiosity.
- Cocaine increases motor activity, and at high doses, it causes tremors and convulsions, followed by respiratory and vasomotor depression.

Sympathetic nervous system:

Peripherally, cocaine potentiates the action of norepinephrine, and it produces the fight or flight syndrome characteristic of adrenergic stimulation. This is associated with tachycardia, hypertension, pupillary dilation, and peripheral vasoconstriction.

Hyperthermia:

Cocaine is unique among illicit drugs in that death can result not only as a function of dose but also from the drug's propensity to cause hyperthermia. Even a small dose of intranasal cocaine impairs sweating and cutaneous vasodilatation. Perception of thermal discomfort is also decreased.

Therapeutic uses:

Cocaine has a **local anesthetic action** that represents the only current rationale for the therapeutic use of cocaine. For example, cocaine is **applied topically** as a local anesthetic during eye, ear, nose, and throat surgery. Whereas the local anesthetic action of cocaine is due to a block of voltage-activated sodium channels, an interaction with potassium channels may contribute to the ability of cocaine to cause cardiac arrhythmias.

Pharmacokinetics:

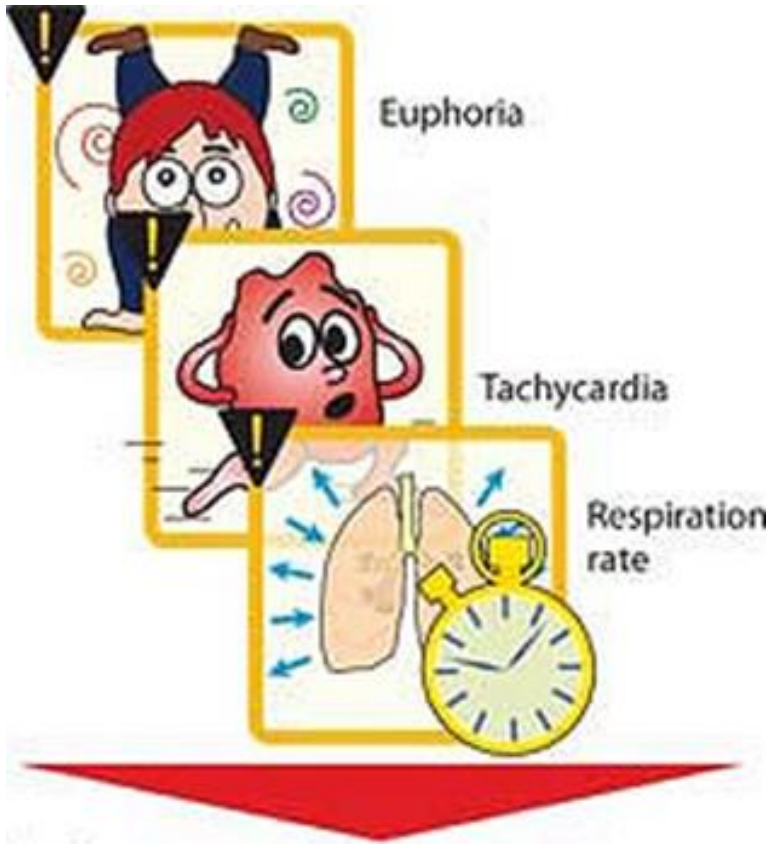
- Cocaine is often self-administered by **chewing, intranasal snorting, smoking, or intravenous (IV) injection.**
- The peak effect occurs at 15 to 20 minutes after intranasal intake of cocaine powder, and the “high” disappears in 1 to 1.5 hours.
- Rapid but short-lived effects are achieved following IV injection of cocaine or by smoking the freebase form of the drug.
- Because the onset of action is most rapid, the potential for over dosage and dependence is greatest with IV injection and crack smoking.
- Cocaine is rapidly de-esterified and demethylated to benzoylecgonine, which is excreted in the urine. Detection of this substance in the urine identifies a user.

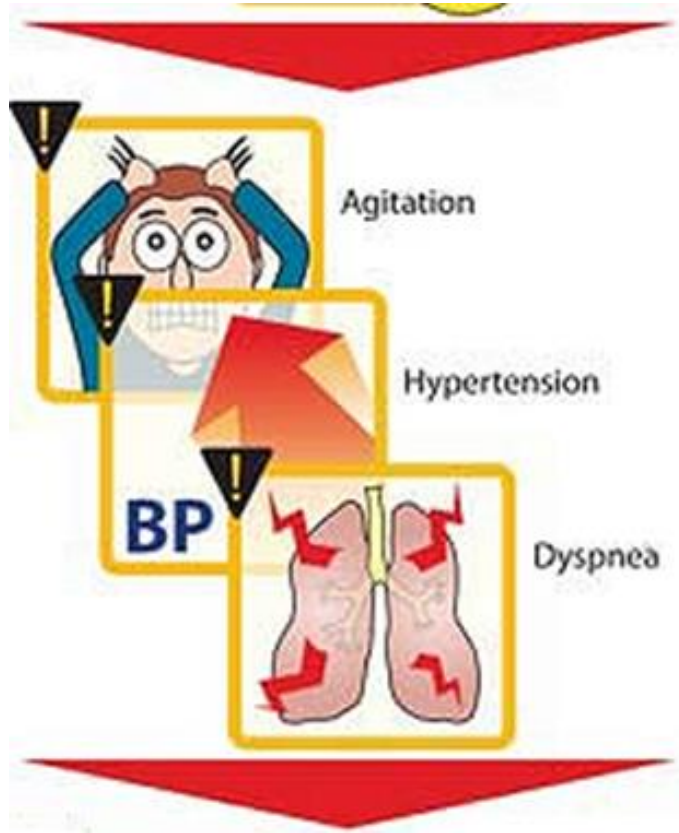
Adverse effects:

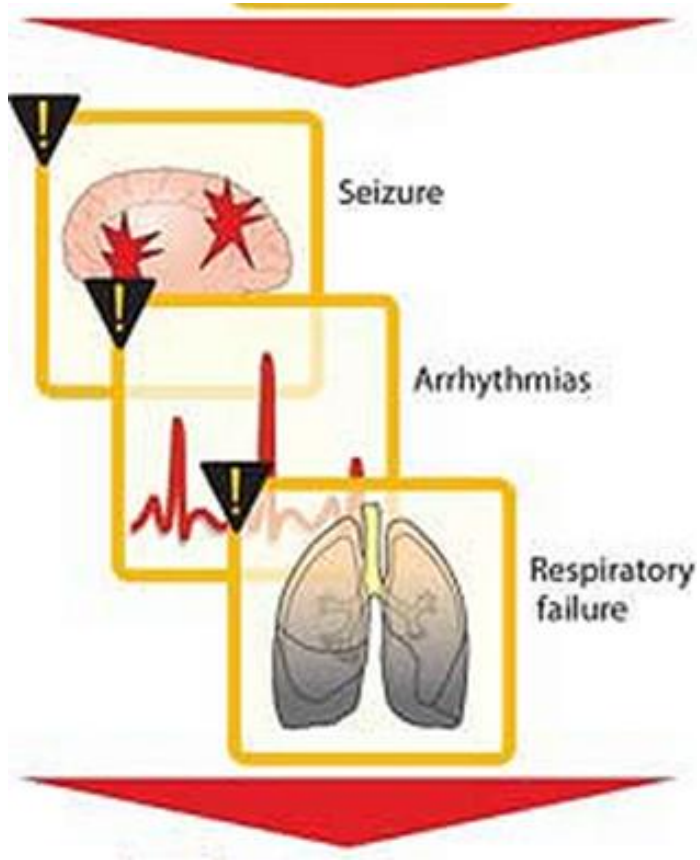
Anxiety: The toxic response to acute cocaine ingestion can precipitate an anxiety reaction that includes hypertension, tachycardia, sweating, and paranoia. Because of the irritability, many users take cocaine with alcohol. A product of cocaine metabolites and ethanol is cocaethylene, which is also psychoactive and believed to contribute to cardiotoxicity.

Depression: Like all stimulant drugs, cocaine stimulation of the CNS is followed by a period of mental depression. Addicts withdrawing from cocaine exhibit physical and emotional depression as well as agitation. The latter symptom can be treated with **benzodiazepines** or **phenothiazines**.

Toxic effects: Cocaine can induce seizures as well as fatal cardiac arrhythmias. Use of IV diazepam and propranolol may be required to control cocaine-induced seizures and cardiac arrhythmias, respectively. The incidence of myocardial infarction in cocaine users is unrelated to dose, to duration of use, or to route of administration. There is no marker to identify those individuals who may have life-threatening cardiac effects after taking cocaine.


Euphoria
Tachycardia
Respiration rate


Agitation
Hypertension
BP
Dyspnea


Seizure
Arrhythmias
Respiratory failure

E- Amphetamine

Amphetamine is a sympathetic amine that shows neurologic and clinical effects quite similar to those of cocaine. **Dextroamphetamine** is the major member of this class of compounds. **Methamphetamine** (also known as "speed") is a derivative of amphetamine available for prescription use. **3,4-Methylenedioxymethamphetamine** (also known as MDMA, or ecstasy) is a synthetic derivative of methamphetamine with both stimulant and hallucinogenic properties

Mechanism of action:

- As with cocaine, the effects of amphetamine on the CNS and peripheral nervous system are indirect; that is, both depend upon an elevation of the level of catecholamine neurotransmitters in synaptic spaces.
- Amphetamine, however, achieves this effect by releasing intracellular stores of catecholamines. Because amphetamine also inhibits monoamine oxidase (MAO), high levels of catecholamines are readily released into synaptic spaces (see figure 9). Despite different mechanisms of action, the behavioral effects of amphetamine and its derivatives are similar to those of cocaine.

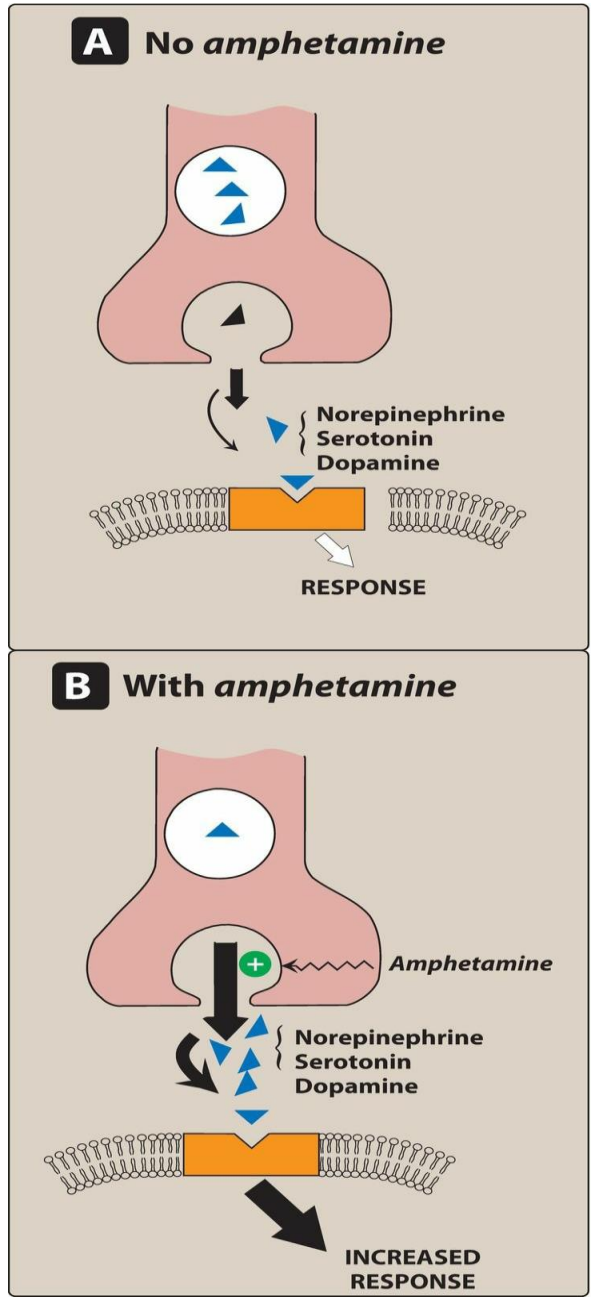


Figure 9: Mechanism of action of amphetamine.

Actions:

CNS:

- The major behavioral effects of amphetamine result from a combination of its dopamine and norepinephrine release-enhancing properties.
- Amphetamine stimulates the entire cerebrospinal axis, cortex, brainstem, and medulla.
- This leads to increased alertness, decreased fatigue, depressed appetite, and insomnia. These CNS stimulant effects of amphetamine and its derivatives have led to their use in therapy for hyperactivity in children, narcolepsy, and for appetite control.
- **At high doses**, psychosis and convulsions may occur.

Sympathetic nervous system:

Amphetamine acts on the adrenergic system, indirectly stimulating the receptors through norepinephrine release.

Therapeutic uses:

Factors that limit the therapeutic usefulness of amphetamine include:

- Psychological and physiological dependence

A- Attention deficit hyperactivity disorder (ADHD): Some young children are hyperkinetic and lack the ability to be involved in any one activity for longer than a few minutes.

- **Dextroamphetamine**, **methamphetamine**, the **mixed amphetamine salts**, and **methylphenidate** help to:

✓ improve attention
✓ alleviate many of the behavioral problems associated with this syndrome
✓ reduce the hyperkinesia that such children demonstrate.

- **Lisdexamfetamine** is a prodrug that is converted to **L-lysine** and the active component **dextroamphetamine** through the hydrolytic actions of red blood cells.
- Atomoxetine is a nonstimulant drug approved for ADHD in children and adults. Unlike methylphenidate, which blocks dopamine reuptake more than norepinephrine reuptake, atomoxetine is more selective for inhibition of norepinephrine reuptake.

B- Narcolepsy:

- Narcolepsy is a relatively rare sleep disorder that is characterized by uncontrollable bouts of sleepiness during the day. It is sometimes accompanied by catalepsy, a loss in muscle control, or even paralysis brought on by strong emotions, such as laughter. However, it is the sleepiness for which the patient is usually treated with drugs such as **amphetamine** or **methylphenidate**.
- Recently, a newer drug, **modafinil**, and its R-enantiomer derivative, armodafinil, have become available to treat narcolepsy.
- Modafinil promotes wakefulness, but it produces less psychoactive and euphoric effects and fewer alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. The mechanism of action remains unclear but may involve the adrenergic and dopaminergic systems.
- Modafinil is well distributed throughout the body and undergoes elimination via hepatic metabolism and excretion in the urine.

c. Appetite suppression

Phentermine and diethylpropion are sympathomimetic amines that are related structurally to amphetamine. These agents are used for appetite suppressant effects in the management of obesity

Pharmacokinetics

- Amphetamine is completely absorbed from the GI tract, metabolized by the liver, and excreted in the urine.
- Amphetamine abusers often administer the drug by IV injection and/or by smoking. The euphoria caused by amphetamine lasts 4 to 6 hours, or four- to eight fold longer than the effects of cocaine.

Adverse effects

The amphetamines may cause addiction, leading to dependence, tolerance, and drug-seeking behavior. In addition, they have the following undesirable effects:

a. CNS effects

- Adverse effects of amphetamine usage include insomnia, irritability, weakness, dizziness, tremor, and hyperactive reflexes. Amphetamine can also cause confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients. [Note: **Benzodiazepines**, such as **lorazepam**, are often used in the management of agitation and CNS stimulation secondary to amphetamine overdose].
- Chronic amphetamine use produces a state of "**amphetamine psychosis**" that resembles the psychotic episodes associated with schizophrenia.
- Whereas long-term amphetamine use is associated with psychological and physical dependence, tolerance to its effects may occur within a few weeks.
- The anorectic effect of amphetamine is due to action in the lateral hypothalamic feeding center.

b- Cardiovascular effects

In addition to CNS effects, amphetamine may cause palpitations, cardiac arrhythmias, hypertension, anginal pain, and circulatory collapse. Headache, chills, and excessive sweating may also occur.

c. Gastrointestinal effects

Amphetamine acts on the GI system, causing anorexia, nausea, vomiting, abdominal cramps, and diarrhea.

d. Contraindications

Patients with hypertension, cardiovascular disease, hyperthyroidism, glaucoma, or a history of drug abuse or those taking MAO inhibitors should not be treated with amphetamine.

F- Methylphenidate

Methylphenidate has CNS stimulant properties similar to those of amphetamine and is often used in the treatment of ADHD. Methylphenidate has abuse potential and is a Schedule II controlled substance. The pharmacologically active isomer, dexmethylphenidate, is also a Schedule II drug used for the treatment of ADHD.

Mechanism of action

Children with ADHD may produce weak dopamine signals, which suggest that once-interesting activities provide fewer rewards to these children. Methylphenidate is a dopamine and norepinephrine transport inhibitor and may act by increasing both dopamine and norepinephrine in the synaptic cleft.

Therapeutic uses

Methylphenidate is used in the treatment of ADHD. It is also effective in the treatment of narcolepsy. Unlike methylphenidate, dexmethylphenidate is not indicated in the treatment of narcolepsy.

Pharmacokinetics

Both methylphenidate and dexmethylphenidate are readily absorbed after oral administration. Methylphenidate is available in extended-release oral formulations and as a transdermal patch for once-daily application. The deesterified product, ritalinic acid, is excreted in urine.

Adverse effects

GI adverse effects are the most common and include abdominal pain and nausea. Other reactions include anorexia, insomnia, nervousness, and fever. In patients with epilepsy, methylphenidate may increase seizure frequency. The drug is contraindicated in patients with glaucoma. Methylphenidate can inhibit the metabolism of warfarin, phenytoin, phenobarbital, primidone, and the tricyclic antidepressants.

The main reference for lectures is:

- **Lippincott's illustrated reviews pharmacology**

Additional references such as:

- **Basic and clinical pharmacology**

And some other related references could be used in the lectures


Thank You!