

DRUGS THAT ACT IN THE CNS

CNS Stimulants

Dr Karamallah S. Mahmood

PhD Clinical Pharmacology



CNS Stimulants



Psychomotor **stimulants and hallucinogens** 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 hallucinogens produce profound changes in thought patterns and mood.

PSYCHOMOTOR STIMULANTS

Amphetamine ADDERALL

Armodafinil NUVIGIL

Atomoxetine STRATTERA

Caffeine CAFCIT, NO DOZ, VIVARIN

Cocaine

Dexmethylphenidate FOCALIN

Dextroamphetamine DEXEDRINE,
DEXTROSTAT

Lisdexamfetamine VYVANSE

Methamphetamine DESOXYN

Methylphenidate RITALIN, CONCERTA,
DAYTRANA

Modafinil PROVIGIL

Nicotine NICODERM CQ, NICORETTE,
NICOTROL

Theophylline ELIXOPHYLLIN, THEO-24,
THEOCHRON, UNIPHYL

Varenicline CHANTIX

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 certain coffee products (for example, espresso), but it is also present in tea, cola drinks, energy drinks, chocolate candy, and cocoa.

PSYCHOMOTOR STIMULANTS

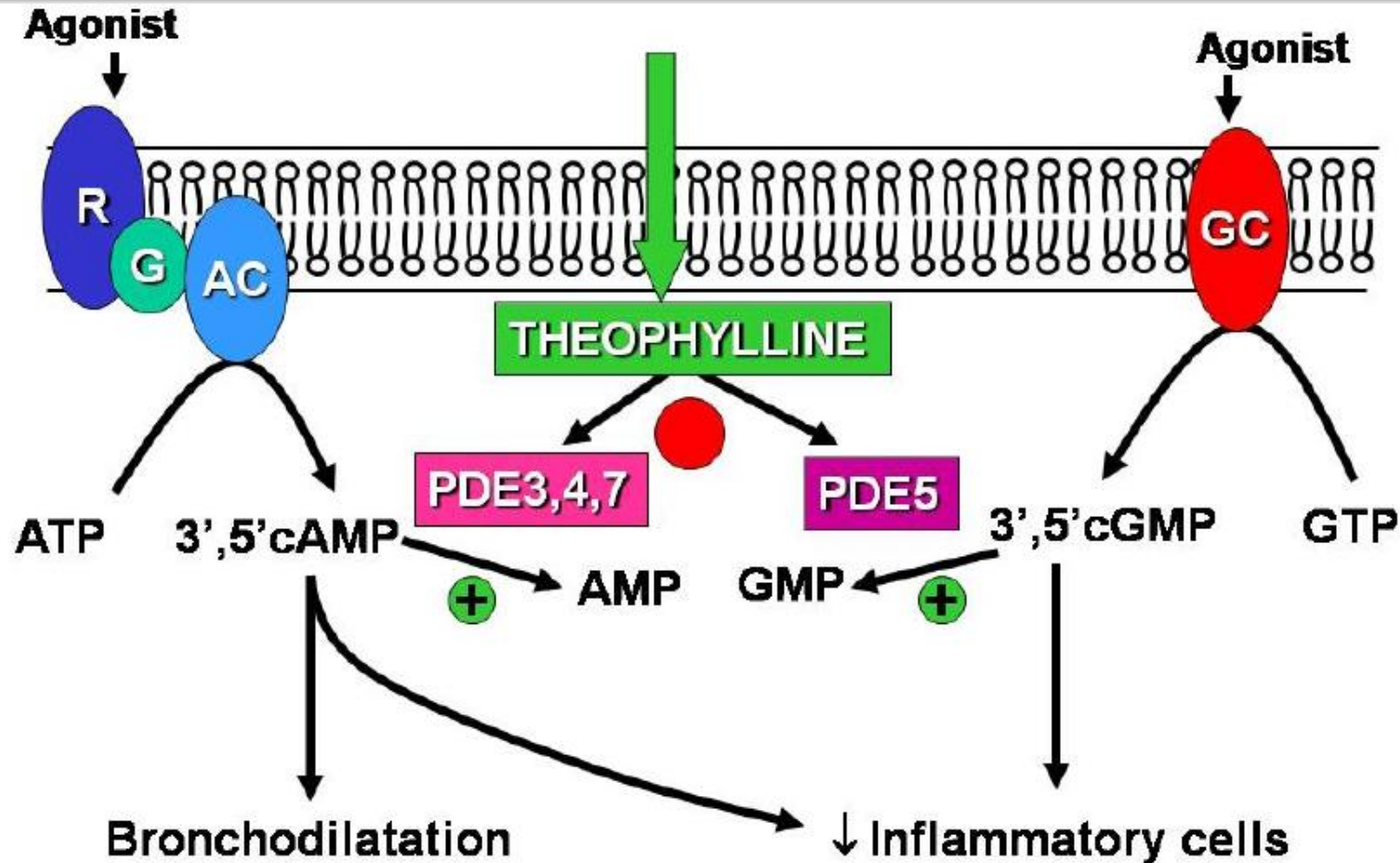


A. Methylxanthines/ Mechanism of action

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

- ✓ Translocation of **extracellular calcium**,
- ✓ Increase in **cAMP and cGMP** caused by inhibition of phosphodiesterase.

PSYCHOMOTOR STIMULANTS/ A. Methylxanthines/ Mechanism of action



Key: R = receptor, Gs = stimulatory G-protein, AC = adenylyl cyclase, GC = guanylyl cyclase, PDE = phosphodiesterase, cAMP = cyclic adenosine monophosphate, ATP = adenosine triphosphate, cGMP = cyclic guanosine monophosphate, GTP = guanosine triphosphate.

PSYCHOMOTOR STIMULANTS



A. Methylxanthines/ Actions

CNS: The caffeine contained in one to two cups of coffee (100 to 200 mg) causes a **decrease in fatigue and increased mental alertness.**

Consumption of 1.5 g of caffeine (12 to 15 cups of coffee) produces **anxiety and tremors.**

The spinal cord is stimulated only by very high doses (2 to 5 g) of caffeine.

Tolerance can rapidly develop to the stimulating properties of caffeine, and **withdrawal** consists of feelings of fatigue and sedation.

PSYCHOMOTOR STIMULANTS



A. Methylxanthines/ Actions

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 methylxanthines stimulate secretion of **gastric acid**, individuals with peptic ulcers should avoid foods and beverages containing methylxanthines..

PSYCHOMOTOR STIMULANTS



A. Methylxanthines/ Pharmacokinetics

The methylxanthines are well absorbed **orally**.

Caffeine distributes throughout the body, including the **brain**.

These drugs cross the **placenta** to the fetus and are secreted into the **breast milk**.

All methylxanthines are metabolized in the liver, generally by the CYP1A2 pathway, and the metabolites are excreted in the urine.

PSYCHOMOTOR STIMULANTS



A. Methylxanthines/ 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 10 g of caffeine (about 100 cups of coffee), which induces cardiac **arrhythmias**.

Lethargy, irritability, and headache occur in users who routinely consume more than 600 mg of caffeine per day (roughly six cups of coffee per day) and then suddenly stop.

PSYCHOMOTOR STIMULANTS



B. Nicotine

Nicotine is the active ingredient in tobacco.

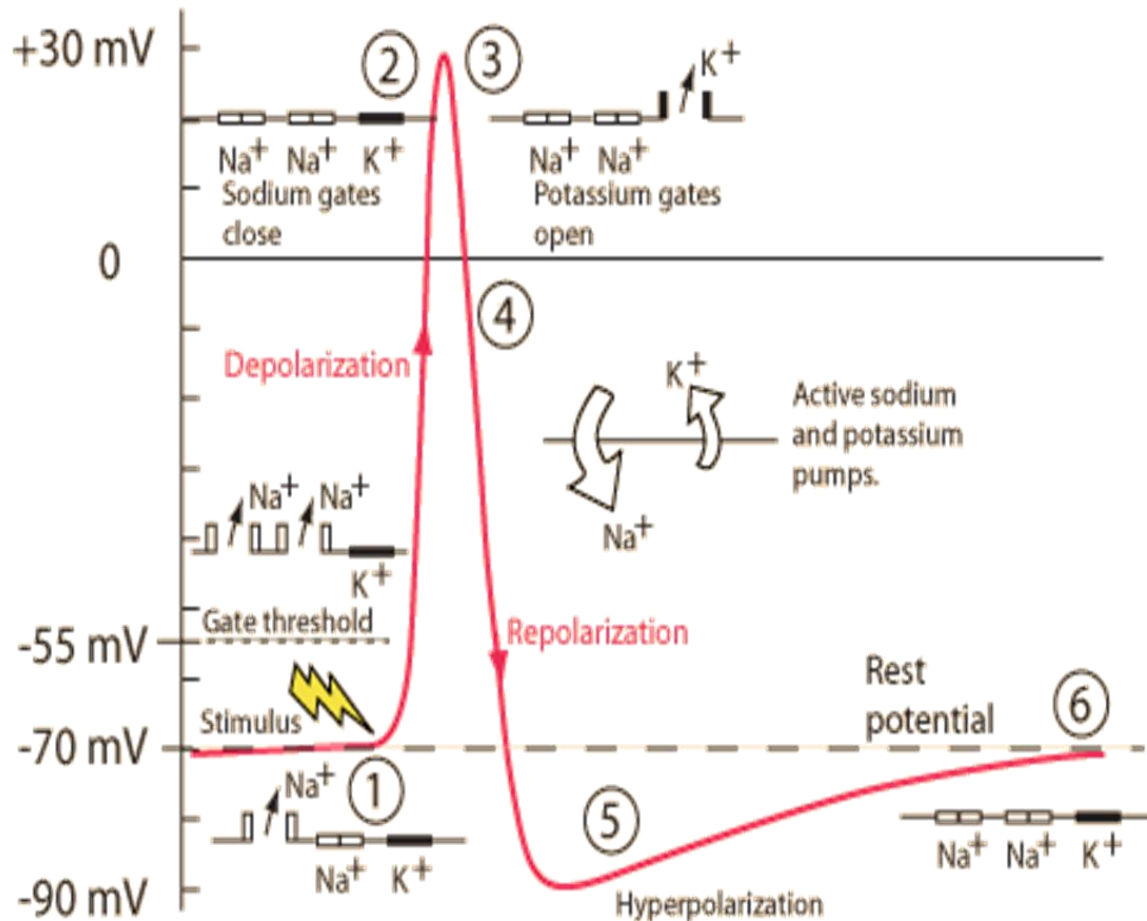
Although this drug is not currently used therapeutically (except in smoking cessation therapy), nicotine remains important because it is **second** only to **caffeine** as the most widely used **CNS stimulant**, and it is second only to **alcohol** as the most **abused drug**.

In combination with the **tars and carbon monoxide** found in cigarette smoke, nicotine represents a serious risk factor for lung and cardiovascular disease, various cancers, and other illnesses.

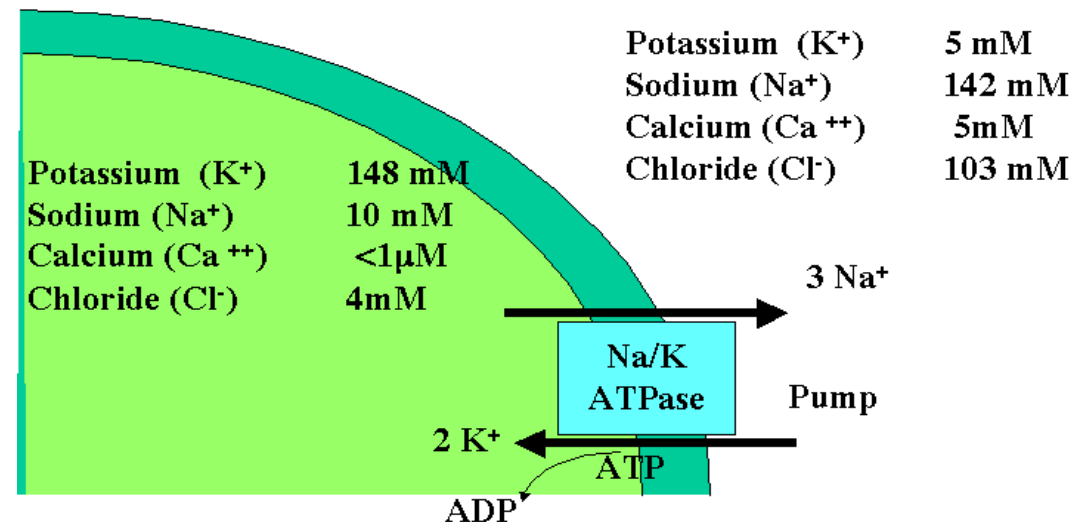
Dependency on the drug is not easily overcome.

PSYCHOMOTOR STIMULANTS/ B. Nicotine/ Mechanism of action:

In low doses, nicotine causes **ganglionic stimulation by depolarization**. At high doses, nicotine causes **ganglionic blockade**.



Membrane potential



PSYCHOMOTOR STIMULANTS

B. Nicotine/ 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.

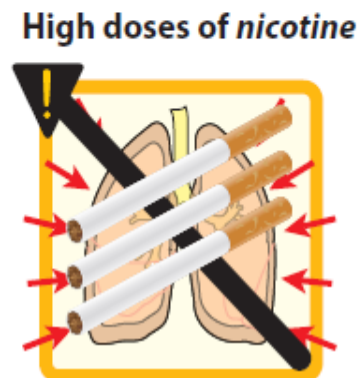
High doses of nicotine result in central **respiratory paralysis** and severe **hypotension** caused by medullary paralysis.

Nicotine is also an **appetite suppressant**.

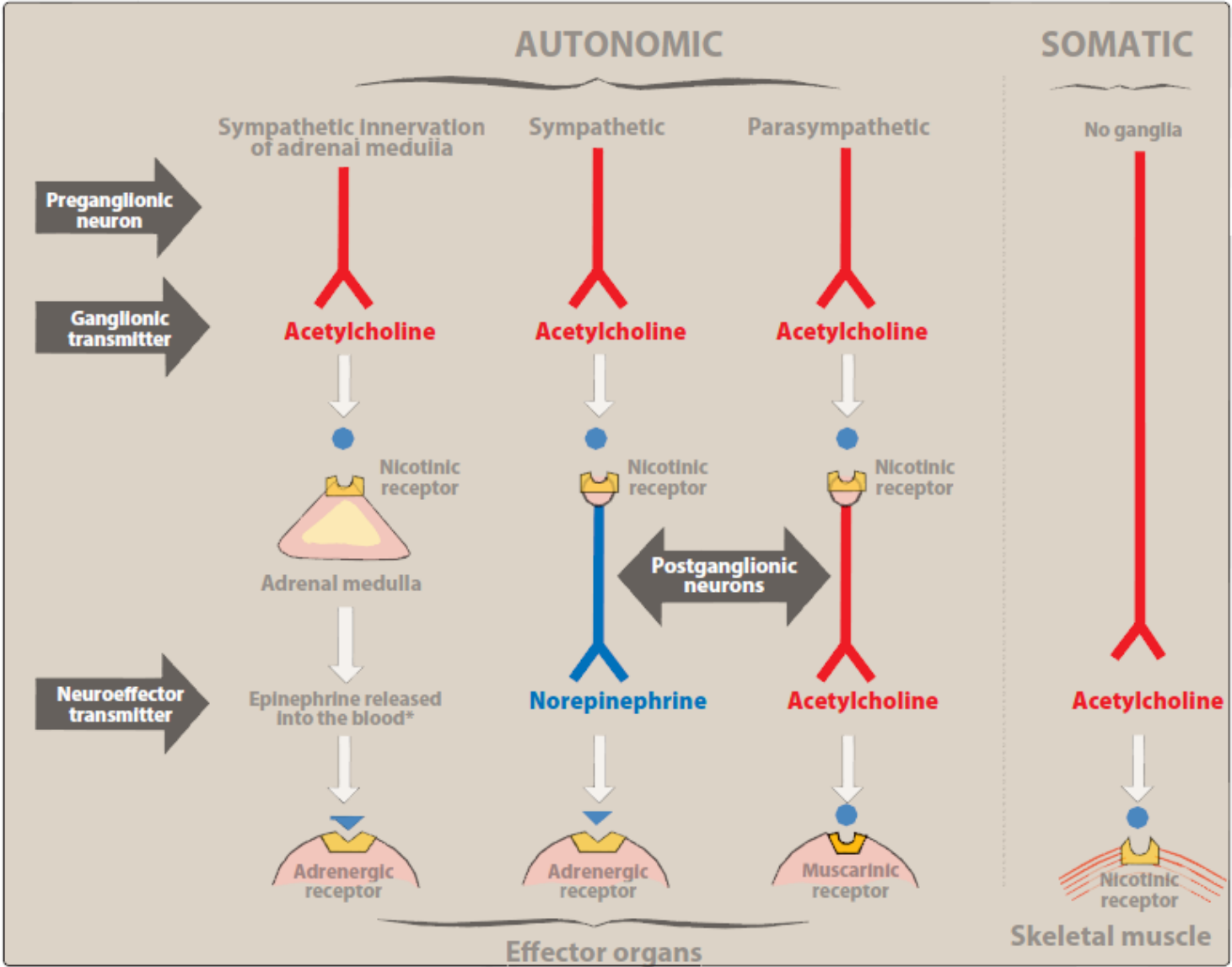
Arousal and relaxation



Respiratory paralysis



PSYCHOMOTOR STIMULANTS/ B. Nicotine/ Mechanism of action:



PSYCHOMOTOR STIMULANTS



B. Nicotine/ Actions:

Peripheral effects: The peripheral effects of nicotine are complex.

Stimulation of **sympathetic ganglia** as well as of the **adrenal medulla** increases **blood pressure and heart rate**.

Many patients with peripheral vascular disease experience an exacerbation of symptoms with smoking.

In addition, nicotine-induced vasoconstriction can decrease coronary blood flow, adversely affecting a patient with angina.

PSYCHOMOTOR STIMULANTS



B. Nicotine/ Actions:

Peripheral effects:

Stimulation of parasympathetic ganglia also increases motor **activity of the bowel**.

At higher doses, **blood pressure falls** and activity **ceases in both the GI tract and bladder** musculature as a result of a nicotine-induced block of parasympathetic ganglia.

PSYCHOMOTOR STIMULANTS



B. Nicotine/ Pharmacokinetics::

Because nicotine is highly lipid soluble, absorption readily occurs via the **oral** mucosa, lungs, GI mucosa, and skin.

Nicotine crosses the **placental** membrane and is secreted in the **breast milk**.

By inhaling tobacco smoke, the average smoker takes in 1 to 2 mg of nicotine per cigarette.

The acute lethal dose is **60 mg**.

More than 90% of the nicotine inhaled in smoke is absorbed.

Tolerance to the toxic effects of nicotine develops rapidly, often within days.

B. Nicotine/ Withdrawal syndrome:

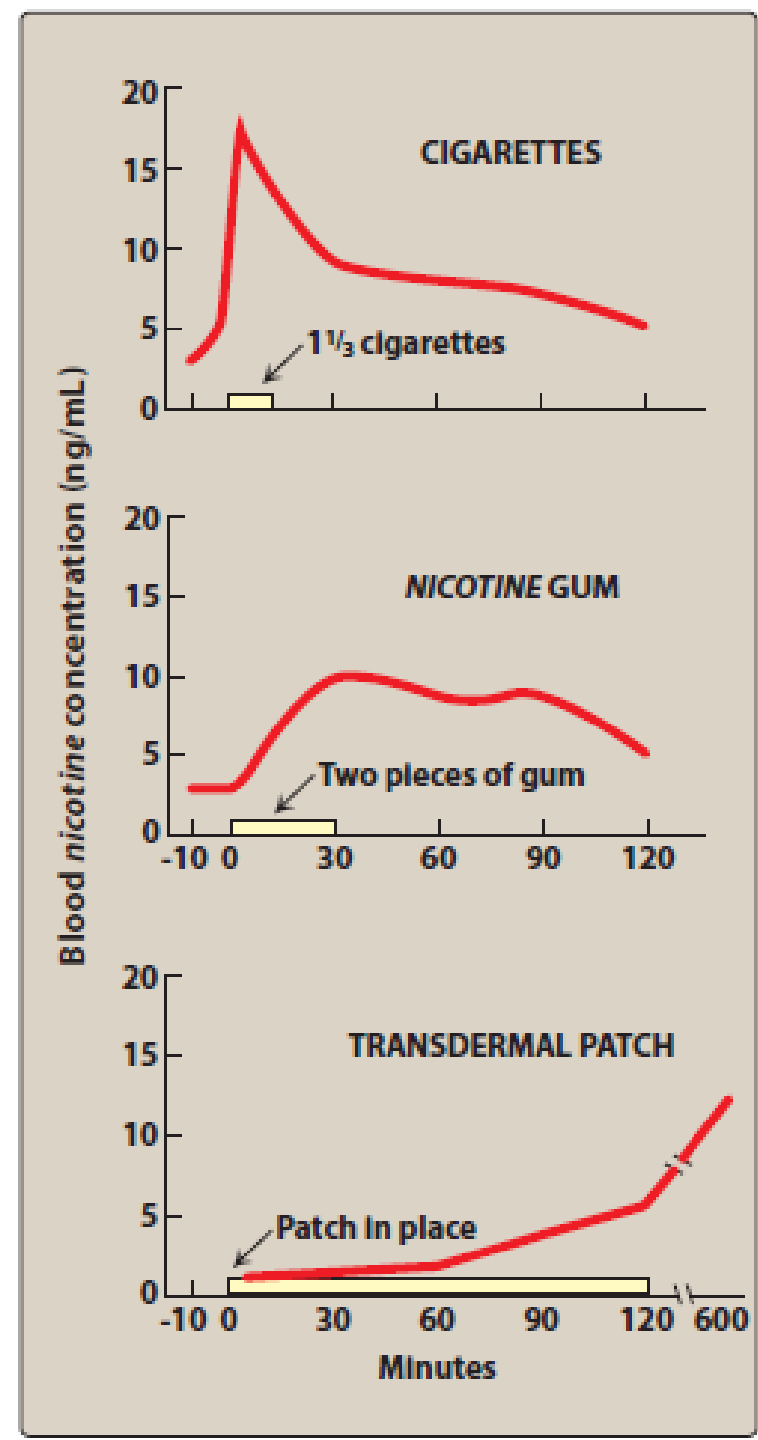
As with the other drugs in this class, nicotine is an **addictive** substance, and physical **dependence** develops rapidly and can be severe.

Withdrawal is characterized by irritability, anxiety, restlessness, difficulty concentrating, headaches, and insomnia.

Appetite is affected, and GI upset often occurs.

The transdermal patch and chewing gum containing nicotine have been shown to reduce nicotine withdrawal symptoms and to help smokers stop smoking.

Bupropion, an antidepressant, can reduce the craving for cigarettes.



PSYCHOMOTOR STIMULANTS



C. Varenicline

Varenicline is a **partial agonist at neuronal nicotinic** acetylcholine receptors in the CNS.

Because varenicline is only a partial agonist at these receptors, it produces **less euphoric** effects than nicotine (nicotine is a full agonist at these receptors).

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.

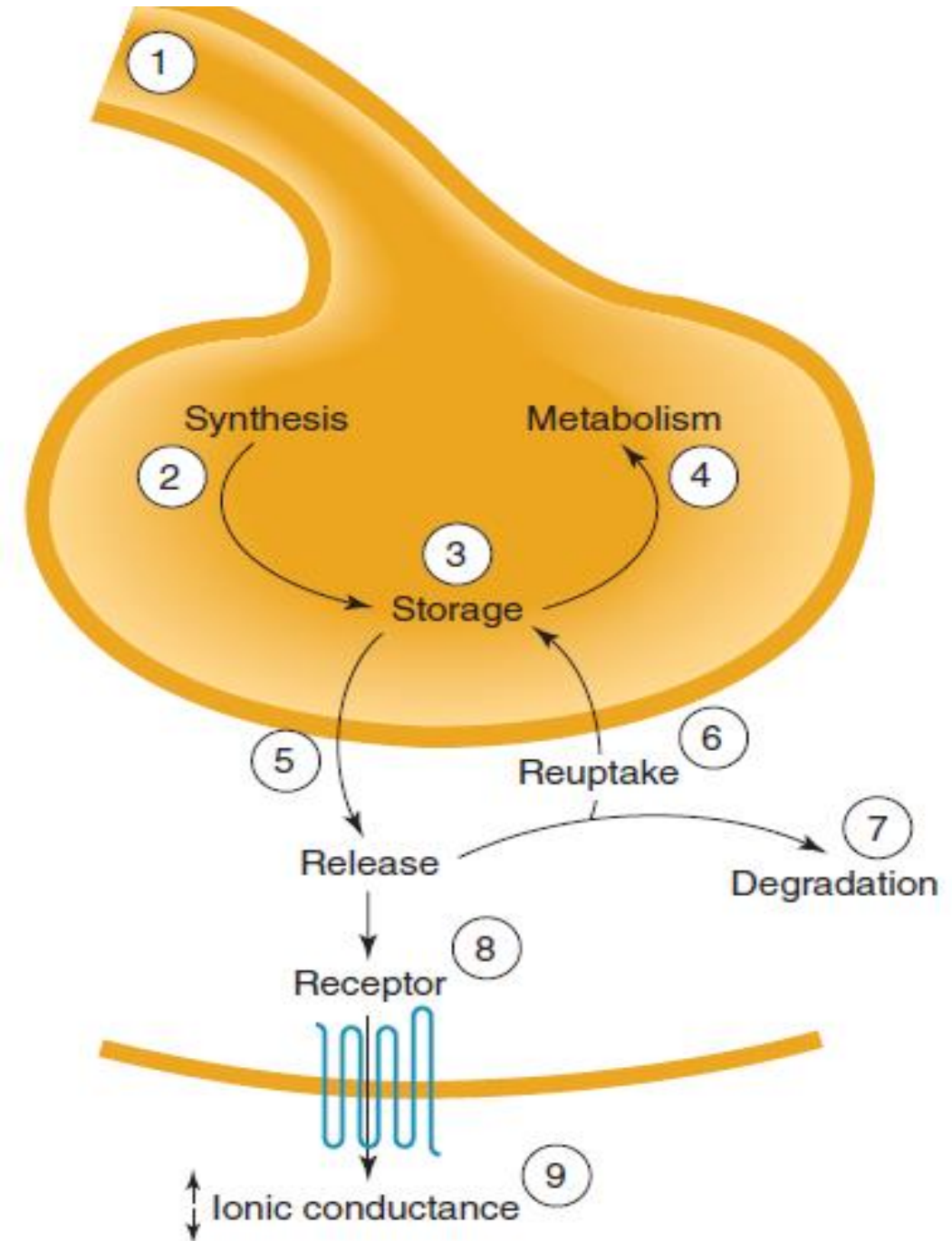
Patients taking varenicline **should be monitored** for suicidal thoughts, vivid nightmares, and mood changes.

PSYCHOMOTOR STIMULANTS

D. Cocaine

Cocaine is a widely available and highly **addictive** & **abusive** drug.

The primary mechanism of action underlying the effects of cocaine is blockade of **reuptake of the monoamines** (norepinephrine, serotonin, and dopamine) into the presynaptic terminals.



PSYCHOMOTOR STIMULANTS/ D. Cocaine

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 the vicious cycle of craving for cocaine that temporarily relieves severe depression.

