DRUGS THAT ACT IN THE CNS

Introduction to CNS Pharmacology
Lecture - 1

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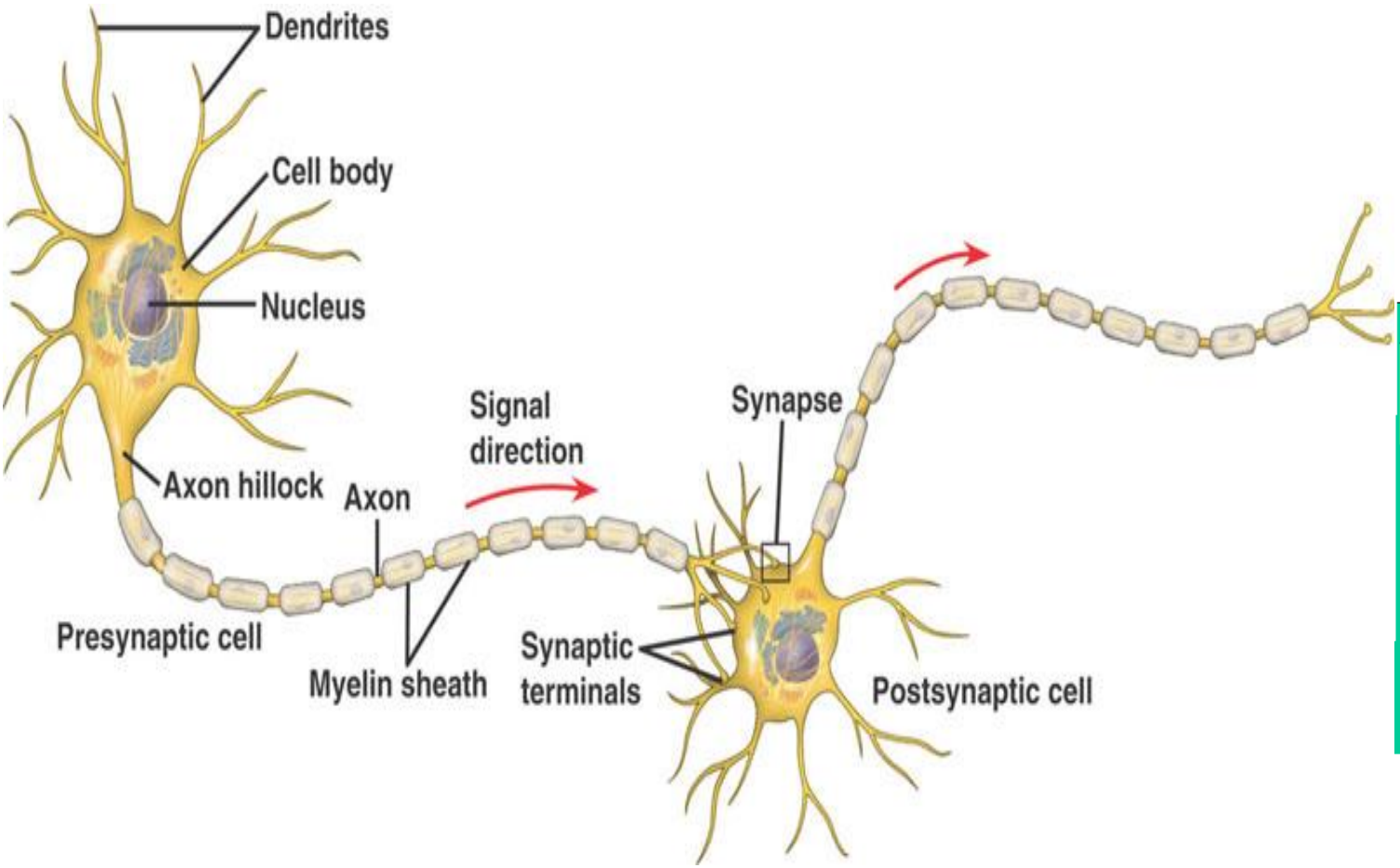
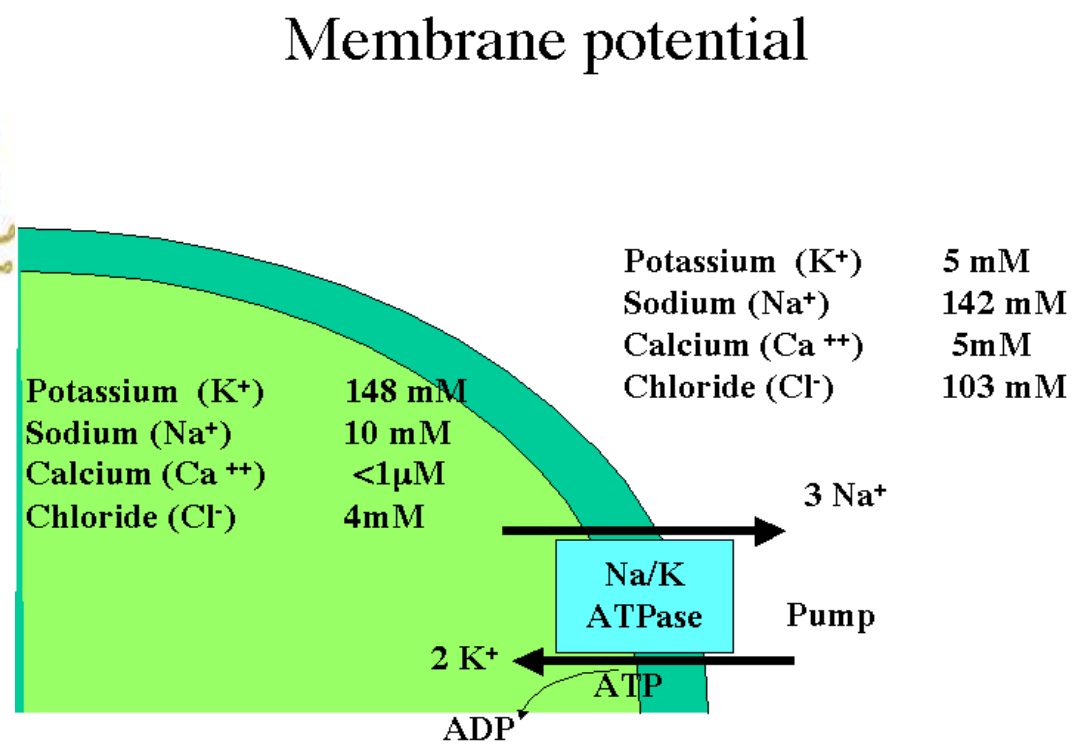
Neuron .. Structure and Function





Neuron .. Structure and Function

Neurons are **electrically excitable** cells composed, in general, of one or more dendrites, a single soma, a single axon and one or more axon terminals.

Dendrites are designed to capture the **neurotransmitters** released by the presynaptic neuron and have a high concentration of **ligand-gated ion channels**.

The axon hillock is characterized by having a very high concentration of **voltage-activated sodium channels.** In general, it is considered to be the spike initiation zone for action potentials, i.e. the trigger zone.

Neuron .. Structure and Function

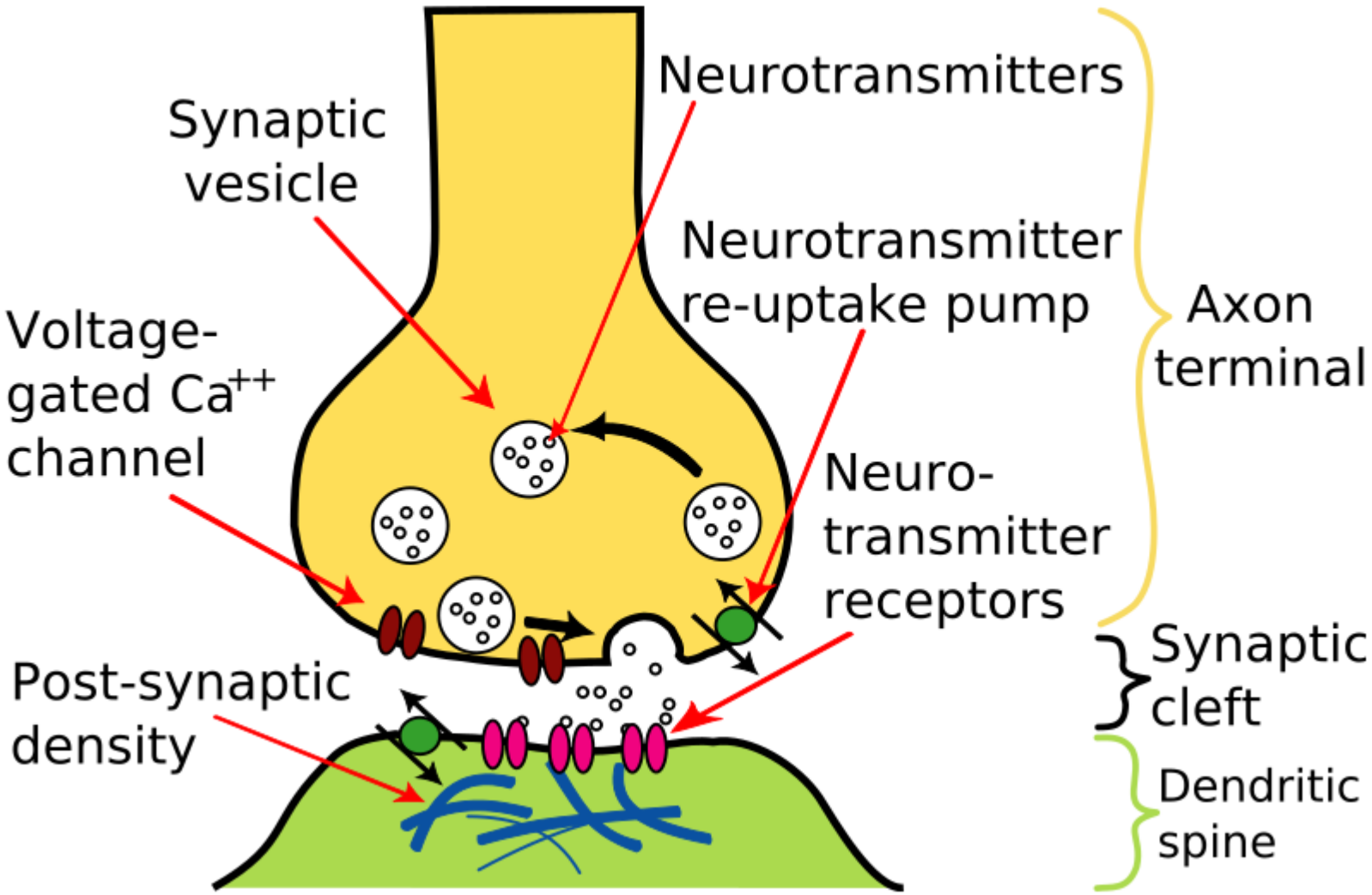
The axon is **insulated by a myelin** sheath. Myelin is composed of either Schwann cells (in the peripheral nervous system) or oligodendrocytes (in the central nervous system), both of which are types of glial cells.

These nodes of Ranvier can be considered to be "mini axon hillocks", as their purpose is to **boost the signal** in order to prevent significant signal decay.

At the furthest end, the axon loses its insulation and begins to branch into several axon terminals.

These **presynaptic terminals**, or synaptic boutons, are a specialized area within the axon of the presynaptic cell that contains neurotransmitters enclosed in small membrane-bound spheres called **synaptic vesicles**.

Synapsis

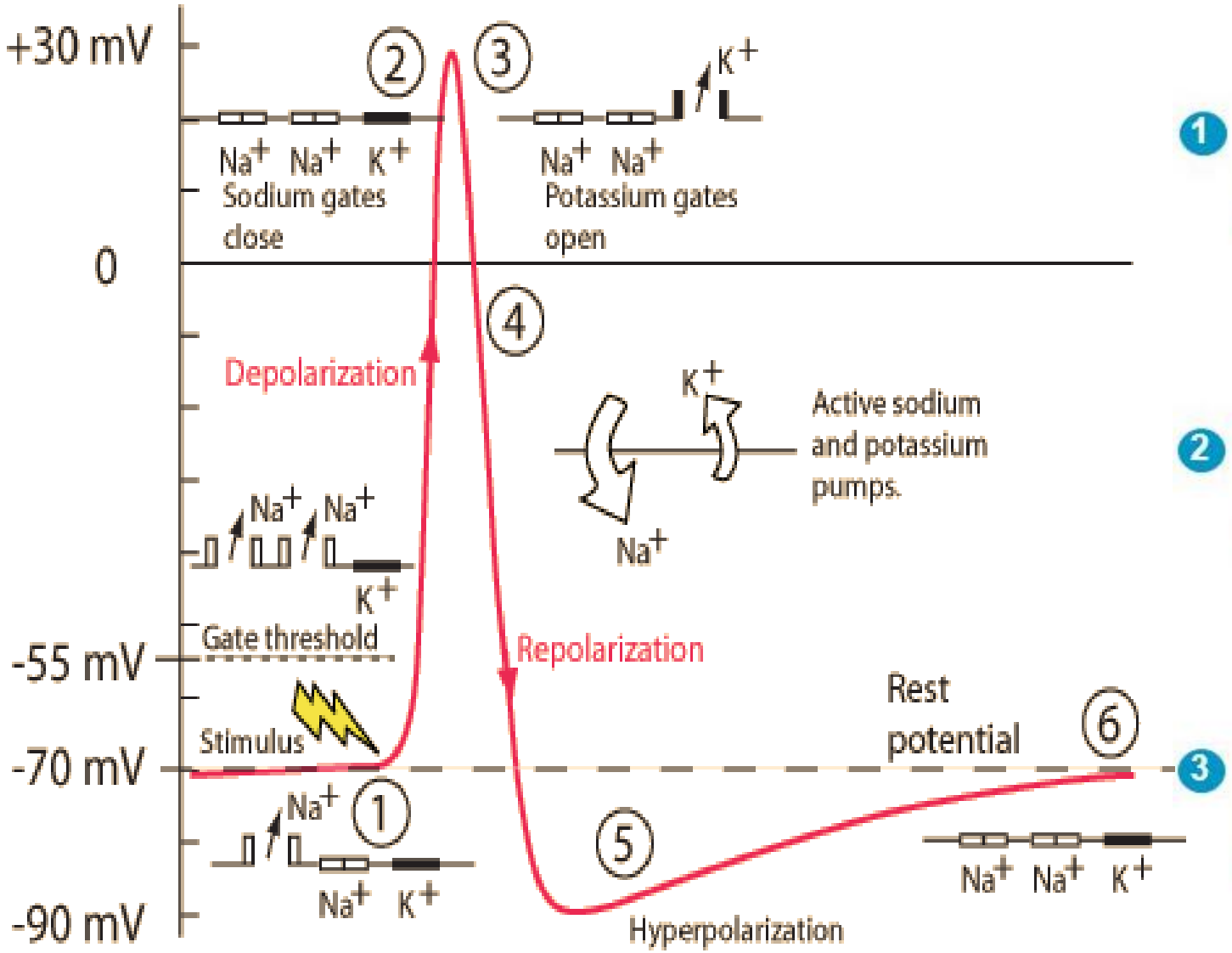

Neurotransmitters
Synaptic vesicle
Neurotransmitter re-uptake pump
Voltage-gated Ca++ channel
Neuro-transmitter receptors
Post-synaptic density
Axon terminal
Synaptic cleft
Dendritic spine

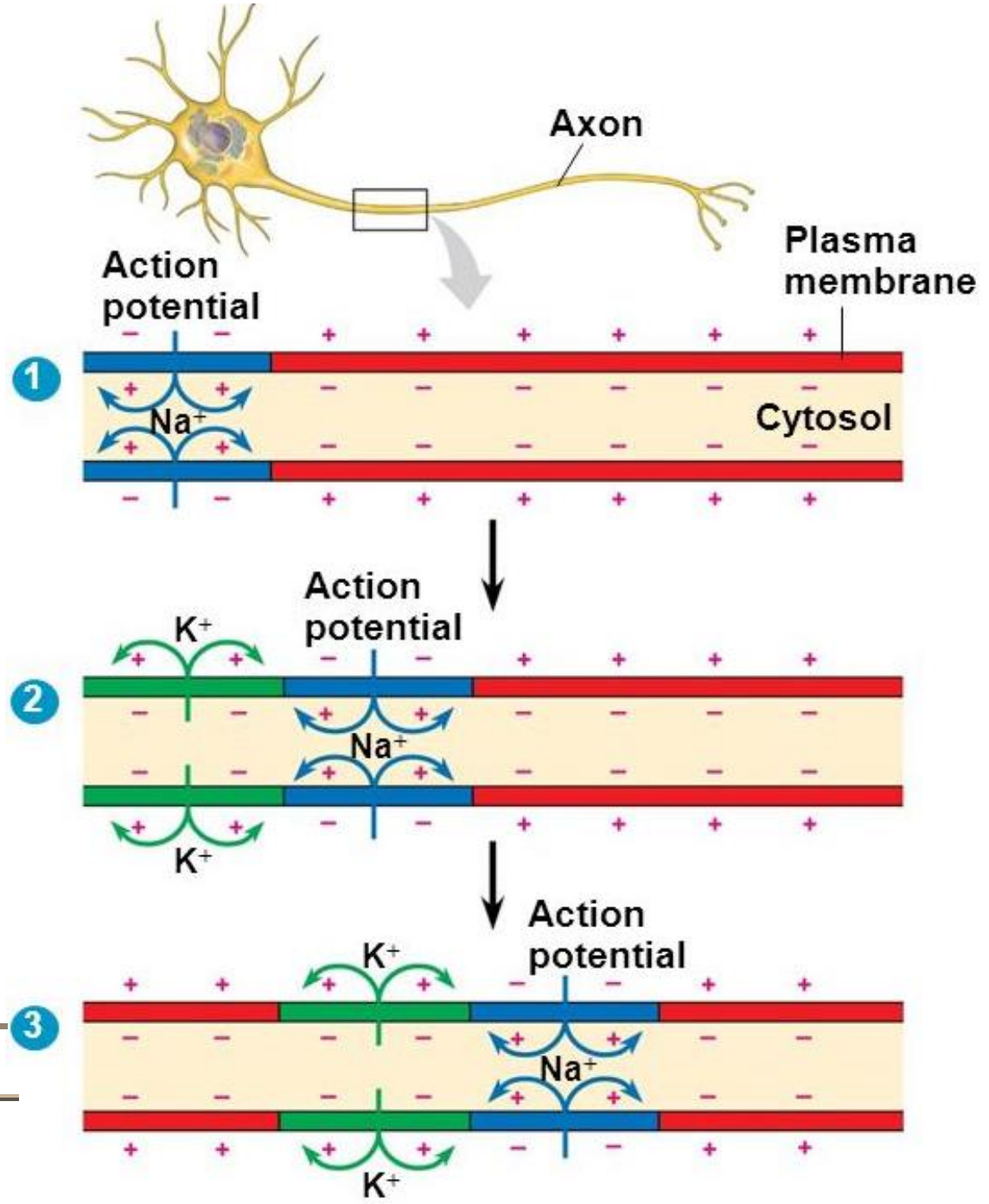
Synapsis

When an action potential arrives at the end of the pre-synaptic axon (top), it causes the release of **neurotransmitter** molecules that open ion channels in the post-synaptic neuron (bottom).

The combined excitatory and inhibitory postsynaptic potentials of such inputs can begin a **new action potential** in the post-synaptic neuron.

Neuronal Action Potential





Neuronal Action Potential

Nearly all cell membranes in animals maintain a voltage difference between the exterior and interior of the cell, called the **membrane potential**.

A typical voltage across an animal cell membrane is −70 mV. This means that the interior of the cell has a negative voltage of approximately one-fifteenth of a volt relative to the exterior

This electrical polarization results from a complex interplay between protein structures embedded in the membrane called **ion pumps** and **ion channels**.

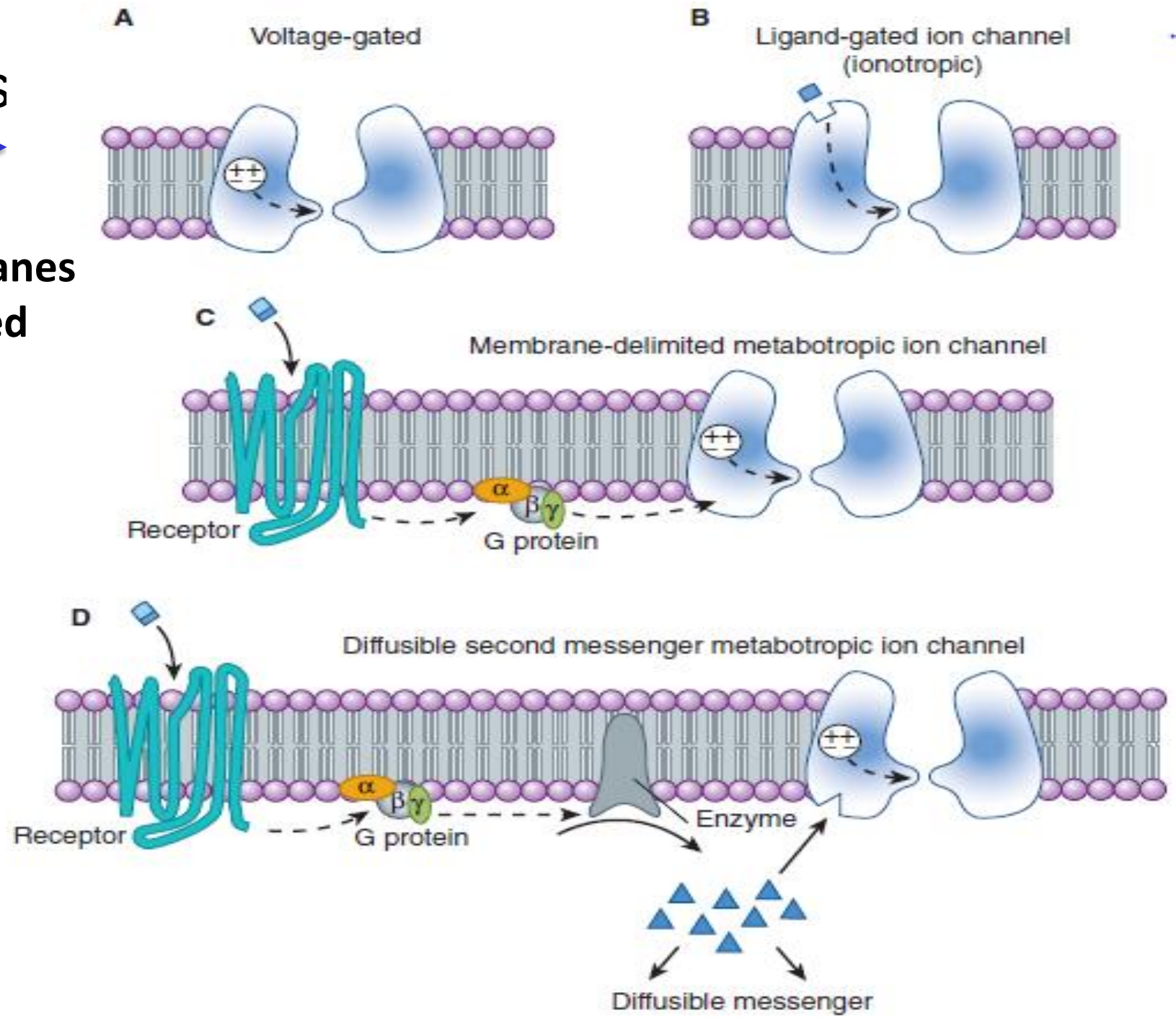
The membrane potential starts out at −70 mV at time zero. A stimulus is applied at time = 1 ms, which raises the membrane potential above −55 mV (**the threshold potential**).

After the stimulus is applied, the membrane potential rapidly rises to a peak potential of +35 mV at time = 2 ms.

Just as quickly, the potential then drops and overshoots to −90 mV at time = 3 ms, and finally the resting potential of −70 mV

Types of Ion Channels

Ion channels of neuronal membranes are of 2 major types: voltage gated and ligand gated



Types of Ion Channels

Voltage-gated ion channels respond to changes in **membrane potential**. They are concentrated on the axons of nerve cells and include the **sodium** channels responsible for action potential propagation. Cell bodies and dendrites also have voltage-sensitive ion channels for **potassium and calcium**.

Ligand-gated ion channels, also called **ionotropic receptors**, respond to chemical **neurotransmitters** that bind to receptor subunits present in their macromolecular structure.

Neurotransmitters also bind to **G protein-coupled receptors (metabotropic receptors)** that can modulate voltage-gated ion channels. Neurotransmitter-coupled ion channels are found on cell bodies and on both the presynaptic and postsynaptic sides of synapses.

Types of Receptor-Channel Coupling

In the case of ligand-gated ion channels, activation (or inactivation) is initiated by the interaction between chemical **neurotransmitters and their receptors.**

Coupling may be:

(1) through a receptor that acts **directly** on the channel protein (B),

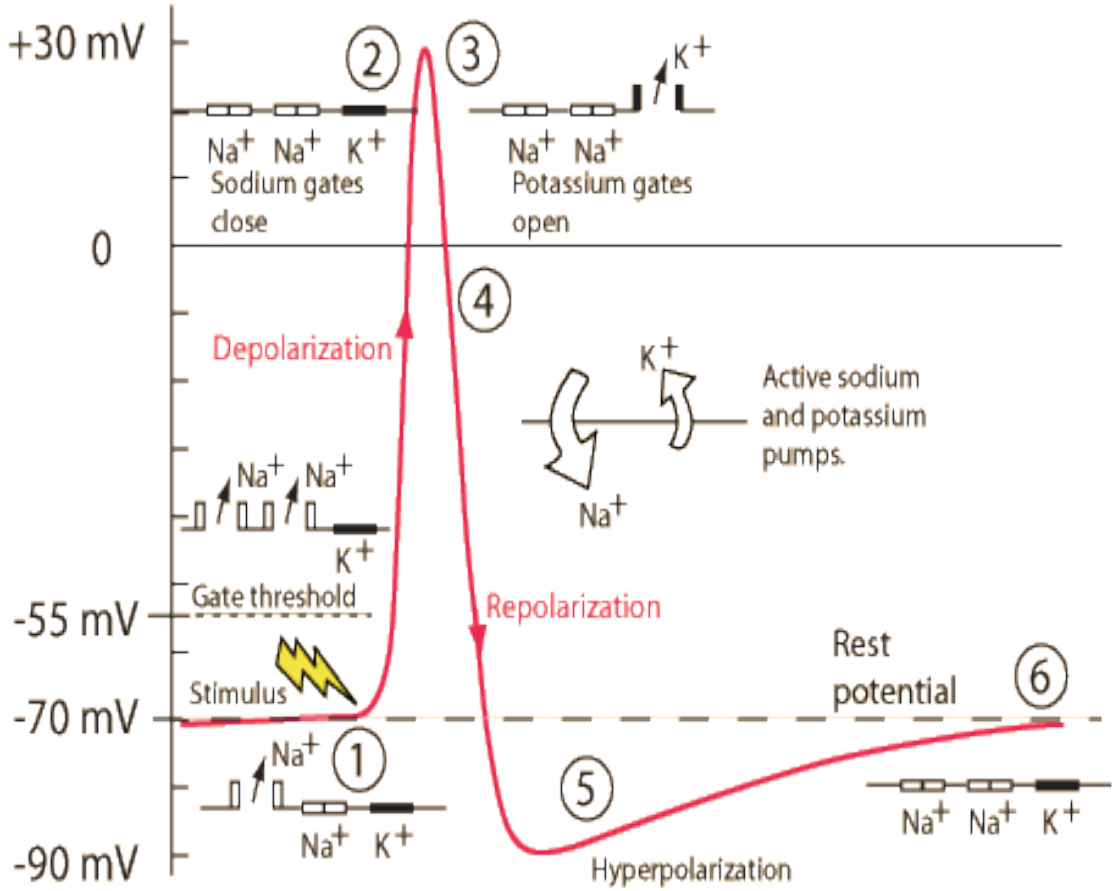
(2) through a receptor that is coupled to **the ion channel through a G protein** (C),

(3) through a receptor coupled to a G protein that modulates the formation of diffusible **second messengers**, including cyclic adenosine monophosphate (cAMP), inositol trisphosphate (IP3), and diacylglycerol (DAG), which secondarily modulate ion channels (D).

Role of the Ion Current Carried by the Channel

Excitatory postsynaptic potentials (EPSPs) are usually generated by the **opening of sodium or calcium channels**. In some synapses, similar depolarizing potentials result from the closing of potassium channels.

Inhibitory postsynaptic potentials (IPSPs) are usually generated by the **opening of potassium or chloride channels.**



SITES & MECHANISMS OF DRUG ACTION

A small number of neuropharmacologic agents exert their effects through direct interactions with molecular **components of ion channels** on axons. Examples include certain anticonvulsants, local anesthetics, and some drugs used in general anesthesia.

However, the effects of **most** therapeutically important CNS drugs are exerted mainly at **synapses**.

SITES & MECHANISMS OF DRUG ACTION

Drugs may alter:

(1) The action potential in the presynaptic fiber;

(2) synthesis of transmitter;

(3) storage;

(4) metabolism;

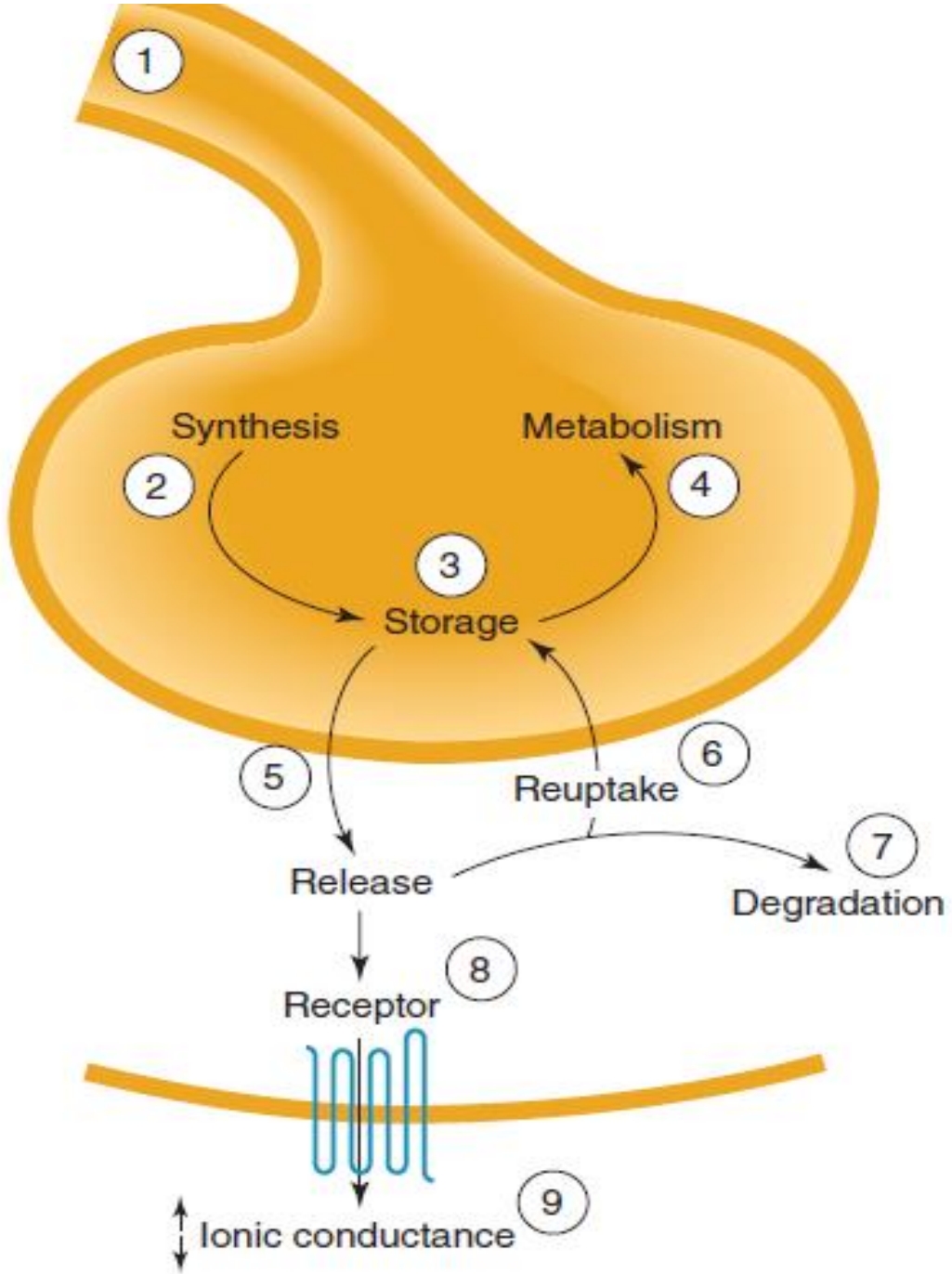
(5) release;

(6) reuptake;

(7) degradation;

(8) receptor for the transmitter;

(9) receptor-induced decrease or increase in ionic conduction



TRANSMITTERS AT CENTRAL SYNAPSES

Criteria for Transmitter Status

To be accepted as a neurotransmitter, a candidate chemical must

(1) Be **present in higher concentration in the synaptic area** than in other areas (ie, must be localized in appropriate areas),

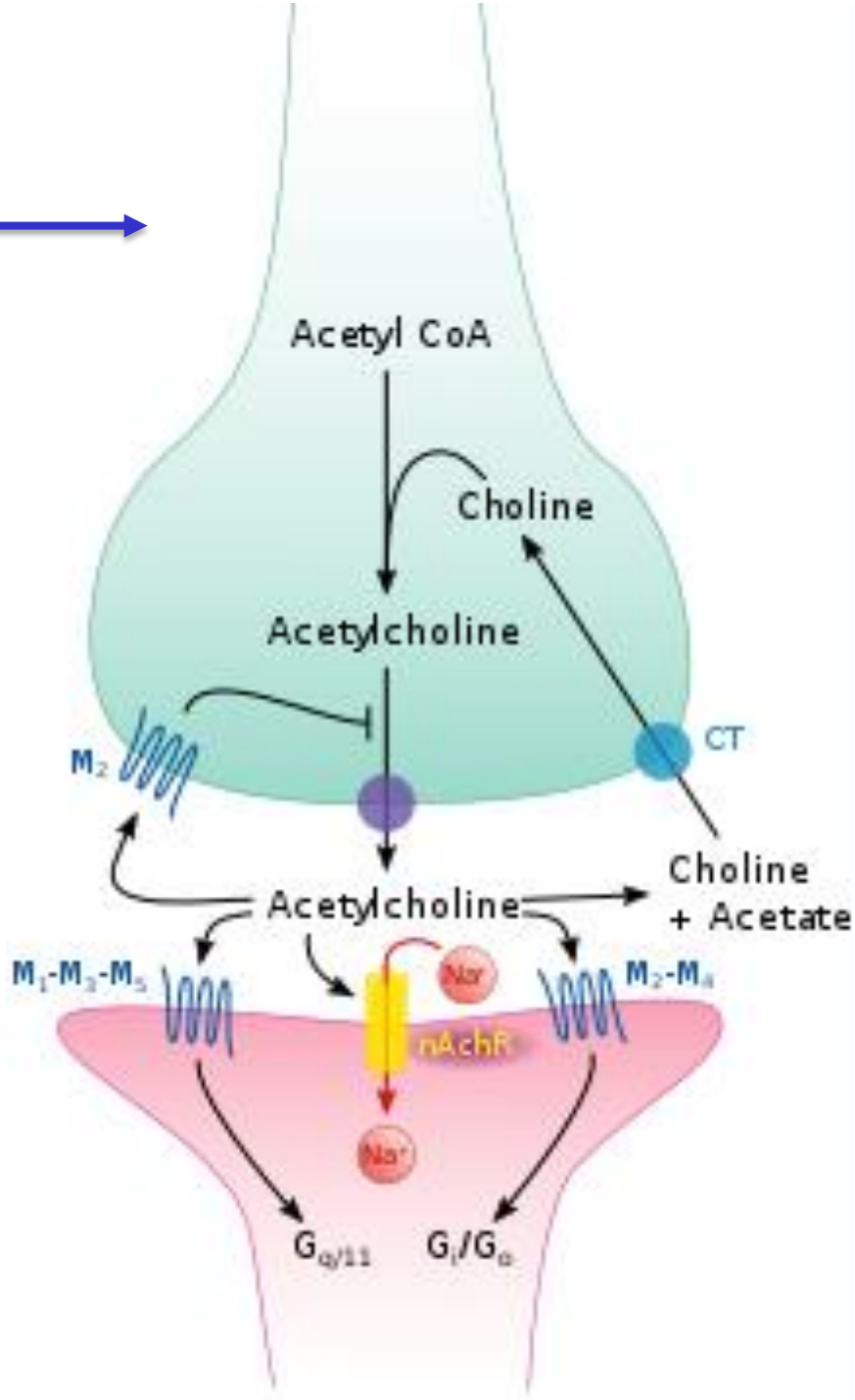
(2) Be **released by electrical or chemical stimulation**,

(3) Produce the same sort of postsynaptic response that is seen with physiologic activation of the synapse (ie, must exhibit synaptic mimicry).

Transmitter	Anatomical Distribution	Receptor Subtypes	Receptor Mechanisms
Acetylcholine	Cell bodies at all levels, short and long axons	Muscarinic, M_1; blocked by pirenzepine and atropine	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG
		Muscarinic, M_2; blocked by atropine	Inhibitory; ↑ K^+ conductance; ↓ cAMP
	Motoneuron-Renshaw cell synapse	Nicotinic, N	Excitatory; ↑ cation conductance
Dopamine	Cell bodies at all levels, short, medium, and long axons	D_1; blocked by phenothiazines	Inhibitory; ↑cAMP
		D_2; blocked by phenothiazines and haloperidol	Inhibitory (presynaptic); ↓ Ca^{2+} conductance;
			Inhibitory (postsynaptic); ↑ K^+ conductance; cAMP
Norepinephrine	Cell bodies in pons and brain stem project to all levels	$Alpha_1$; blocked by prazosin	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG
		$Alpha_2$; activated by clonidine	Inhibitory (presynaptic); ↓ Ca^{2+} conductance
			Inhibitory (postsynaptic); ↑ K^+ conductance; cAMP
		$Beta_1$; blocked by propranolol	Excitatory; ↓ K^+ conductance; ↑ cAMP
		$Beta_2$; blocked by propranolol	Inhibitory; ↑ electrogenic sodium pump
Serotonin (5-hydroxy-tryptamine)	Cell bodies in midbrain and pons project to all levels	5-HT_{1A}; buspirone is a partial agonist	Inhibitory; ↑ K^+ conductance
		5-HT_{2A}; blocked by clozapine, risperidone, and olanzapine	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG
		5-HT_3; blocked by ondansetron	Excitatory; ↑ cation conductance
		5-HT_4	Excitatory; ↓ K^+ conductance; ↑ cAMP
GABA	Supraspinal interneurons; spinal interneurons involved in presynaptic inhibition	$GABA_A$; facilitated by benzodiazepines and zolpidem	Inhibitory; ↑ Cl^- conductance
		$GABA_B$; activated by baclofen	Inhibitory (presynaptic); ↓ Ca^{2+} conductance
			Inhibitory (postsynaptic); ↑ K^+ conductance
Glutamate, aspartate	Relay neurons at all levels	Four subtypes; NMDA subtype blocked by phencyclidine, ketamine, and memantine	Excitatory; ↑ Ca^{2+} or cation conductance
		Metabotropic subtypes	Inhibitory (presynaptic); ↓ Ca^{2+} conductance ↓ cAMP
			Excitatory (postsynaptic); ↓ K^+ conductance, ↑ IP^3 and DAG
Glycine	Interneurons in spinal cord and brain stem	Single subtype; blocked by strychnine	Inhibitory; ↑ Cl^- conductance
Opioid peptides	Cell bodies at all levels	Three major subtypes: μ, δ, κ	Inhibitory (presynaptic); ↓ Ca^{2+} conductance; ↓cAMP
			Inhibitory (postsynaptic); ↑ K^+ conductance; ↓cAMP

A. Acetylcholine

- ✓ Approximately **5% of brain neurons** have receptors for acetylcholine (ACh).
- ✓ Most CNS responses to ACh are mediated by a large family of G protein-coupled **muscarinic M1 receptors** that lead to **slow excitation** when activated.
- ✓ The ionic mechanism of slow excitation involves **a decrease in membrane permeability to potassium**.
- ✓ Drugs affecting the activity of cholinergic systems in the brain include the acetylcholinesterase inhibitors used in Alzheimer's disease (eg, tacrine) and the muscarinic blocking agents used in parkinsonism (eg, benztropine).



B. Dopamine

- ✓ Dopamine exerts slow **inhibitory actions** at synapses in specific neuronal systems commonly via G protein-coupled **activation of potassium channels** (postsynaptic) or **inactivation of calcium channels** (presynaptic).
- ✓ The **D2 receptor** is the main dopamine subtype in basal ganglia neurons, and it is widely distributed at the supraspinal level.
- ✓ Dopaminergic pathways include the nigrostriatal, mesolimbic, and uberoinfundibular tracts.
- ✓ In addition to the 2 receptors other dopamine receptor subtypes have been identified (**D3, D4, and D5**).
- ✓ **Drugs that block the activity of dopaminergic** pathways include older (eg, chlorpromazine, haloperidol), which may cause parkinsonian symptoms.
- ✓ **Drugs that increase brain dopaminergic activity** include CNS stimulants (eg, amphetamine), and commonly used antiparkinsonism drugs (eg, levodopa).

C. Norepinephrine

- ✓ Noradrenergic neuron cell bodies are mainly located in the brain stem and the lateral tegmental area of the pons.
- ✓ These neurons fan out broadly to provide most regions of the CNS with diffuse noradrenergic input.
- ✓ **Excitatory** effects are produced by **activation** of **α1 and β1 receptors**.
- ✓ **Inhibitory** effects are caused by **activation of α2 and β2 receptors**.
- ✓ **CNS stimulants** (eg, amphetamines,cocaine), monoamine oxidase inhibitors (eg, phenelzine), and tricyclic antidepressants (eg, amitriptyline) are examples of drugs that **enhance** the activity of noradrenergic pathways.

D. Serotonin/ 5-HT

- ✓ Most serotonin (5-hydroxytryptamine; 5-HT) pathways originate from cell bodies in the raphe or midline regions of the pons and upper brain stem; these pathways innervate most regions of the CNS.
- ✓ Multiple 5-HT receptor subtypes have been identified and, with the exception of the 5-HT$_3$ subtype, all are **metabotropic**.
- ✓ 5-HT1$_A$ receptors and GABA$_B$ receptors share the same **potassium channel**.
- ✓ Serotonin can cause **excitation or inhibition** of CNS neurons depending on the receptor subtype activated.
- ✓ Both excitatory and inhibitory actions can occur on the same neuron if appropriate receptors are present.
- ✓ Most of the agents used in the treatment of major **depressive disorders** affect serotonergic pathways (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors).

D. Serotonin … Cont.

- ✓ The actions of some CNS stimulants and newer antipsychotic drugs (eg, olanzapine) also appear to be mediated via effects on serotonergic transmission.
- ✓ Reserpine, which may cause severe depression of mood, depletes vesicular

E. Glutamic Acid

- ✓ The Most neurons in the brain are **excited** by glutamic acid.
- ✓ High concentrations of glutamic acid in synaptic vesicles is achieved by the vesicular glutamate transporter (**VGLUT**).
- ✓ Both ionotropic and metabotropic receptors have been characterized.
- ✓ Subtypes of glutamate receptors include the N-methyl-D-aspartate (**NMDA**) receptor, which is blocked by phencyclidine (PCP) and ketamine.
- ✓ NMDA receptors appear to play a role in synaptic plasticity related to **learning and memory.**

E. Glutamic Acid … Cont.

- ✓ Memantine is an NMDA antagonist introduced for treatment of Alzheimer's dementia.
- ✓ Excessive activation of NMDA receptors after neuronal injury may be responsible for cell death.
- ✓ Glutamate metabotropic receptor activation can result in G protein-coupled activation of phospholipase C or inhibition of adenylyl cyclase.

F. GABA and Glycine

- ✓ GABA is the primary neurotransmitter mediating **IPSPs** in neurons in the brain; it is also important in the spinal cord.
- ✓ $GABA_A$ receptor **activation opens chloride ion channels.**
- ✓ GABAB receptors (activated by baclofen, a centrally acting muscle relaxant) are coupled to G proteins that either open potassium channels or close calcium channels.
- ✓ Fast IPSPs are blocked by $GABA_A$ receptor antagonists, and slow IPSPs are blocked by $GABA_B$ receptor antagonists.
- ✓ Drugs that influence $GABA_A$ receptor systems include **sedative-hypnotics** (eg, barbiturates, benzodiazepines, zolpidem) and some **anticonvulsants** (eg, gabapentin, tiagabine, vigabatrin).
- ✓ Glycine receptors, which are more numerous in the cord than in the brain, are blocked by strychnine, a spinal convulsant.

G. Peptide Transmitters

- ✓ The best-defined peptides are the **opioid peptides (beta-endorphin, met- and leu-enkephalin, and dynorphin),** which are distributed at all levels of the neuraxis.
- ✓ Some of the important therapeutic actions of opioid analgesics (eg, morphine) are mediated via **activation** of receptors for these endogenous peptides.
- ✓ Another peptide **substance P** is a mediator of slow **EPSPs** in neurons involved in nociceptive sensory pathways in the spinal cord and brain stem.

- ✓ Peptide transmitters differ from nonpeptide transmitters in that:

(1) the peptides are **synthesized in the cell body** and transported to the nerve ending via axonal transport,

(2) **no reuptake or enzyme mechanisms** have been identified for terminating their actions.

I. Endocannabinoids

- ✓ These are widely distributed brain lipid derivatives (eg, 2-arachidonyl-glycerol) that bind to **receptors for cannabinoids** found in marijuana.
- ✓ They are synthesized and released postsynaptically after membrane depolarization but **travel backward acting presynaptically (retrograde)** to decrease transmitter release, via their interaction with a specific cannabinoid receptor **CB1**.