CELLULAR BASIS OF NERVOUS SYSTEM

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Learning objectives

Preparation (self-studying – study following topics prior to the tutorial)

Neuron: structure, functional organisation (receptive zone, initial segment, axon, nerve ending). Basic classification of neurons. Glial cells: types and basic function. Blood-brain barrier. Structure of electrical and chemical synapse. Neurotransmitters: basic types, excitatory vs. inhibitory. Resting membrane potential. Local response of membrane potential vs. action potential (ion currents, conduction with/without decrement). Basis of action potential conduction through axon. Types of nerve fibres.

Content

1. Synapse

Electrical synapse: structure, function.

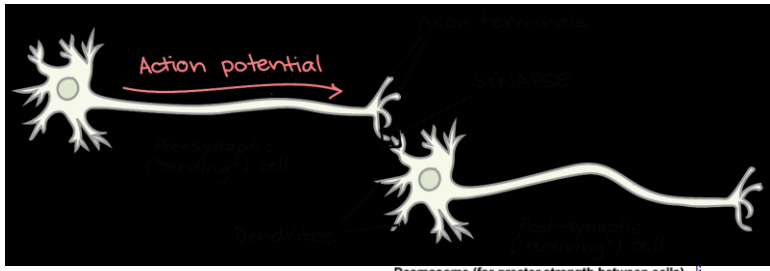
Structure of chemical synapse. Exocytosis of neurotransmitter. Mechanism of synaptic transmission. Excitatory, inhibitory and modulatory synapses.

2. Neurotransmitters and their receptors

Basic classification of neurotransmitters, excitatory vs. inhibitory. Glutamate, metabotropic and inotropic glutamate receptors – their distribution, function, physiological significance. GABA, GABAA receptor – function and physiological significance. Dopamine, dopaminergic receptors – classification, examples of distribution, physiological significance.

Synapse – types of synpase

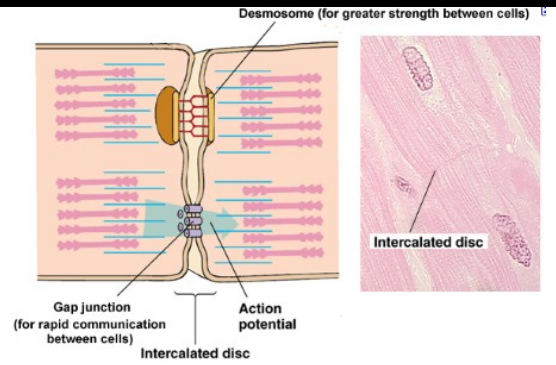
- Site of transmission of information from one cell to another (neuro-neuro or neuro-muscular)
- Types of synapse :



ELECTRICAL SYNAPSE (GAP JUNCTIONS)

- Low resistence pathway that allows direct current flow (through Gap Junctions)
- Very fast and Bidirectional

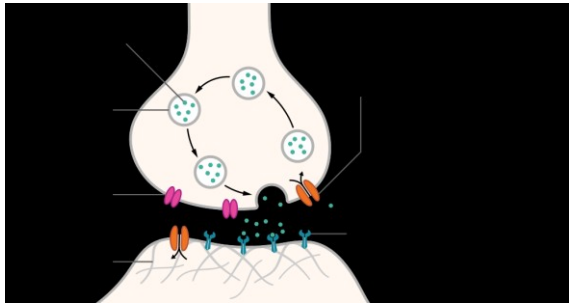
Example : rapid cell-cell conduction is important for simultaneous activation and contraction in tissues like ventricular muscle, uterus and bladder.

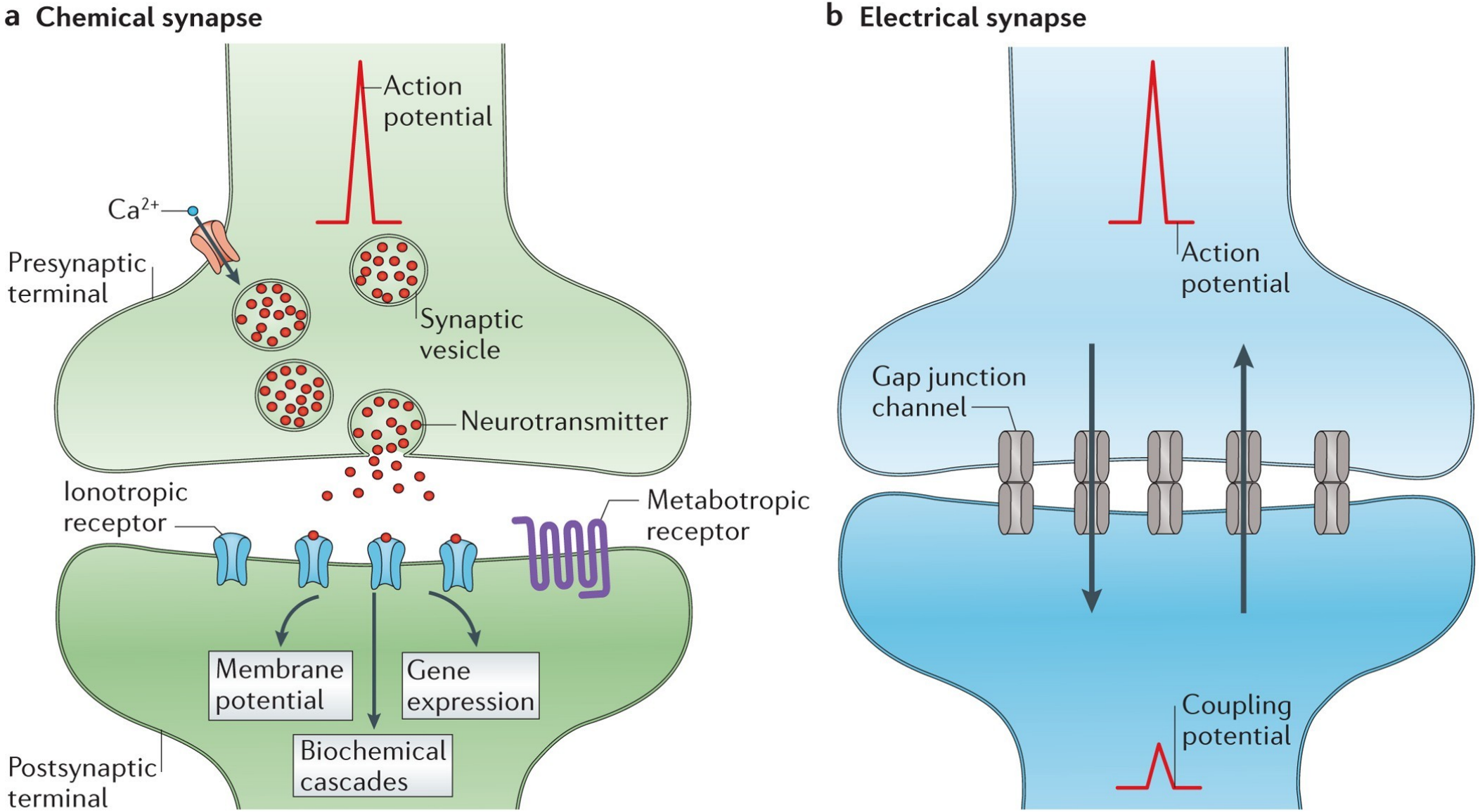


CHEMICAL SYNAPSE

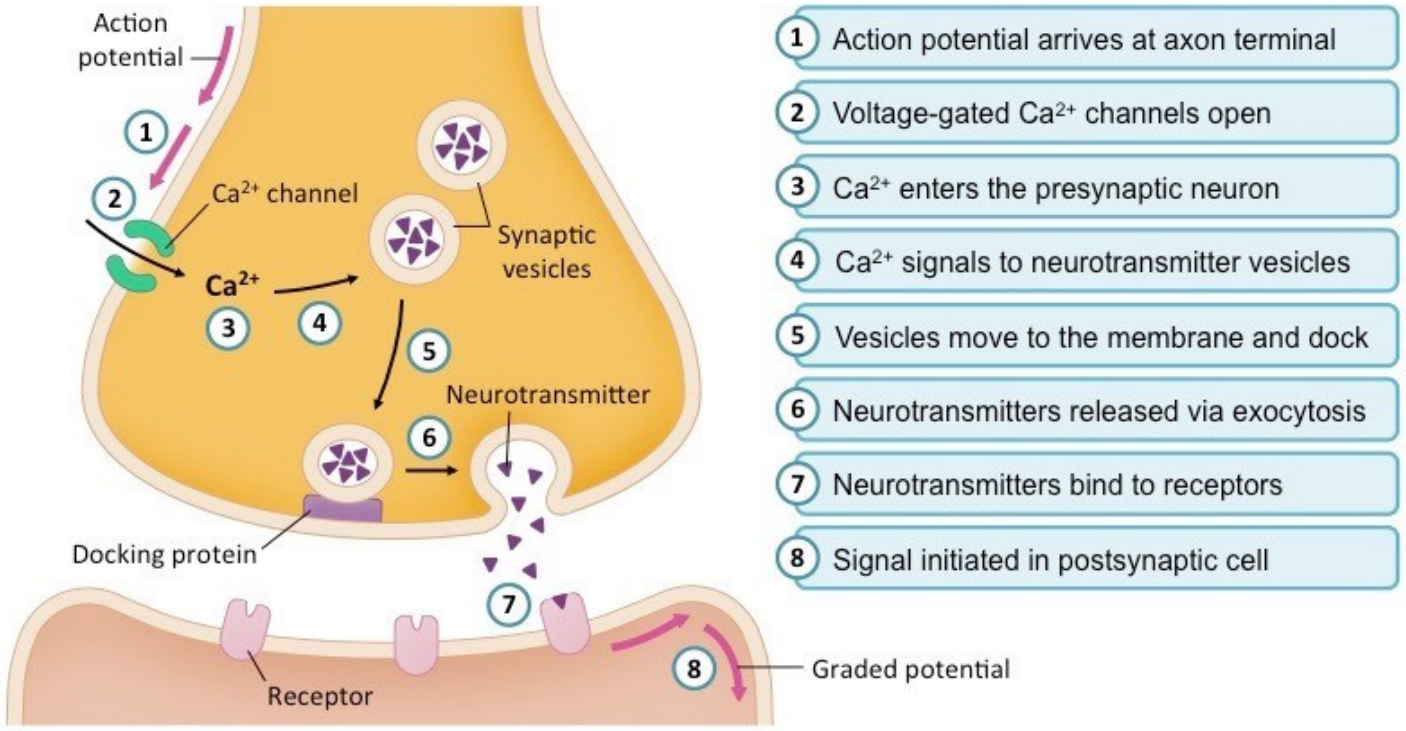
- Depends on release of tranmitter
- Operates only in one direction (Presynaptic cell – SYNAPTIC CLEFT – Postsynaptic cell)
- Synaptic delay

Example : Neuro-muscular Junction (NMJ)




a Chemical synapse
Action potential
Ca2+
Presynaptic terminal
Synaptic vesicle
Neurotransmitter
Ionotropic receptor
Metabotropic receptor
Membrane potential
Gene expression
Biochemical cascades
Postsynaptic terminal
b Electrical synapse
Action potential
Gap junction channel
Coupling potential

Synaptic transmission (eg ; NMJ)



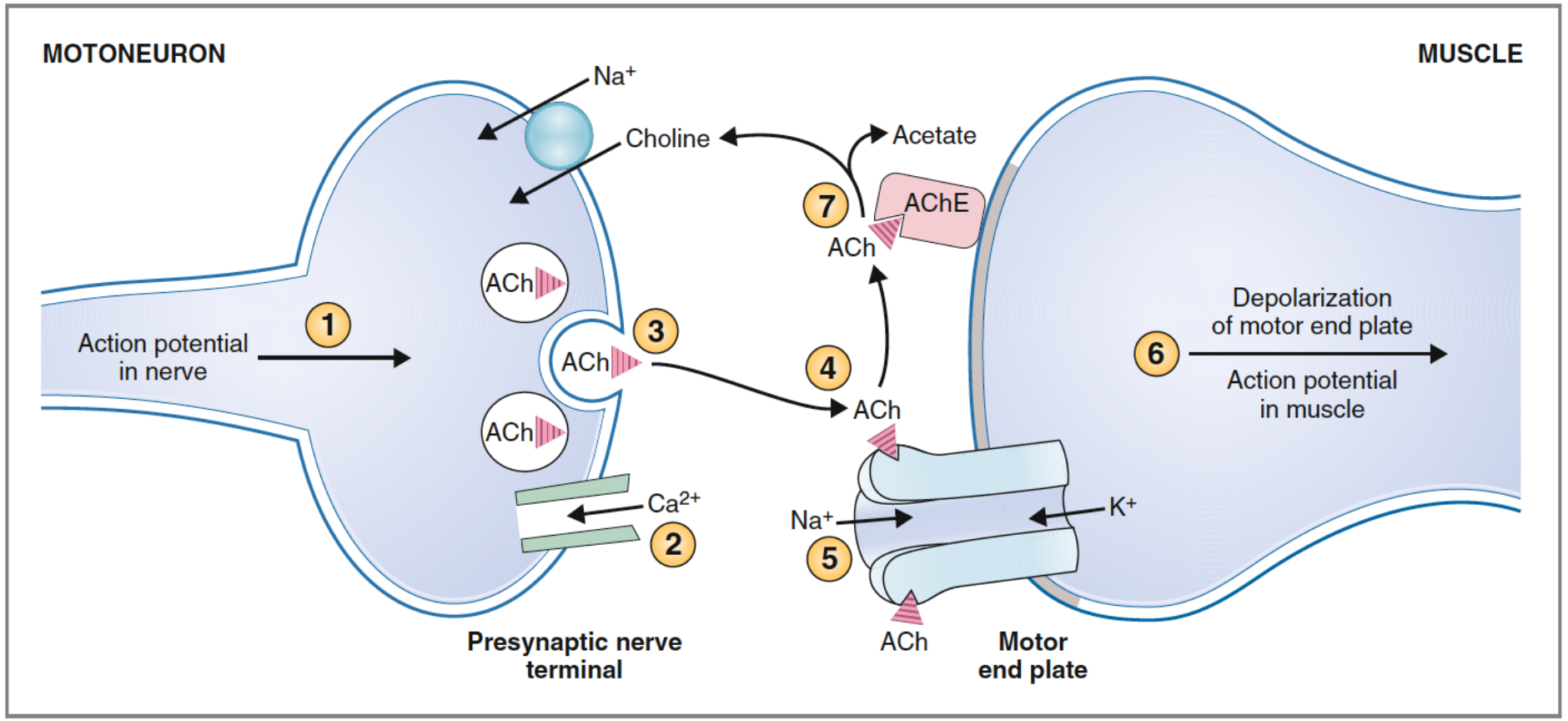
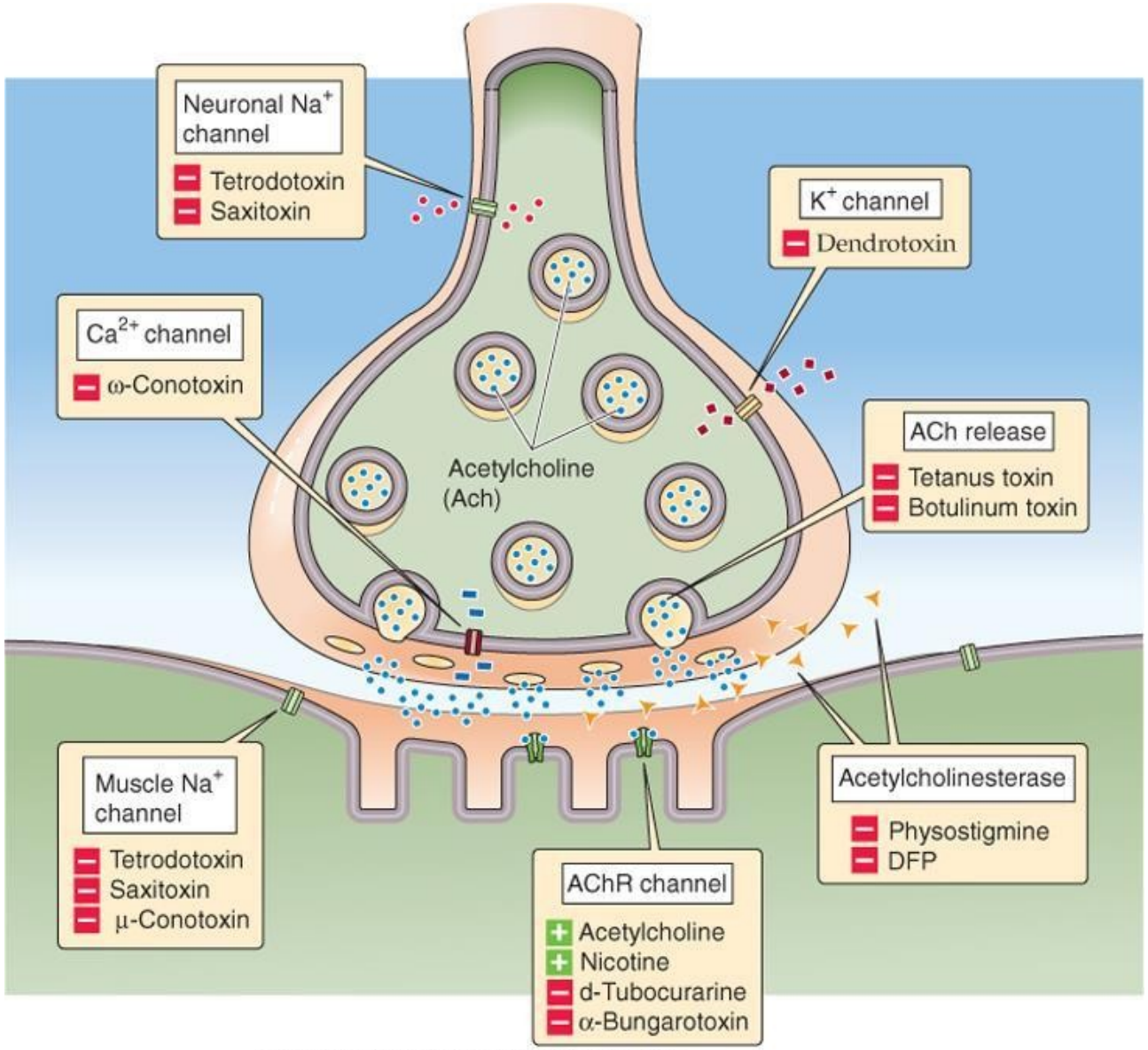


Figure 1-16 **Sequence of events in neuromuscular transmission.** *1,* Action potential travels down the motoneuron to the presynaptic terminal. *2,* Depolarization of the presynaptic terminal opens Ca^{2+} channels, and Ca^{2+} flows into the terminal. *3,* Acetylcholine (ACh) is extruded into the synapse by exocytosis. *4,* ACh binds to its receptor on the motor end plate. *5,* Channels for Na^{+} and K^{+} are opened in the motor end plate. *6,* Depolarization of the motor end plate causes action potentials to be generated in the adjacent muscle tissue. *7,* ACh is degraded to choline and acetate by acetylcholinesterase (AChE); choline is taken back into the presynaptic terminal on an Na^{+}-choline cotransporter.



Boron & Boulpaep: Medical Physiology, 2nd Edition.

Types of synaptic arrangement

- **One-to-one synapse**

A single action potential in presynaptic cell causes a single action potential in post-synaptic cell (e.g ; NMJ)

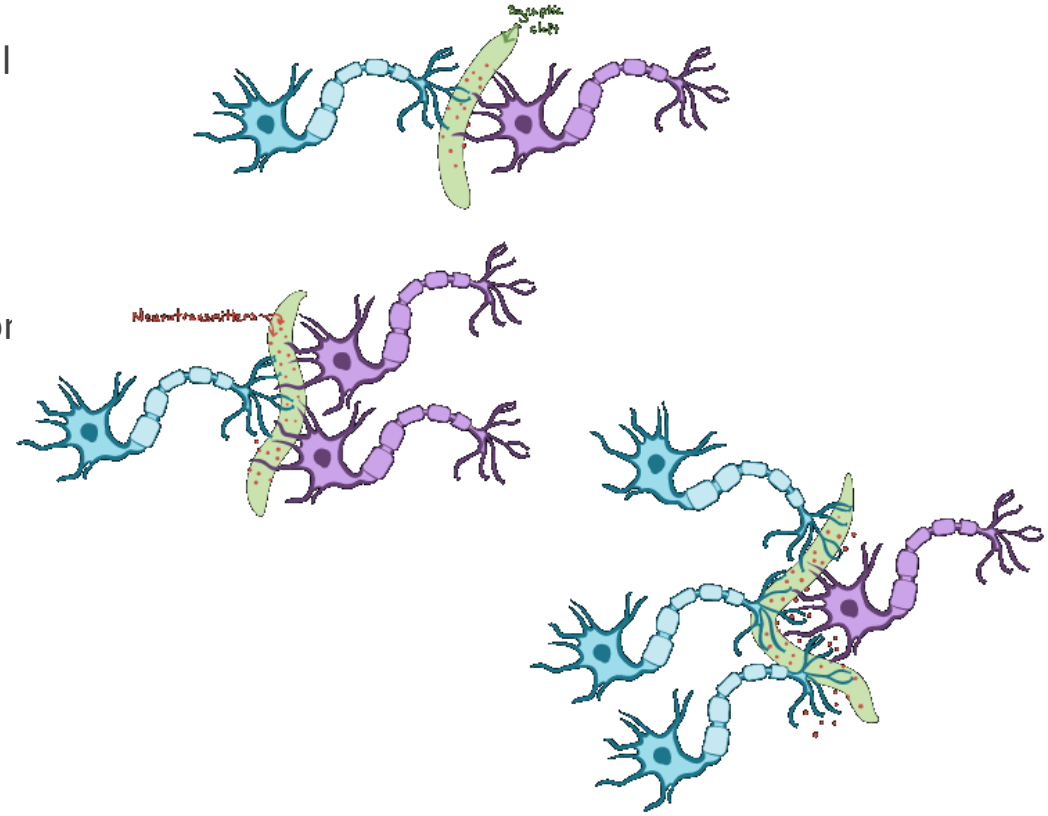
- **One-to-many synapse**

A single action potential in presynaptic cell causes a burst of action potentials in many postsynaptic cells – Rare! (e.g; synapse of motorneuron with renshaw cells of spinal cord)

- **Many-to-one synapse**

The commonest arrangement . Many presynaptic cells converge on postsynaptic cells, inputs summate, and the sum of the inputs determines whether postsynaptic cell will fire an action potential or not

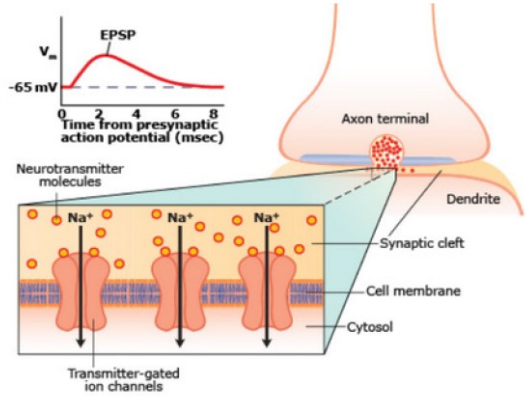
Inputs can be excitatory or inhibitory



EPSP & IPSP

Excitatory postsynaptic potential (EPSP)

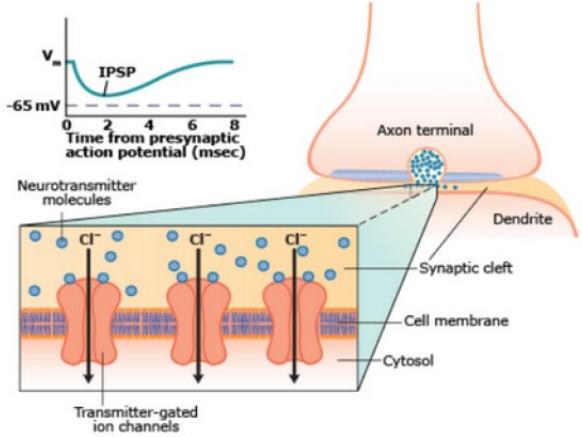
- Transmitters **depolarize**.
- Increased conductance of the postsynaptic membrane to both Na+ and K+-
- Main current flow is an **influx of Na+.**
- Transmitters include acetylcholine, glutamate, and aspartate.



▲ **Figure 5–3.1** Characteristics of an Excitatory Postsynaptic Potential

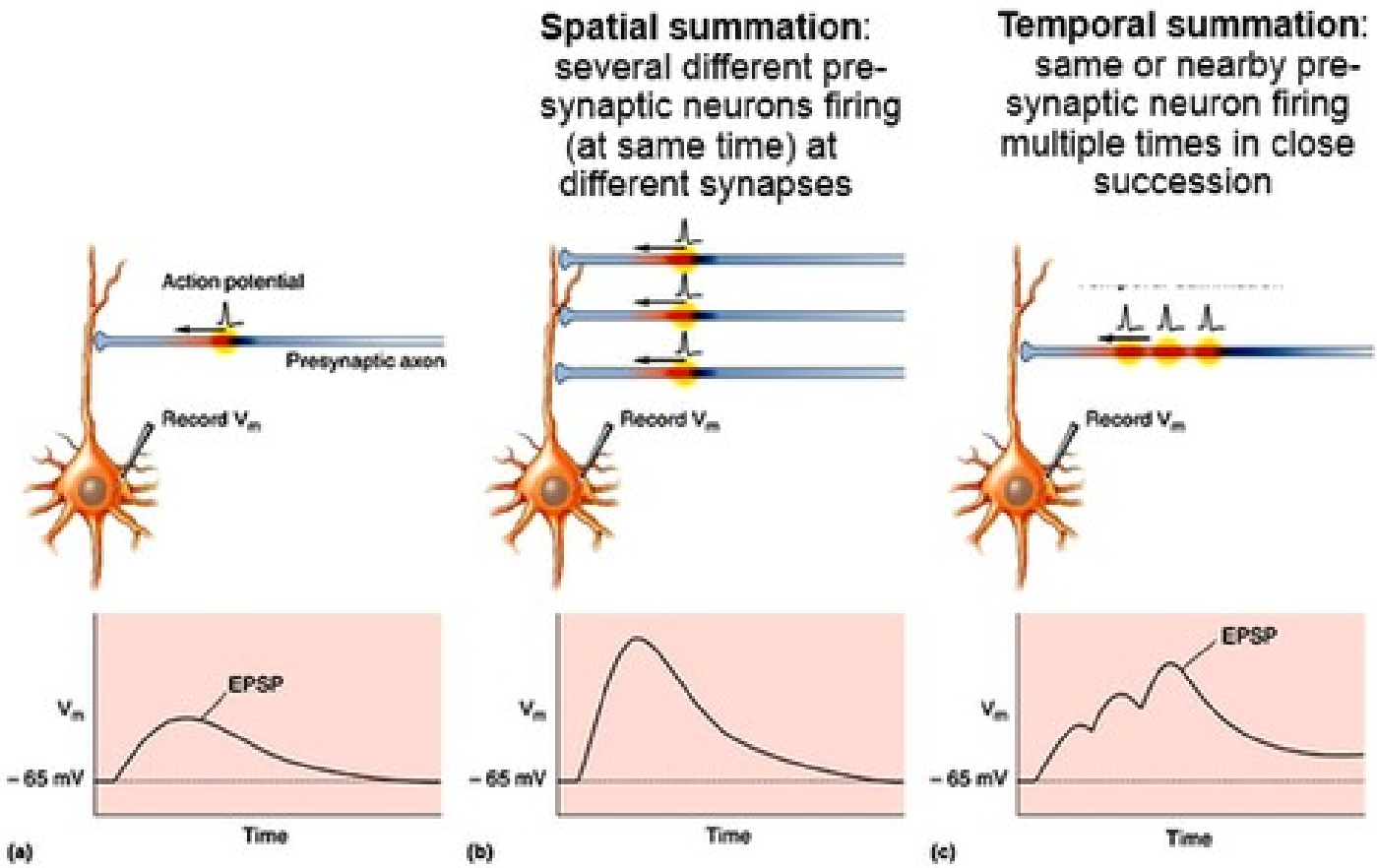
Inhibitory postsynaptic potential (IPSP)

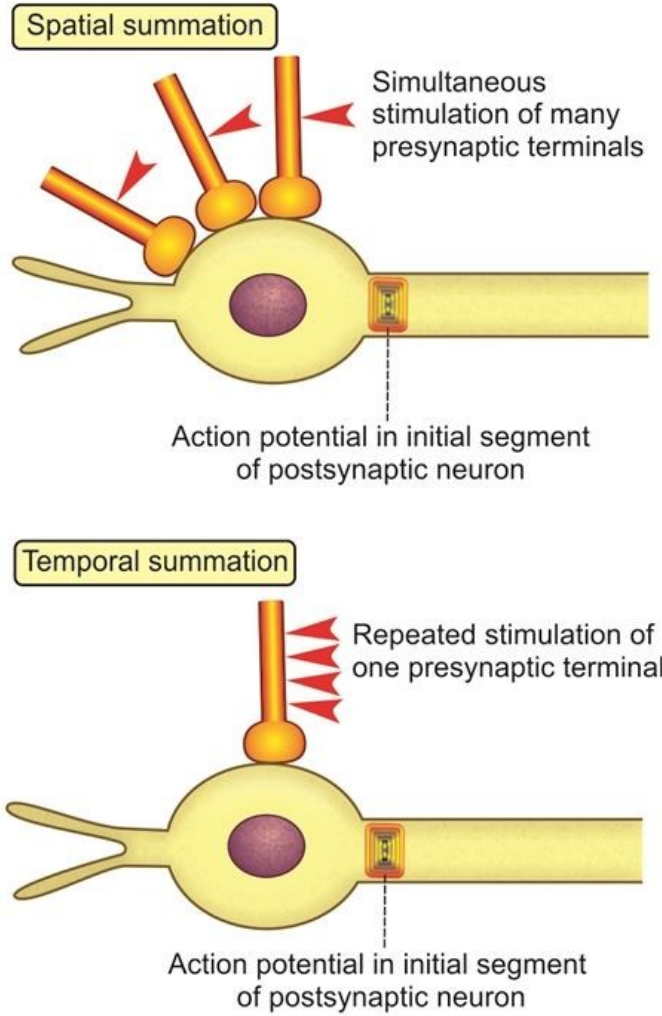
- Transmitters in most cases **hyperpolarize**.
- Increased conductance of the postsynaptic membrane to **Cl- (influx)** or possibly K+ (efflux).
- Transmitters include GABA, glycine.



▲ **Figure 5–3.2** Characteristics of an Inhibitory Postsynaptic Potential

Temporal Vs Spatial Summation of PSP





Neurotransmitter

- Synthesized in the presynaptic cell and stored in a vesicle
- Released from presynaptic cell upon stimulation
- It bind to its receptor (ionotropic or metabotropic) on postsynaptic cell and produces a physiological response
- It‘s Rapidly removed from synaptic cleft by re-uptake or removal by enzyme

- Based on their effect on Post-Synaptic cells we can classify them into :
- EXCITATORY NEUROTRANSMITTER
- INHIBITORY NEUROTRANSMITTER
- MODULATORY NEUROTRANSMITTER (Neuromodulators)

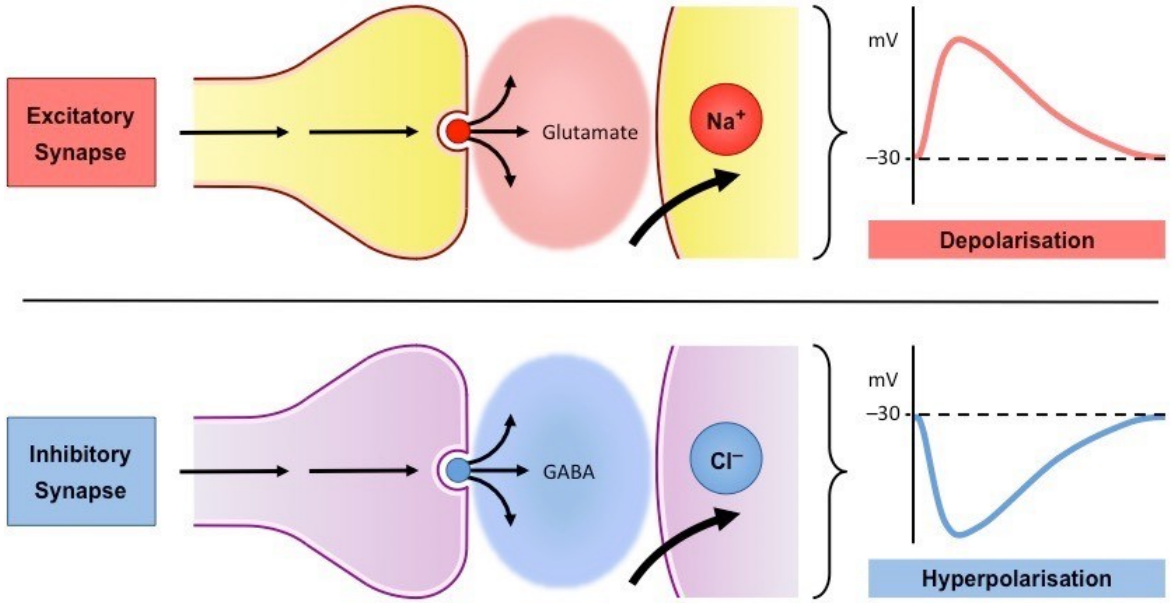
Excitatory and Inhibitory Neurotranmiter

Excitatory NT :

- Depolarizes the postsynaptic potential (closer to threshold) and causes the initiation and propagation of Action Potential
- Example : Glutamtate, Aspartate, Acetylcholine ,

Inhibitory NT :

- Hyperpolarizes the postsynaptic potential (away from threshold) , Action potential generation and propagation is inhibited
- Example : GABA , Glycine



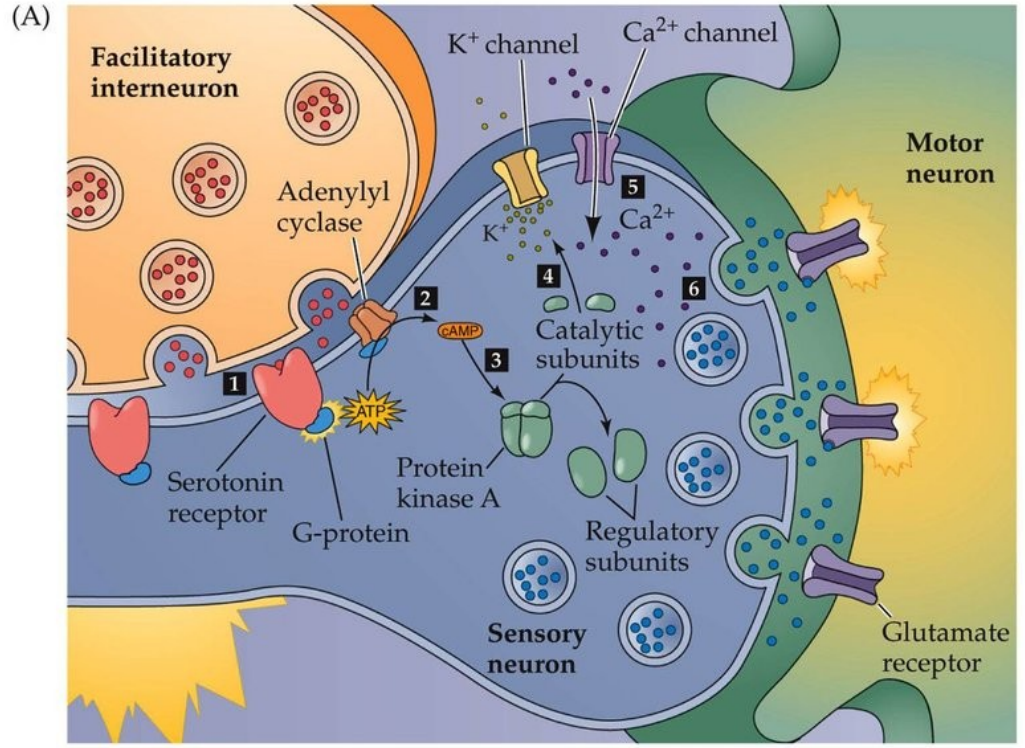
Modulatory synapse and neuromodulators

Modulatory Synapse- Neuromodulators :

- Are NOT directly involved in synaptic transmission

modulate the process

- Rather regulates or modifies the effect of other excitatory or inhibitory synapses by acting on their presynaptic or postsynaptic membrane
- Example : Serotonin, Histamine, Norepinephrin

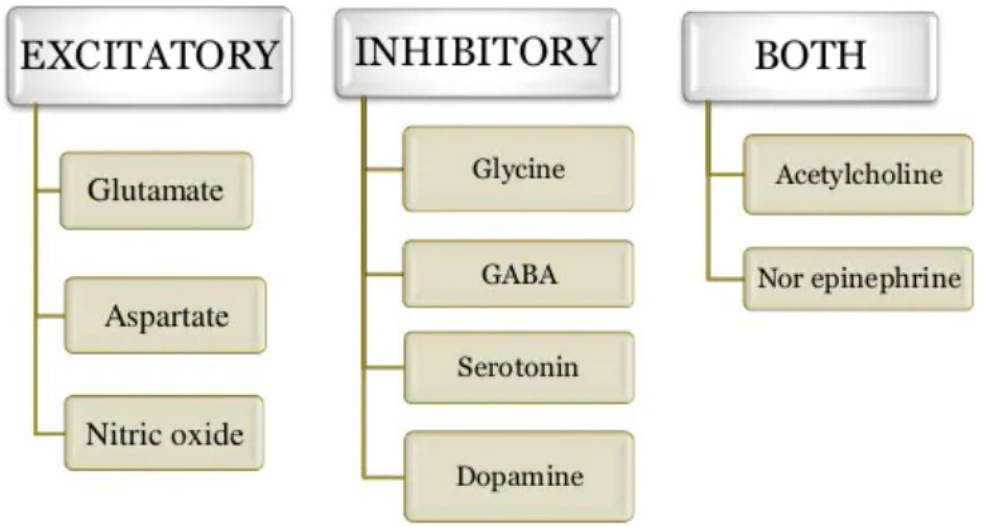


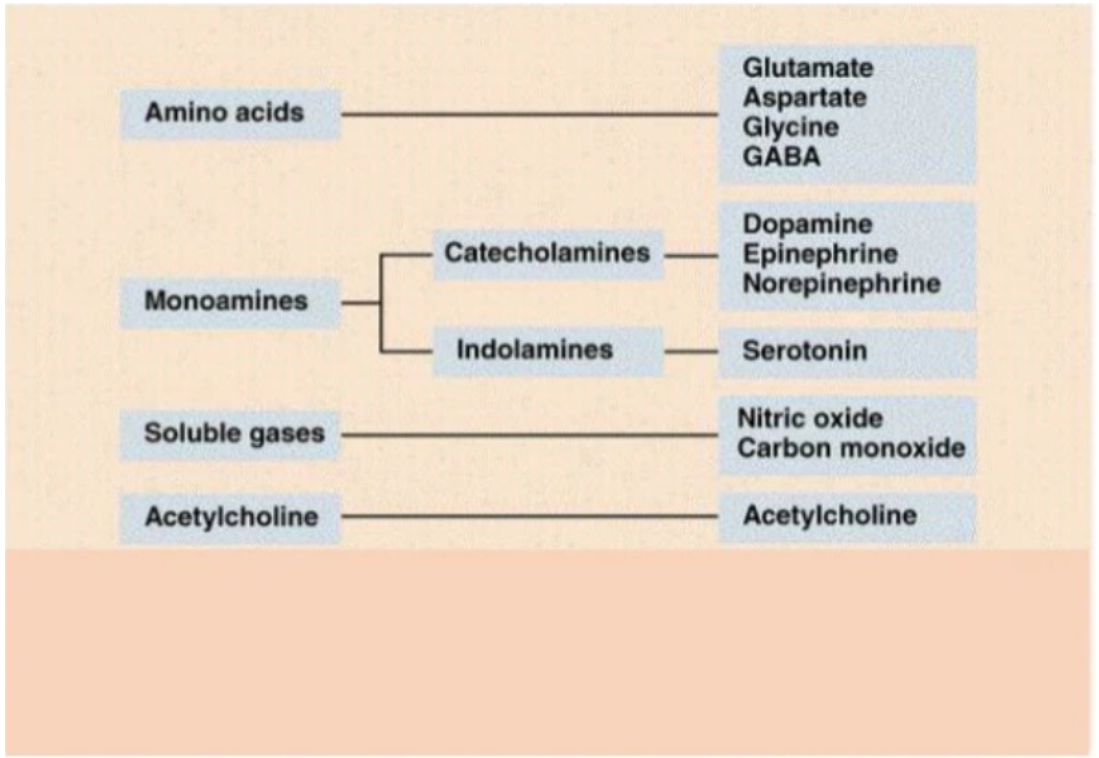
NEUROSCIENCE, Fourth Edition, Figure 8.5 (Part 1)

Classification based on chemical structure

Table 1-4 Classification of Neurotransmitter Substances

Choline Esters	Biogenic Amines	Amino Acids	Neuropeptides
Acetylcholine (ACh)	Dopamine	γ-Aminobutyric acid (GABA)	Adrenocorticotropin (ACTH)
	Epinephrine	Glutamate	Cholecystokinin
	Histamine	Glycine	Dynorphin
	Norepinephrine		Endorphins
	Serotonin		Enkephalins
			Glucose-dependent insulinotropic peptide (GIP)
			Glucagon
			Neurotensin
			Oxytocin
			Secretin
			Substance P
			Thyrotropin-releasing hormone (TRH)
			Vasopressin
			Vasoactive intestinal peptide (VIP)


EXCITATORY
Glutamate
Aspartate
Nitric oxide
INHIBITORY
Glycine
GABA
Serotonin
Dopamine
BOTH
Acetylcholine
Nor epinephrine


Amino acids
Glutamate
Aspartate
Glycine
GABA
Monoamines
Catecholamines
Dopamine
Epinephrine
Norepinephrine
Indolamines
Serotonin
Soluble gases
Nitric oxide
Carbon monoxide
Acetylcholine
Acetylcholine

neurotranmitters (Ionotropic and metabotropic receptors)

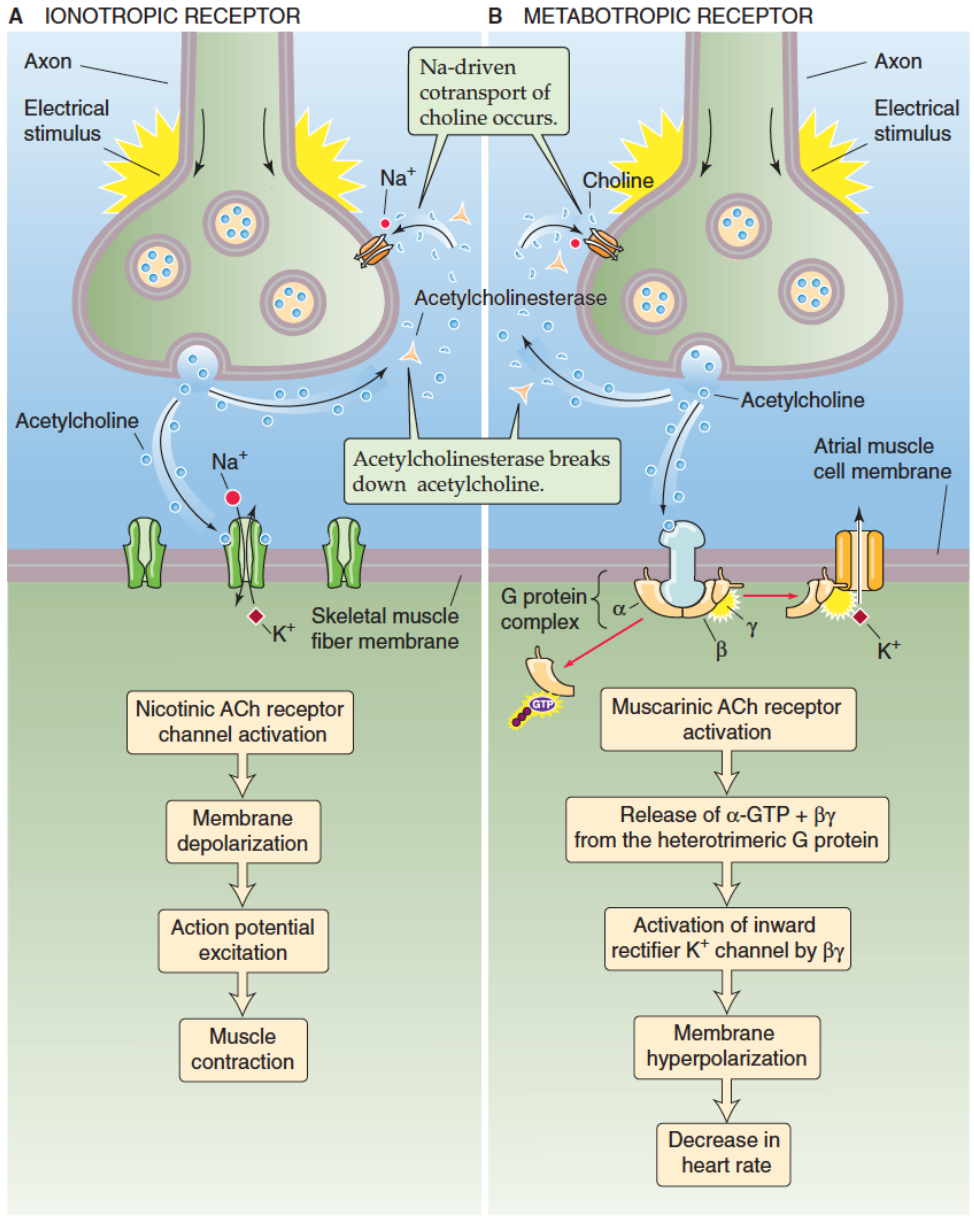


Figure 8-3 Ionotropic and metabotropic ACh receptors. **A,** This example illustrates a nicotinic AChR, which is a ligand-gated channel on the postsynaptic membrane. In a skeletal muscle, the end result is muscle contraction. **B,** This example illustrates a muscarinic AChR, which is coupled to a heterotrimeric G protein. In a cardiac muscle, the end result is decreased heart rate. Note that the presynaptic release of ACh is similar here and in **A**.

Glutamate

- The main **excitatory** transmitter in CNS – causes EPSP (specially in spinal cord and Cerebellum)
- Precursor to GABA
- Action terminated by presynaptic membrane reuptake of GABA
- Involved in most aspects of normal brain function including congnetion, memory and learning

There 4 subtypes of Glutamate receptors ;

❑ **3 ionotropic receptors (Ligand-gated Ion channels)**

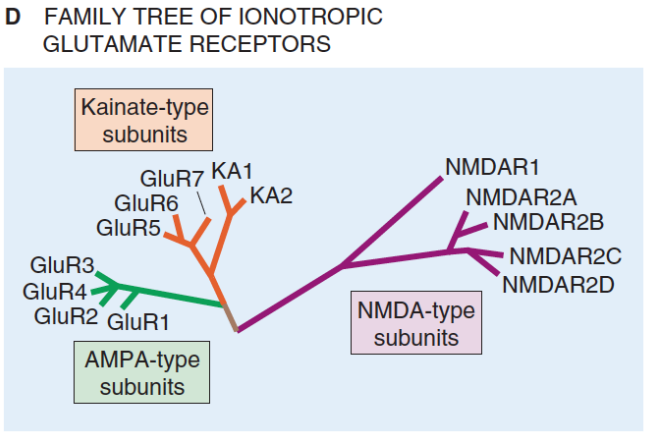
Quicker transmission of information

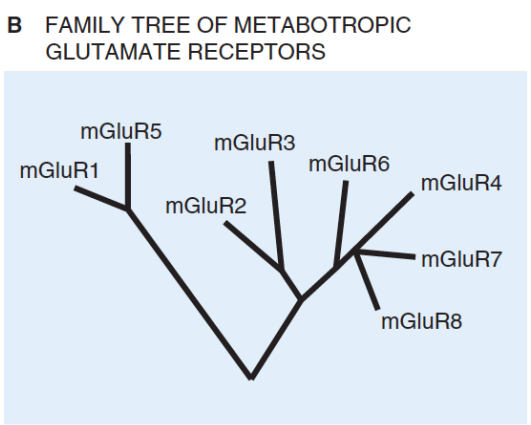
- AMPA
- Kainate
- NMDA

❑ **1 metabotropic receptors (GPCR)**

More prolonged stimulus

- 3 classes mGlutRs



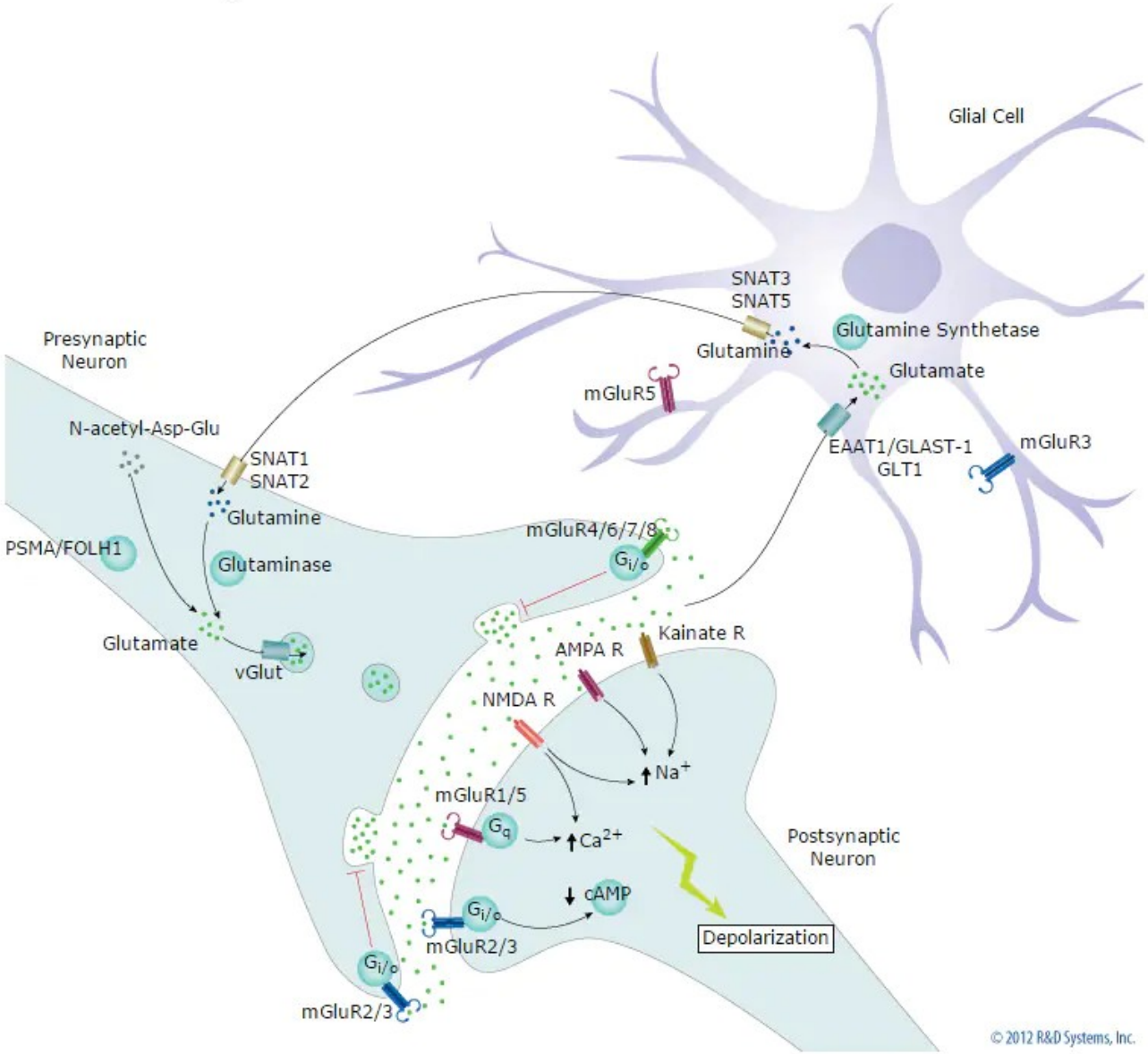


Ionotropic glutamate receptors

TABLE 13-2 Ionotropic Glutamate Receptors

Class of Receptor	Agonist	Antagonist	Kinetics	Permeability
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid	CNQX (6-cyano-7-nitroquinoxaline-2,3-dione) GYKI53655 (2,3-benzodiazepine derivatives)	Fast	Na^+, K^+ (Ca^{2+} in a few cases)
NMDA	*N*-Methyl-D-aspartate	APV (2-amino-5-phosphonovaleric acid)	Slow	Na^+, K^+, Ca^{2+}
Kainate	Kainic acid Domoic acid	CNQX UBP296 ((*RS*)-1-(2-amino-2-carboxyethyl)-3-(2-carboxybenzyl) pyrimidine-2,4-dione)	Fast	Na^+, K^+

Synaptic Neurotransmission Pathways: Glutamatergic Excitation



Glutamate

- Binding of glutamate to the AMPA and kainate receptors produces EPSPs.
- Binding of glutamate to the NMDA receptor has special properties that allow it not only to regulate the entry of ions, but also to allow those ions to act as second messengers to change the biochemical and structural properties of the cell.
- These changes are important for the production of new memories, as they initiate a cascade of events that leads to changes in the shape and number of spines at synaptic sites.

Glutamate

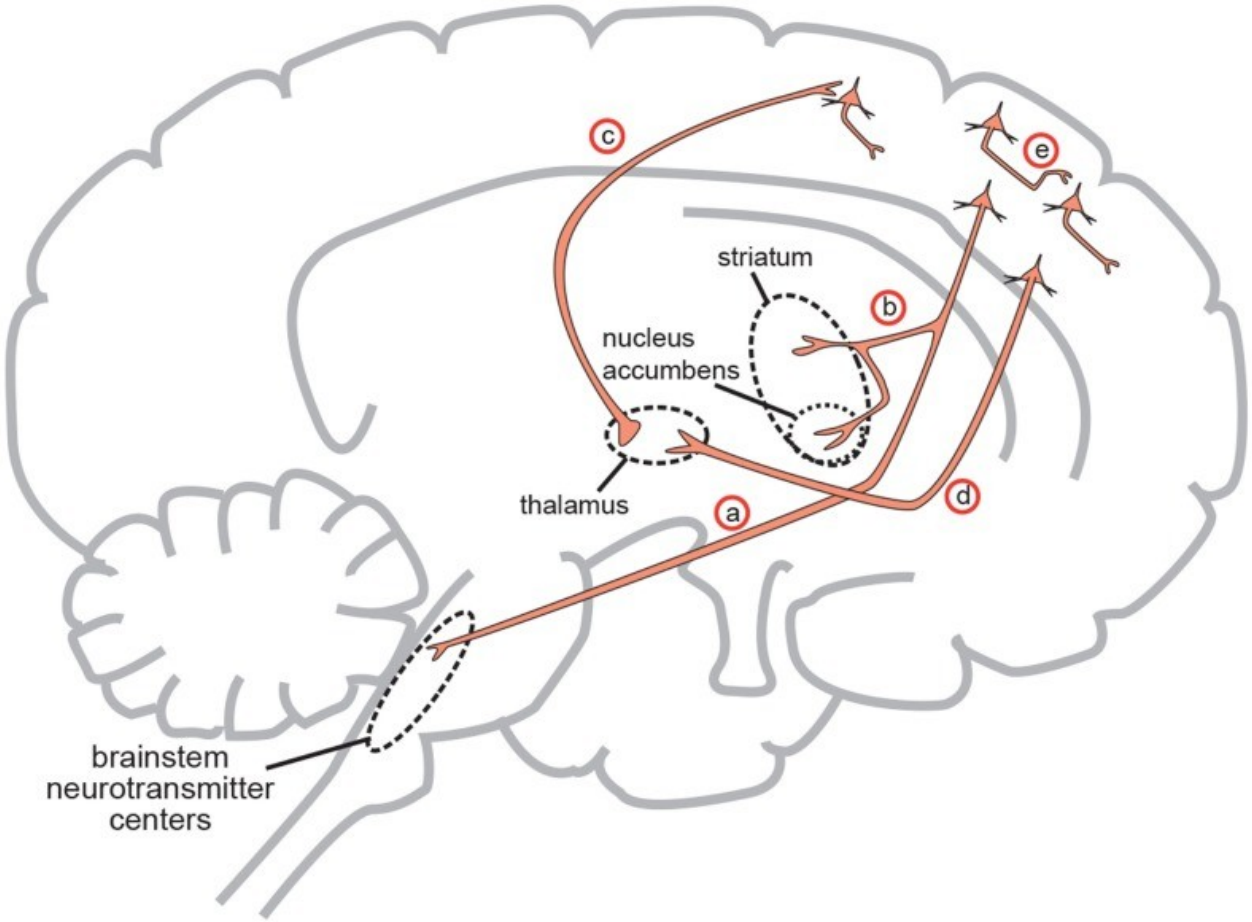
- Overactivity of glutamate in the brain is thought to play a role in the development of epilepsy.
- Too much glutamate can produce excitotoxicity, which is excessive activity of receptors that can literally excite neurons to death.
- Excitotoxicity appears to be an unfortunate consequence of a particular form of brain damage, known as ischemia.

- Disease associated with Glutamate receptor mutation or Autoantigen/antibody interaction with glutamate receptors :

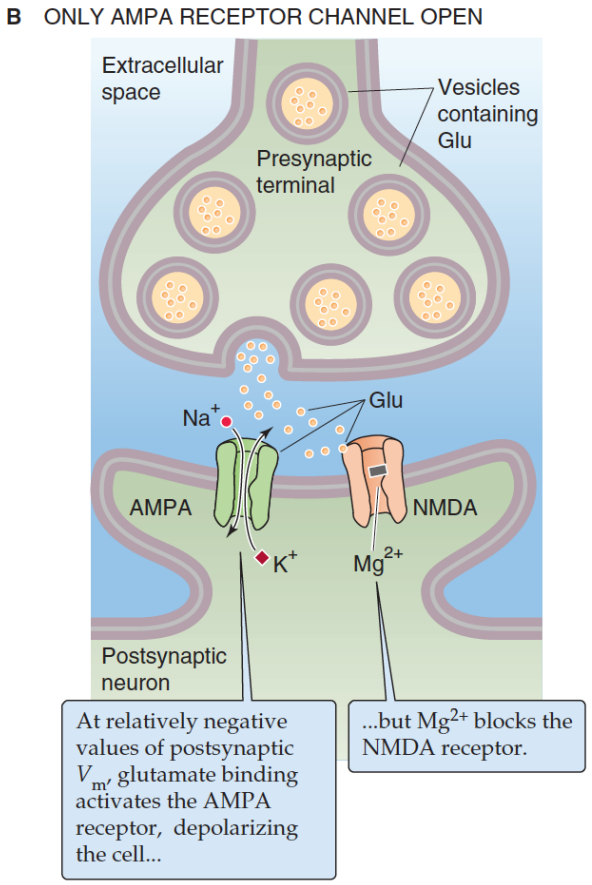
Autism, Hungtington disease , Diabetes , ADHD , Parkinson disease , Epilepsy ,

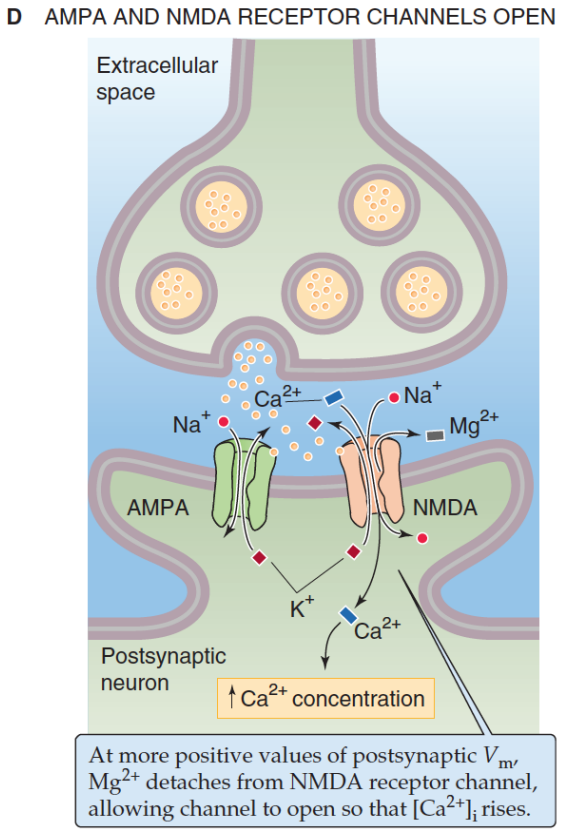
Mood disorders (depression, schizophrenia)

Key Glutamate Pathways



NMDA receptors is also voltage-dependent

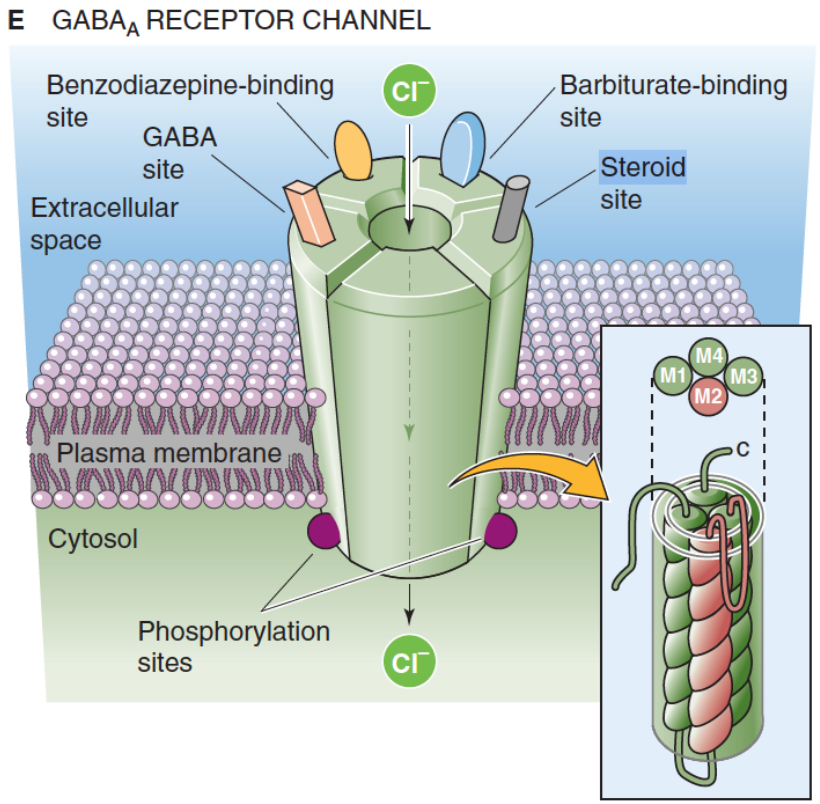




GABA

The major **inhibitory** transmitters of the central nervoussystem.

- GABA predominates in the brain. (40% receptors)
- Utilize Cl- channels to initiate IPSP.
- Action terminated by reuptake by the presynaptic membrane.



- **<u>There are two main types of GABA receptors</u>**:
- $GABA_a$ is an **ionotropic receptor** (linked to Cl- channel → hyperpolarizes (inhibits))
- Note : GABAa is site of action of **barbiturates (duration of opening)** and **benzodiazepines (frequency of opening)**
- $GABA_b$ is **metabotropic receptor** (coupled with G-protein to K+ channel → hyperpolarizes (inhibits))

- Both appear to be important in dampening oscillatory, reverberatory excitation between the thalamus and cortex

Hungtington disease

- **Huntington's disease** is associated with GABA deficiency.
- The disease is characterized by hyperkinetic choreiform movements related to a deficiency of GABA in the projections from the striatum to the globus pallidus.
- The characteristic uncontrolled movements are, in part, attributed to lack of GABA-dependent inhibition of neural pathways

Dopamine

Dopaminergic System

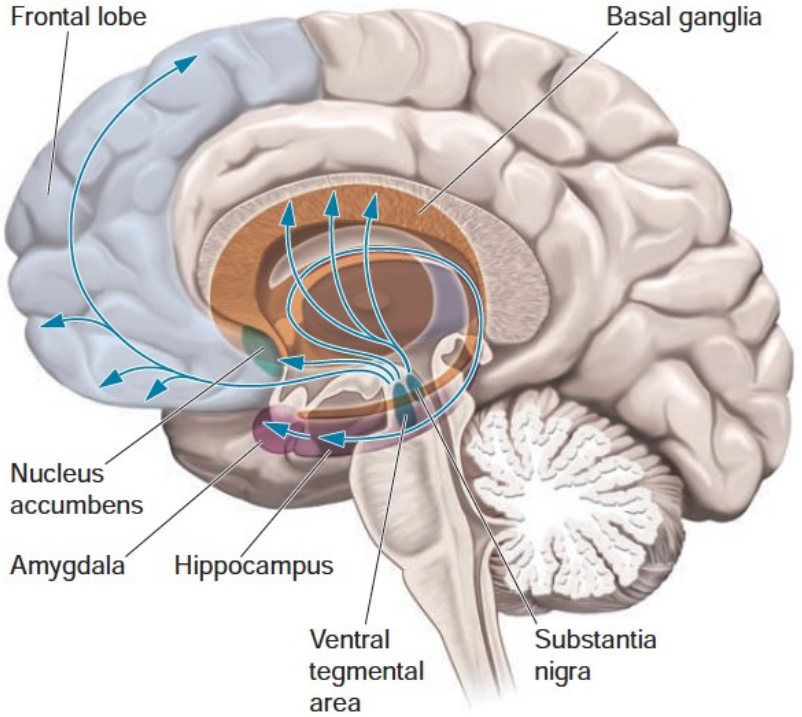
- Dopamine is the main neurotransmitter used in the dopaminergic system.

- There are actually three dopaminergic subsystems:

1. the nigrostriatal
2. the mesolimbic
3. the mesocortical

- These subsystems are differentiated by

1. the location of their cell bodies
2. the regions of the brain to which they project
3. the effect they have on behavior



Dopamine receptors

Dopamine receptors				
D1-like - Gαs coupled		**D2-like** - Gαi/o coupled		
D1	**D5**	**D2**	**D3**	**D4**
Substantia nigra Nucleus accumbens Olfactory bulb Lower levels: Cerebellum Hippocampus Thalamus Kidney	Substantia nigra Hypothalamus Kidney Heart Sympathetic ganglia	Substantia nigra Nucleus accumbens Ventral tegemental area Lower levels: Heart Blood vessels Adrenal glands Sympathetic ganglia	Olfactory bulb Nucleus accumbens	Heart Blood vessels Substantia nigra Hippocampus Amygdala Gastrointestinal tract

Nigrostiatal system

The nigrostriatal system

- The cell bodies of this system are located in the **substantia nigra** and project to the neostriatum (i.e., the caudate nucleus and putamen, also known as the basal ganglia).
- This subsystem regulates the selection, initiation, and cessation of **motor behaviors**.
- It is the subsystem that is affected by Parkinson's disease.
- In that disorder, the dopaminergic neurons in the substantia nigra die, leading to difficulties with motor control.

Mesolimbic system

The mesolimbic system

- It has its cell bodies in the ventral tegmental area.

- It projects to several parts of the limbic system, including

1. nucleus accumbens
2. ventral portions of the striatum
3. amygdala
4. hippocampus
5. prefrontal cortex

Mesolimbic system

- The cell bodies are located in the ventral tegmental area.
- The axons of these cells project to much of the cortex, especially motor and premotor cortex, as well as prefrontal cortex, where they influence a variety of mental functions.
- One of these functions is working memory, which allows us to keep information “online” for performance of tasks, planning, and strategy preparation for problem solving.