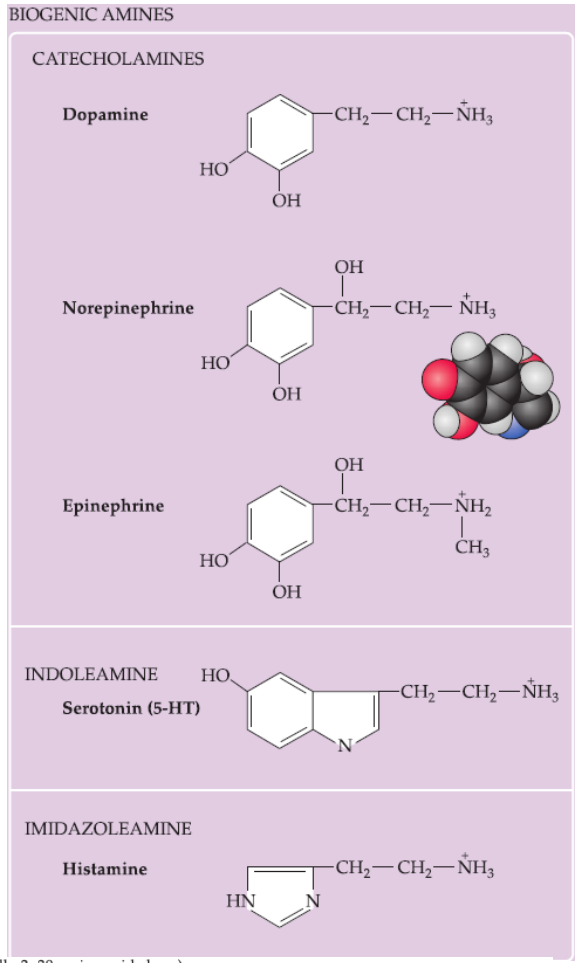
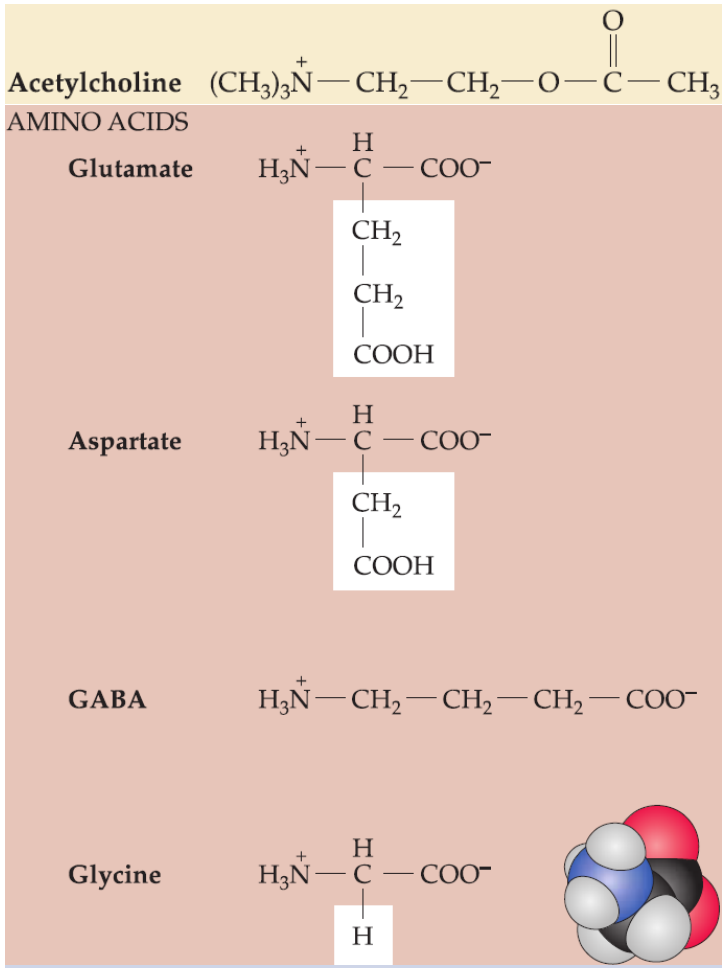
Part 3, Neural Signaling

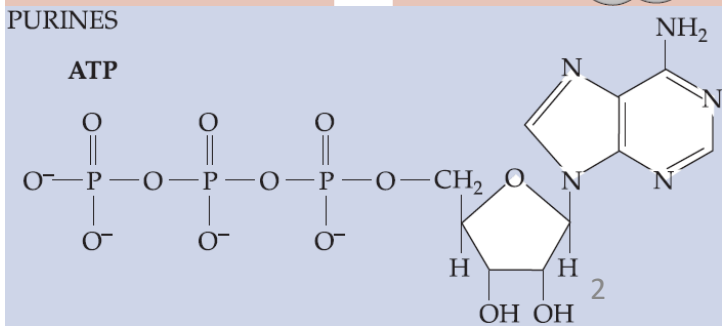
3.4. Neurotransmitters and their receptors

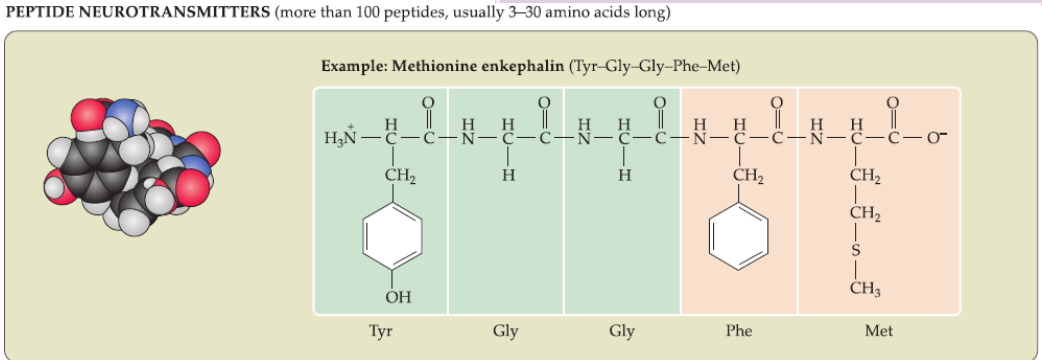
Categories of neurotransmitters

- **Small-molecule transmitters:**
  - acetylcholine.
  - amino acids.
  - purines.
  - **biogenic amines**.
- **Neuropeptides**: 3~30 a.a.



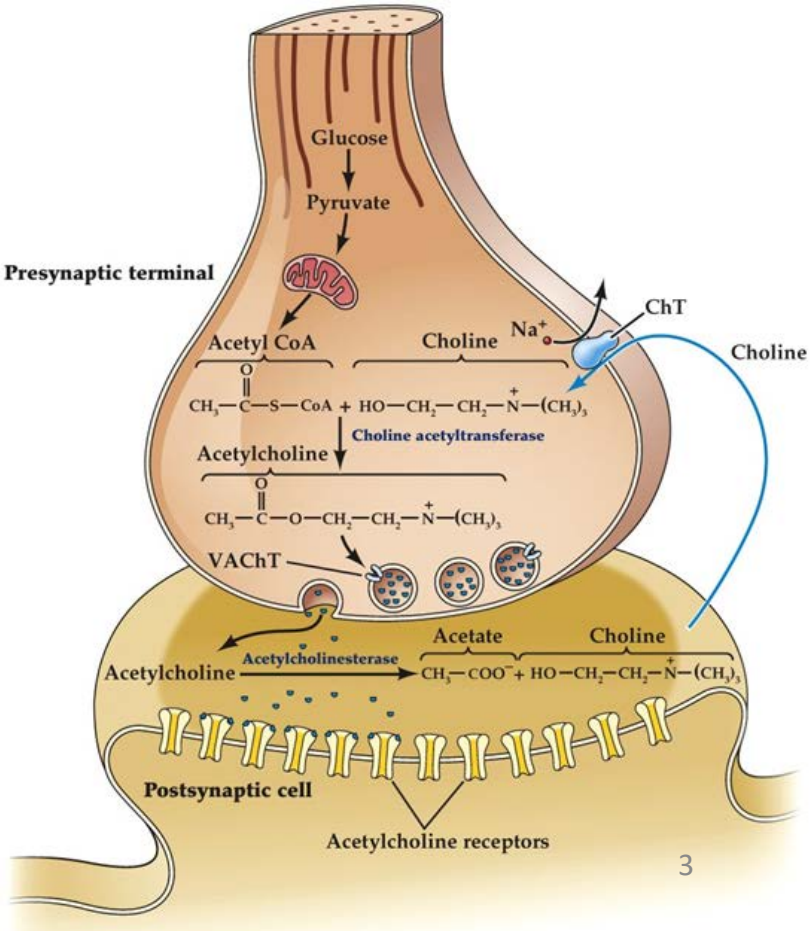






Acetylcholine (ACh)

- Acetylcholine (ACh) was the first substance identified as a neurotransmitter.
  - How?
- ACh serves as a transmitter at skeletal neuromuscular junctions, neuromuscular synapse between the vagus nerve and cardiac muscle fibers, synapses in the ganglia of the visceral motor system, and in the central nervous system.
- Acetylcholine is synthesized in nerve terminals from the precursors acetyl coenzyme A (acetyl CoA, which is synthesized from glucose) and choline, in a reaction catalyzed by choline acetyltransferase (CAT).
- After synthesis in the cytoplasm of the neuron, a vesicular ACh transporter (V AChT) loads approximately 10,000 molecules of ACh into each cholinergic vesicle.



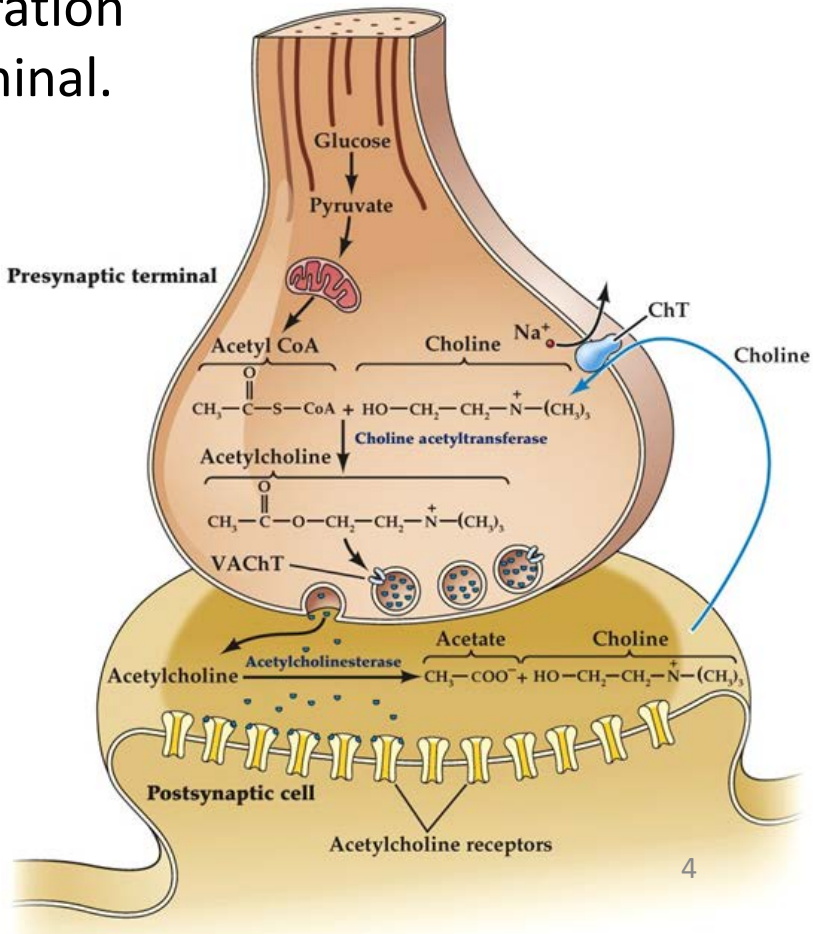
Acetylcholine (ACh)

- The postsynaptic actions of ACh at many cholinergic synapses (the neuromuscular junction in particular) is not terminated by reuptake but by a powerful hydrolytic enzyme, **acetylcholinesterase** (**AChE**).

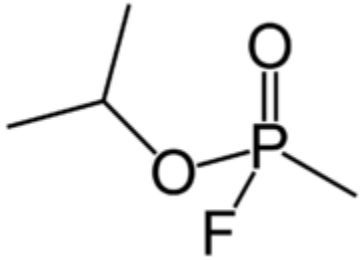
- This enzyme is concentrated in the synaptic cleft, ensuring a rapid decrease in ACh concentration after its release from the presynaptic terminal.

- AChE has a very high catalytic activity (about 5000 molecules of ACh per AChE molecule per second) and rapidly hydrolyzes ACh into acetate and choline.

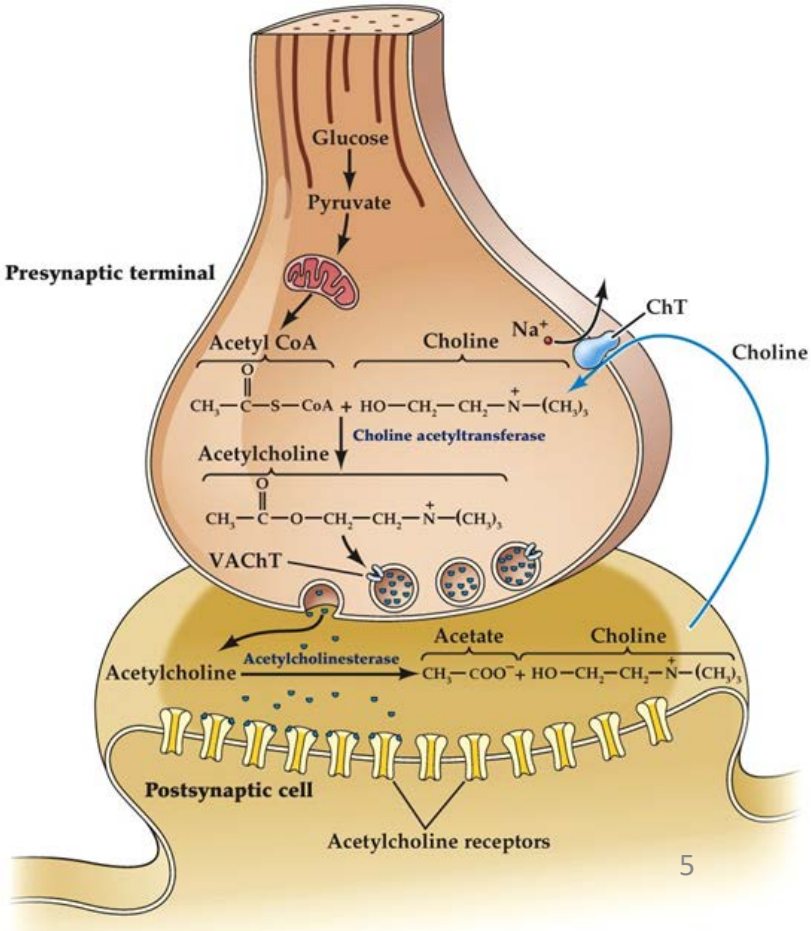
- The choline produced by ACh hydrolysis is recycled by being transported back into nerve terminals, where it is used to resynthesize ACh. By a high-affinity, Na^+-dependent choline co-transporter (ChT).



Drugs interacting with cholinergic enzymes



- Organophosphates: including some potent chemical warfare agents such as “Sarin”, which has been classified as a weapon of mass destruction.
- Organophosphates can be lethal because they inhibit AChE, allowing ACh to accumulate at cholinergic synapses. This buildup of ACh depolarizes the postsynaptic cell and renders it refractory to subsequent ACh release, causing neuromuscular paralysis and other effects.
- The high sensitivity of insects to AChE inhibitors has made organophosphates popular insecticides.
- Sarin was made notorious in 1995 when a group of terrorists released this nerve gas in Tokyo's underground rail system.

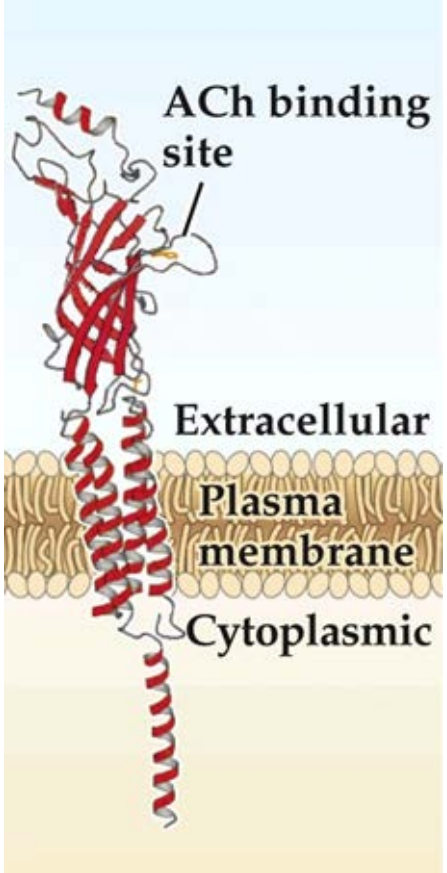


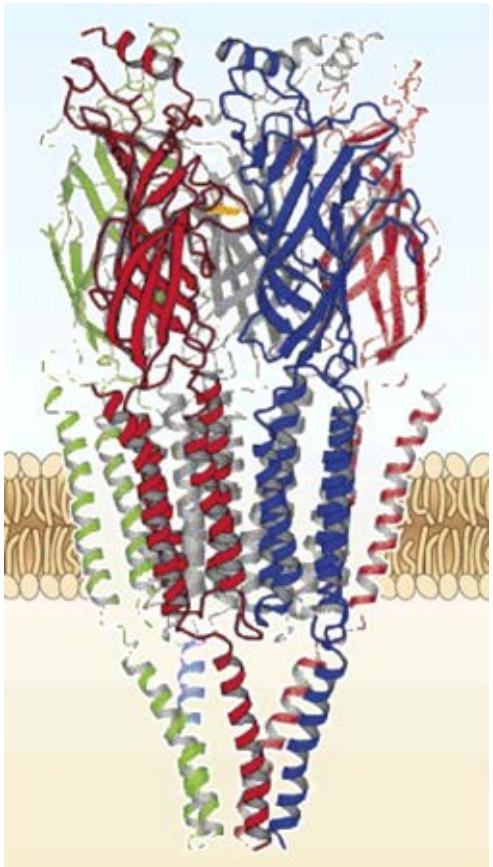
Acetylcholine receptors

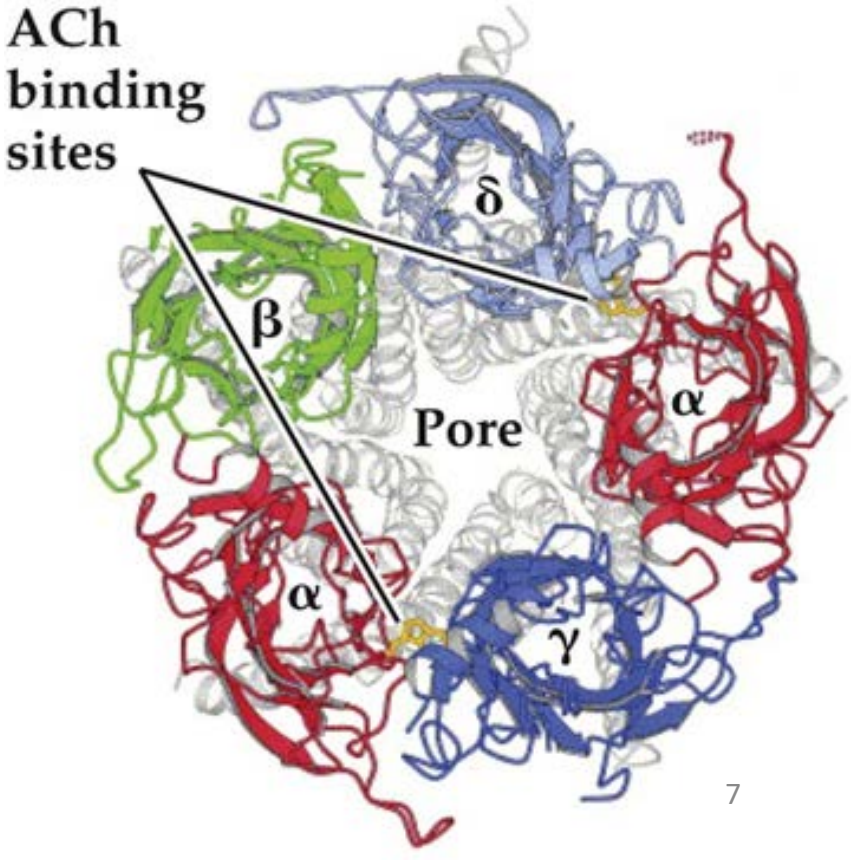
- Many of the postsynaptic actions of ACh are mediated by the **nicotinic ACh receptor (nAChR)**, so named because the CNS stimulant nicotine also binds to these receptors.
  - nAChRs are nonselective cation channels that generate excitatory postsynaptic responses.
  - A number of toxins specifically bind to and block nicotinic receptors. The availability of these highly specific ligands--particularly a component of snake venom called α-bungarotoxin--has provided a valuable way to isolate and purify nAChRs.
  - Nicotinic receptors are large protein complexes consisting of five subunits.
  - Neuromuscular junction nAChR contains two α subunits, which are combined with up to three other types of subunits--β, δ, and either γ or ε--in the ratio 2α:1β :1δ:1γ/ε.
    - Each of the α subunits has a binding site that binds a single molecule of ACh. Both ACh binding sites must be occupied for the receptor to be activated, so that only relatively high concentrations of ACh activate these receptors.
    - These subunits also bind other ligands, such as nicotine and α-bungarotoxin.
  - Neuronal nAChRs differ from those of muscle in that they (1) lack sensitivity to α-bungarotoxin, and (2) comprise only two receptor subunit types (α and β), which are present in a ratio of 3α:2β.

Structure of the nACh receptor

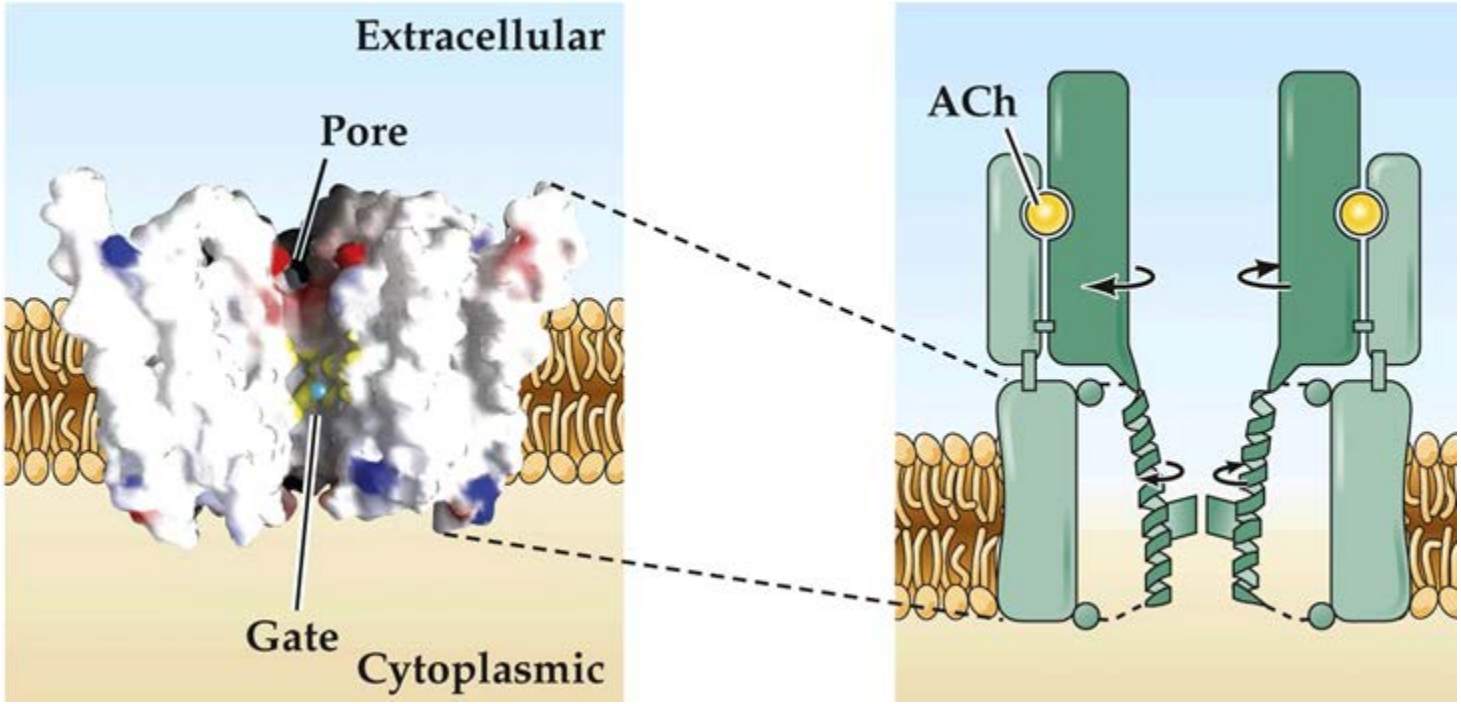
- Each subunit of the receptor contains a large extracellular region (which in α subunits contains the ACh binding site) as well as four membrane-spanning domains.
- The transmembrane domains of the five individual subunits together form a channel with a central membrane-spanning pore.







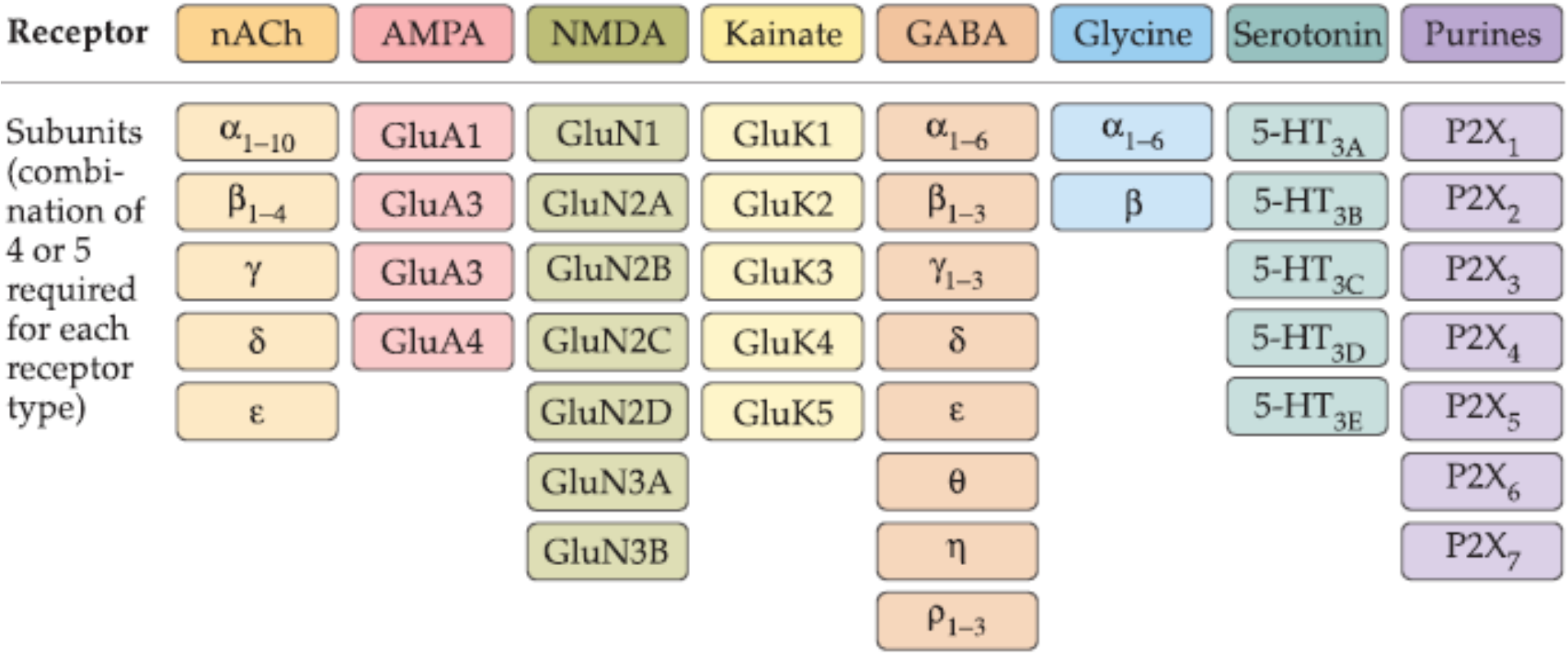
Structure of the nACh receptor



- The width of this pore is substantially larger than that of the pores of voltage-gated ion channels, consistent with the relatively poor ability of nACh receptors to discriminate between different cations. Within this pore is a constriction that may represent the gate of the receptor.

- Binding of ACh to the α subunits is thought to cause a conformational change that rearranges the receptor transmembrane domains, thereby opening the gate and permitting ions to diffuse through the channel pore.

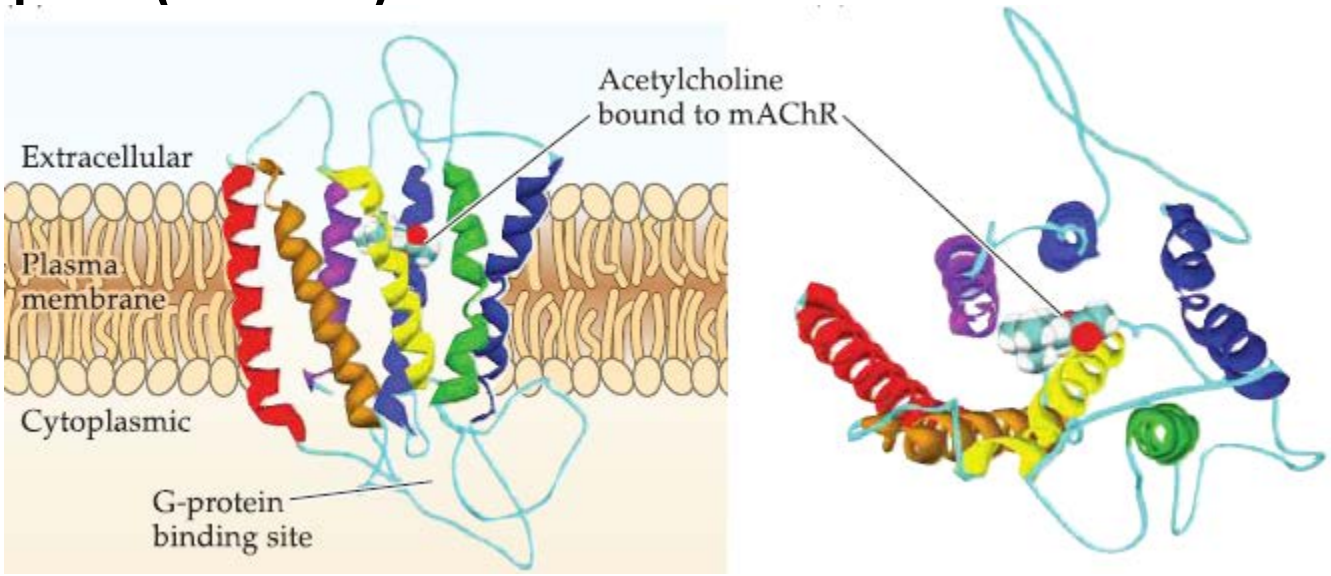
Subunits forming ionotropic neurotransmitter receptors



Muscarinic ACh receptors (mAChRs)

- A second class of ACh receptors is activated by muscarine, a poisonous alkaloid found in some mushrooms, and thus they are referred to as **muscarinic ACh receptors (mAChRs)**.

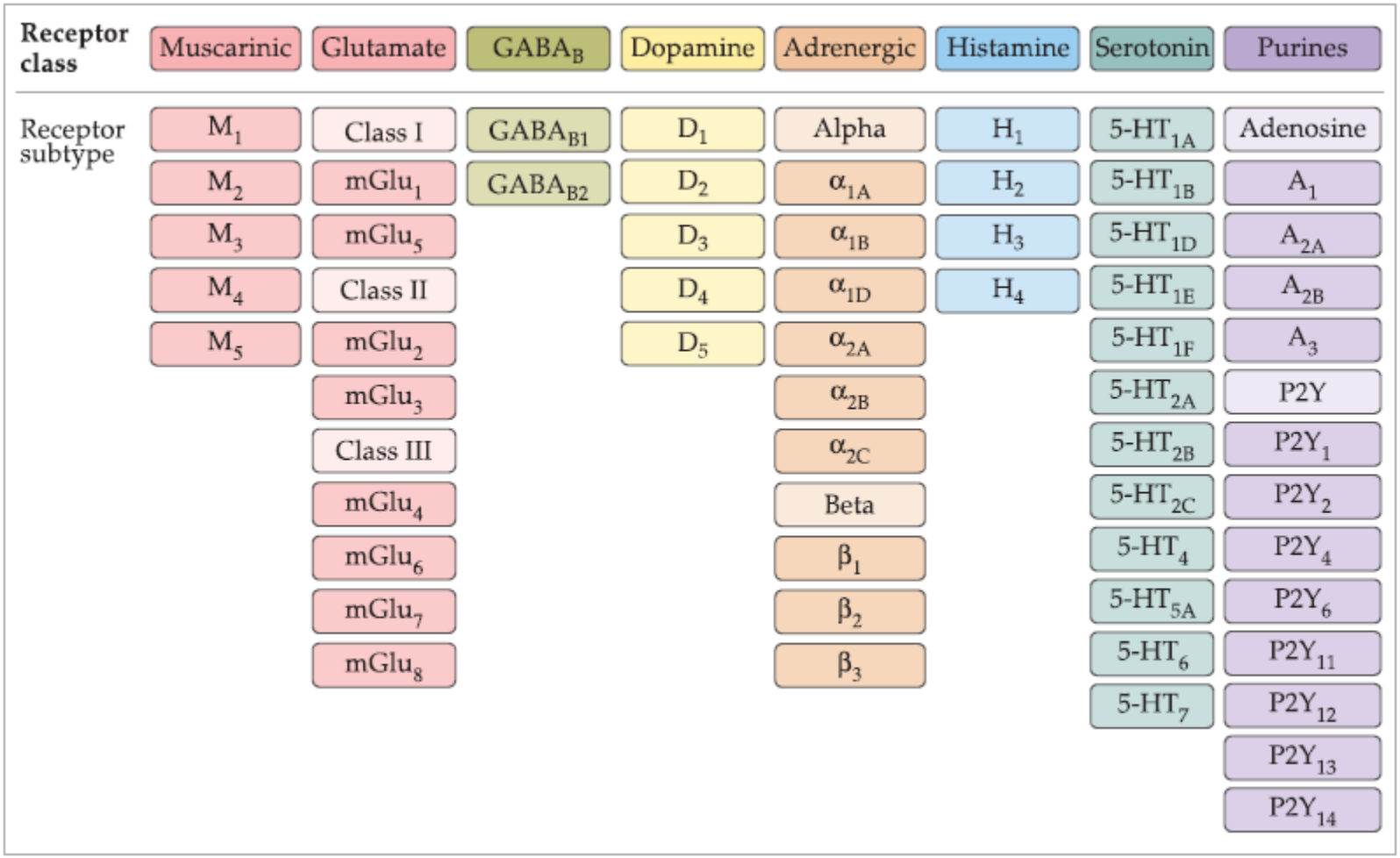
- mAChRs are metabotropic and mediate most of the effects of ACh in the brain.



- Like other metabotropic receptors, mAChRs have seven helical membrane-spanning domains.
- ACh binds to a single binding site on the extracellular surface of the mAChR; this binding site is formed from loops that connect several of the transmembrane helices.
- Binding of ACh to this site causes a conformational change that permits G-proteins to bind to the cytoplasmic domain of the mAChR.

Muscarinic ACh receptors (mAChRs)

- Five subtypes of mAChR are known and are coupled to different types of G-proteins, thereby causing a variety of slow postsynaptic responses.



Muscarinic ACh receptors (mAChRs)

- Muscarinic ACh receptors are highly expressed in the striatum and various other forebrain regions, where they activate inward rectifier K^+ channels or Ca^{2+}-activated K^+ channels, thereby exerting an inhibitory influence on dopamine-mediated motor effects.

- In other parts of the brain, such as the hippocampus, mAChRs are excitatory and act by closing KCNQ-type K^+ channels.

- These receptors are also found in the ganglia of the peripheral nervous system.

- mAChRs mediate peripheral cholinergic responses of autonomic effector organs such as heart, smooth muscle, and exocrine glands and are responsible for the inhibition of heart rate by the vagus nerve.

- Numerous drugs act as mAChR agonists or antagonists; mAChR blockers that are therapeutically useful include atropine (used to dilate the pupil), scopolamine (effective in preventing motion sickness), and ipratropium (useful in the treatment of asthma).

Glutamate

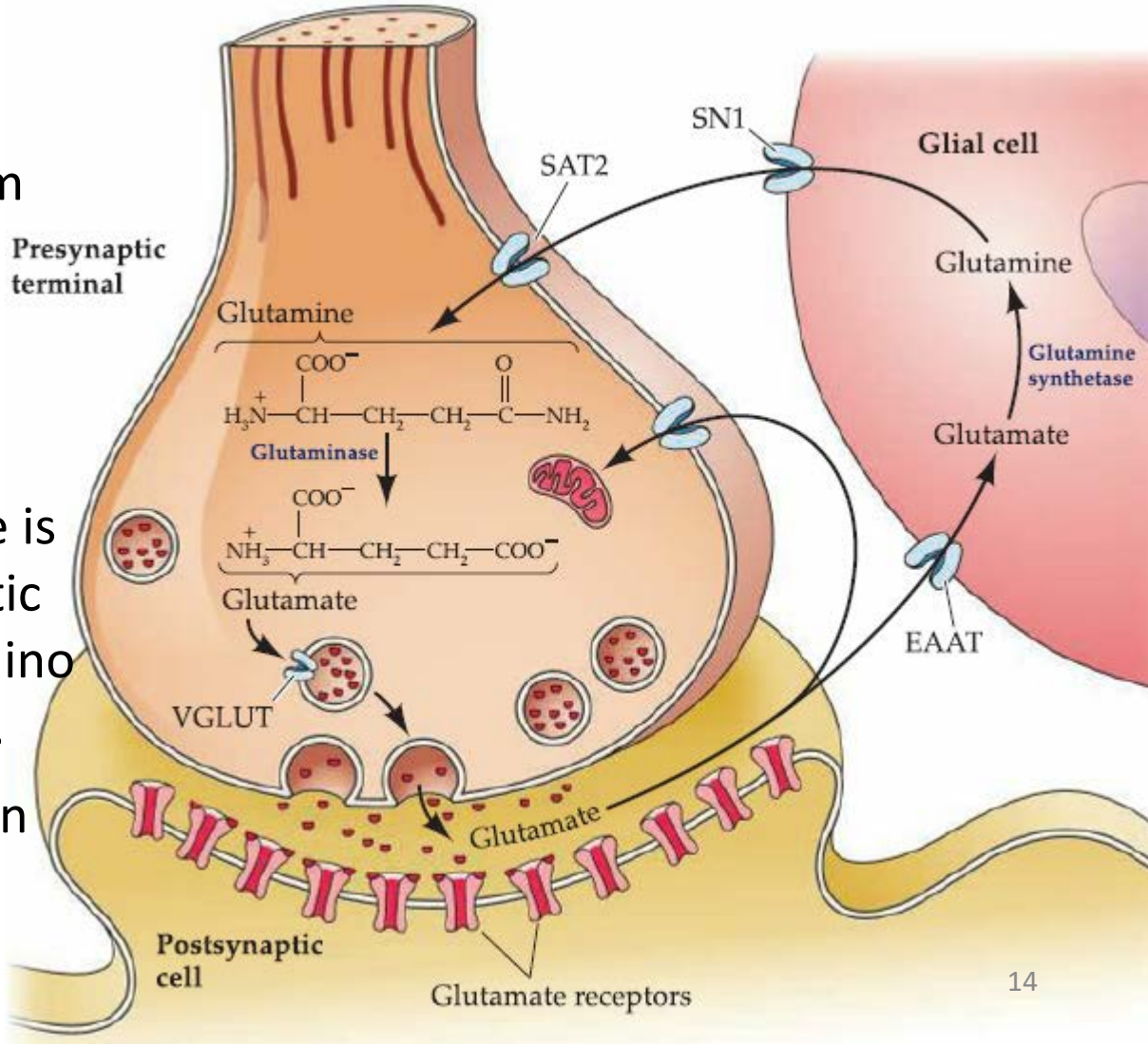
- Glutamate is the most important transmitter for normal brain function.

- Nearly all excitatory neurons in the central nervous system are glutamatergic, and it is estimated that over half of all brain synapses release this neurotransmitter.

- Glutamate is a nonessential amino acid that does not cross the blood-brain barrier and therefore must be synthesized in neurons from local precursors.

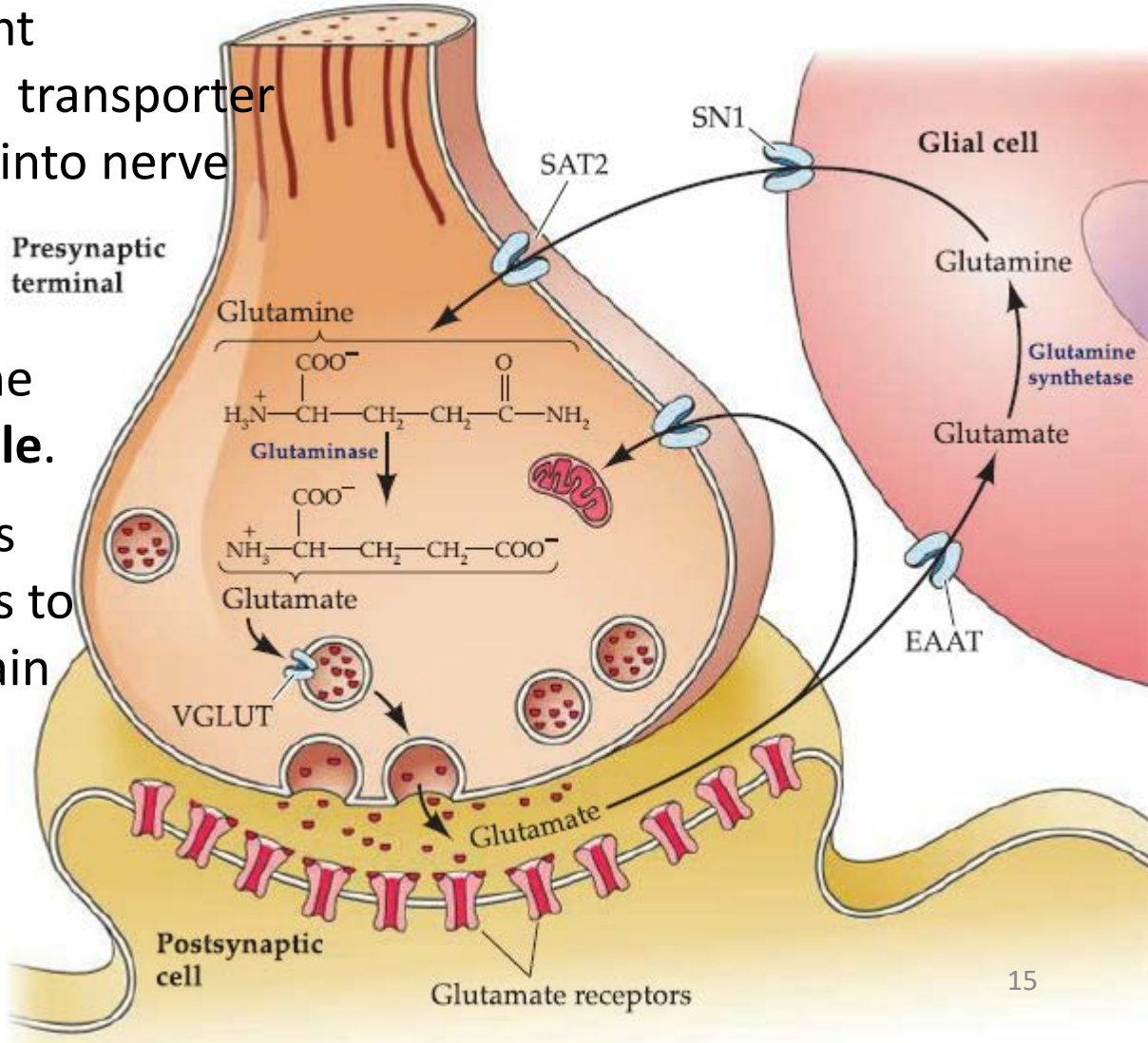
Glutamate

- The most prevalent precursor for glutamate synthesis is glutamine, which is taken up into presynaptic terminals by the system A transporter 2 (SAT2) and is then metabolized to glutamate by the mitochondrial enzyme glutaminase.
- Glutamate synthesized in the presynaptic cytoplasm is packaged into synaptic vesicles by vesicular glutamate transporters (VGLUT).
- Once released, glutamate is removed from the synaptic cleft by the excitatory amino acid transporters (EAATs).
- Some EAATs are present in glial cells and others in presynaptic terminals.



Glutamate

- Glutamate transported into glial cells via EAATs is converted into glutamine by the enzyme glutamine synthetase.
- Glutamine is then transported out of the glial cells by a different transporter, the system N transporter 1 (SN1), and transported into nerve terminals via SAT2.
- This overall sequence of events is referred to as the **glutamate-glutamine cycle**.
- This cycle allows glial cells and presynaptic terminals to cooperate both to maintain an adequate supply of glutamate for synaptic transmission and to terminate postsynaptic glutamate action.



Glutamate receptors

- There are several types of ionotropic glutamate receptors: **AMPA receptors**, **NMDA receptors**, and **kainate receptors** which are named after the agonists that activate them: AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate), NMDA (*N*-rnethyl-D-aspartate), and kainic acid.

- All of these receptors are glutamate-gated cation channels that allow the passage of Na^+ and K^+, similar to the nAChR. Hence AMPA, kainate, and NMDA receptor activation always produces excitatory postsynaptic responses.

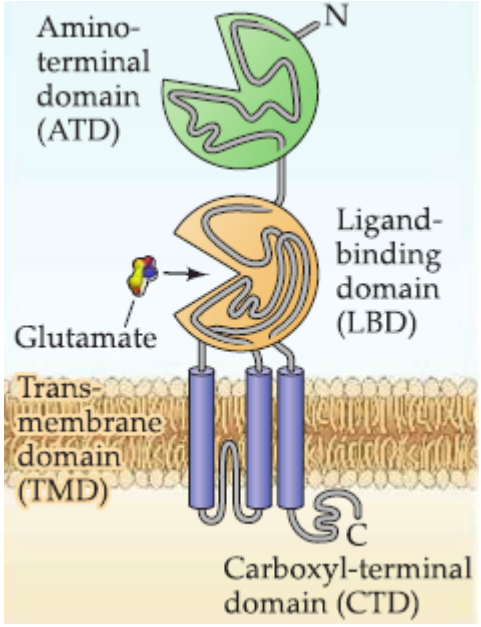
- Most central synapses possess both AMPA and NMDA receptors.

- Antagonist drugs that selectively block either AMPA or NMDA receptors are often used to identify synaptic responses mediated by each receptor type.

AMPA receptors

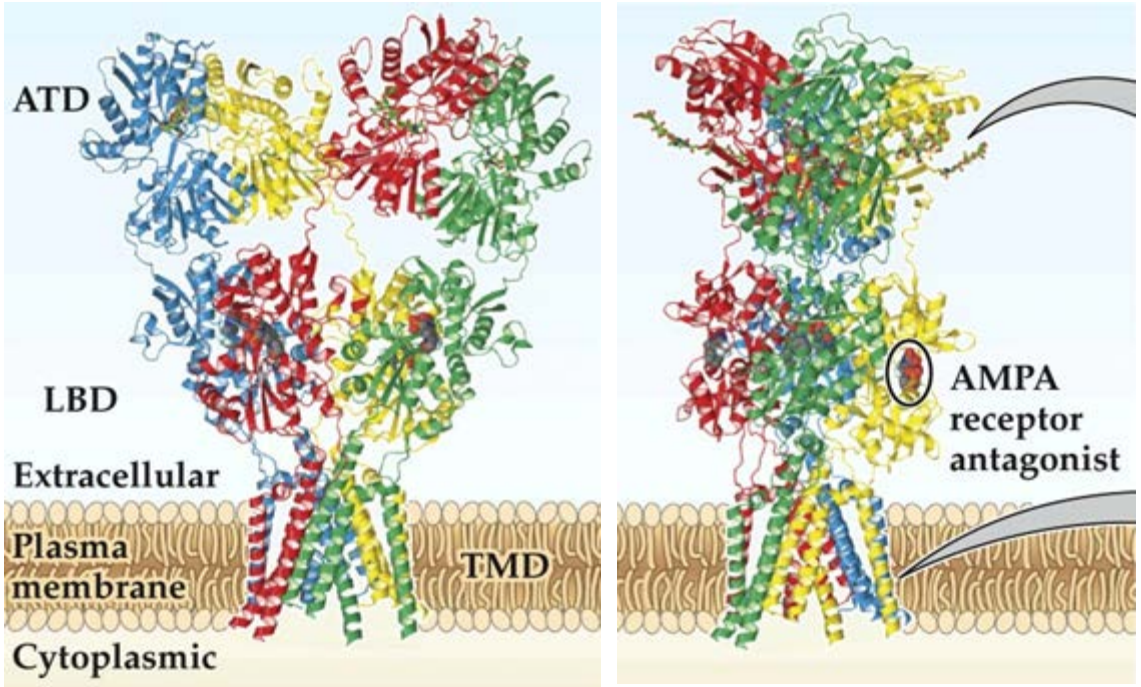
- Like all ionotropic receptors, AMPA receptors are composed of multiple subunits. The four different AMPA receptor subunits are designated GluA1 to GluA4.

- Each subunit has several different domains, including an extracellular ligand-binding domain that is responsible for binding glutamate, and a transmembrane domain that forms part of the ion channel.



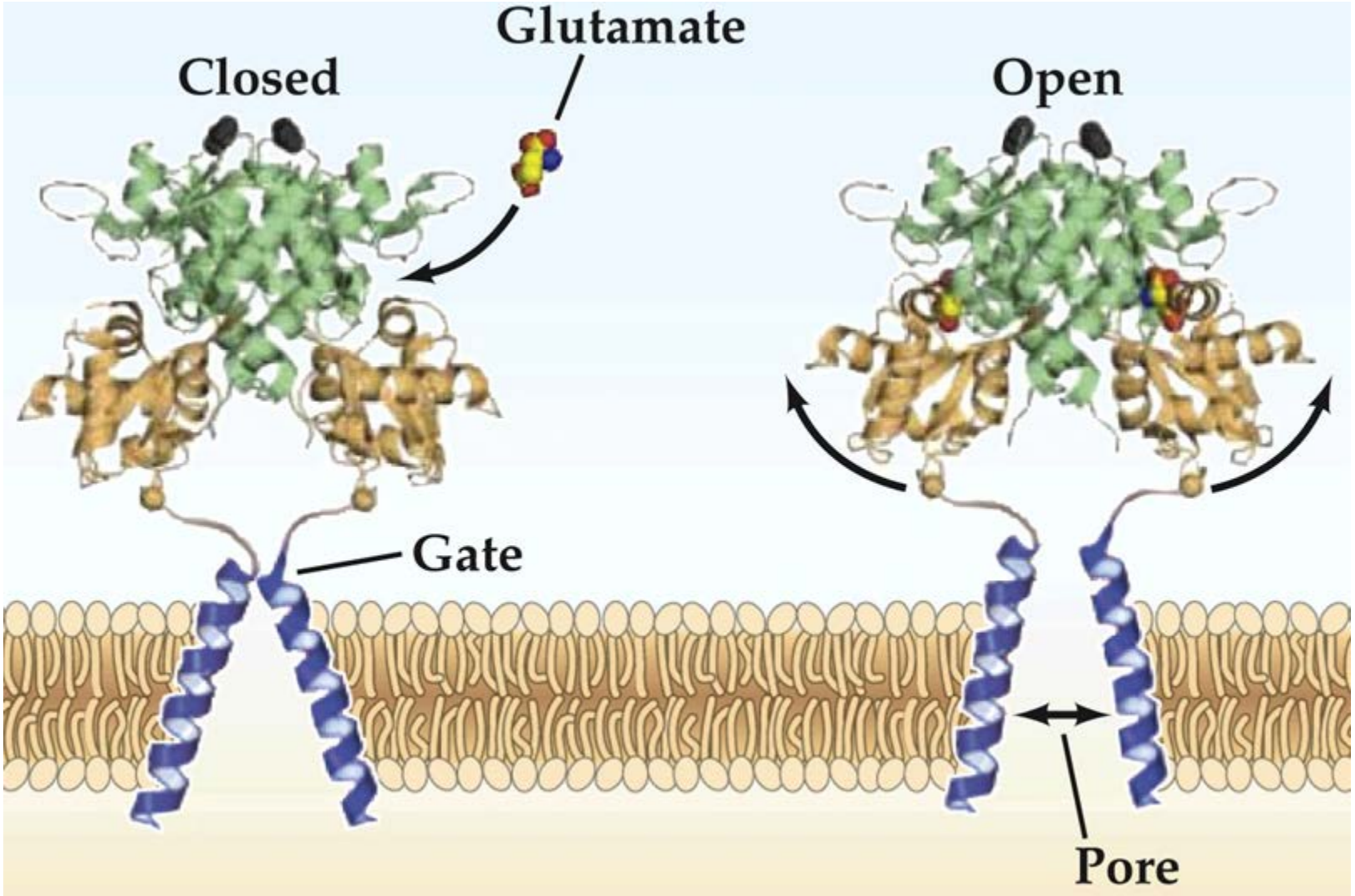
AMPA receptors

- Four different AMPA receptor subunits (GluA1 to GluA4) are organized into the tetrameric structure.
- The extracellular structure of AMPA receptors is asymmetrical and therefore looks different when viewed from its front and side surfaces.
  - The AMPA receptor is Y-shaped, with the large extracellular domains of the subunits narrowing down as the receptor passes through the plasma membrane.
  - After rotating the receptor by 90 degrees, the extracellular ligand-binding domains have a characteristic “clamshell” shape, with glutamate and other ligands binding within the opening of the clamshell.



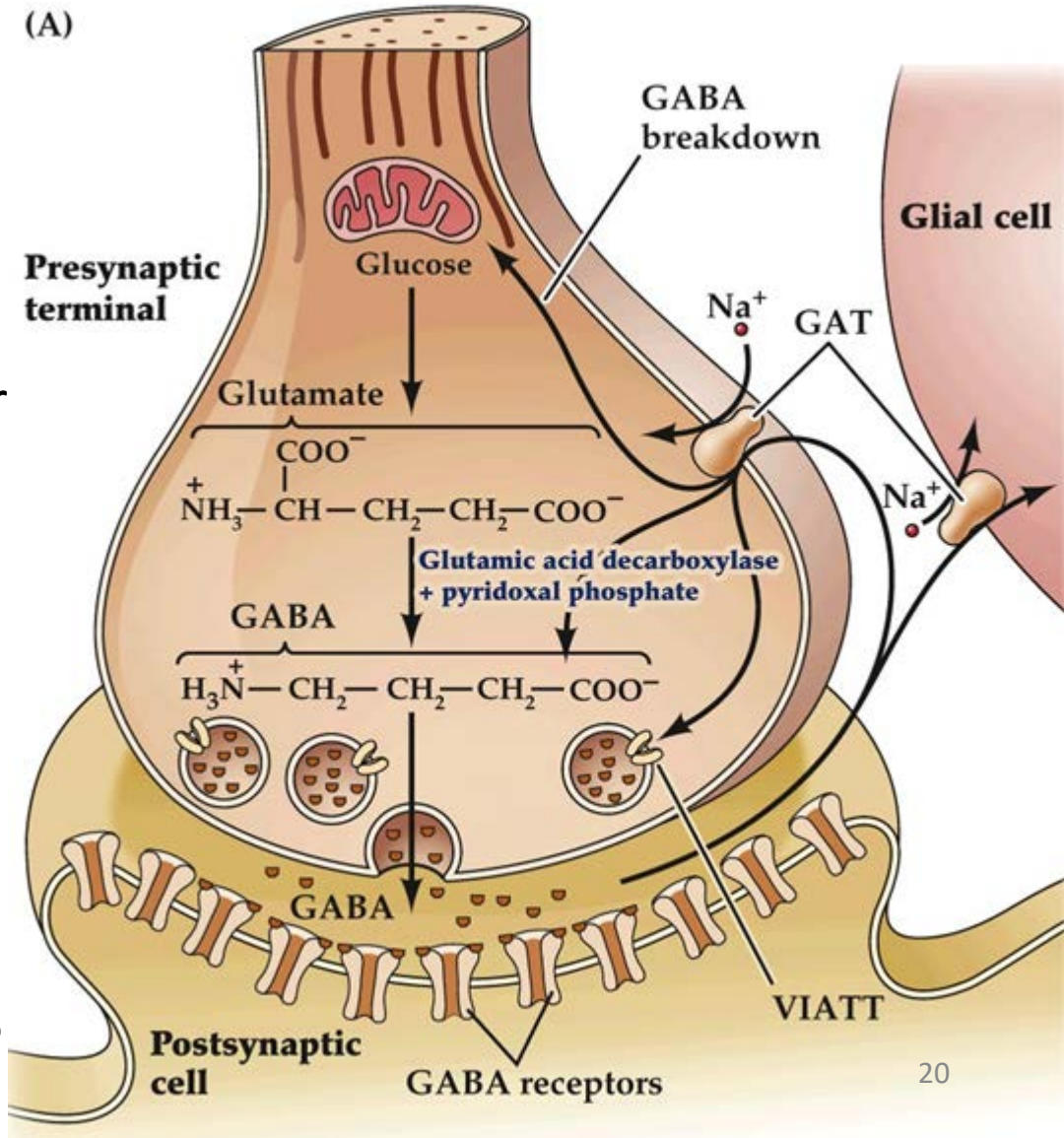
AMPA receptors

- Binding of glutamate causes the clamshell structure to “shut”.
- This movement then causes the gate helices within the transmembrane domain to move and thereby open the channel pore.



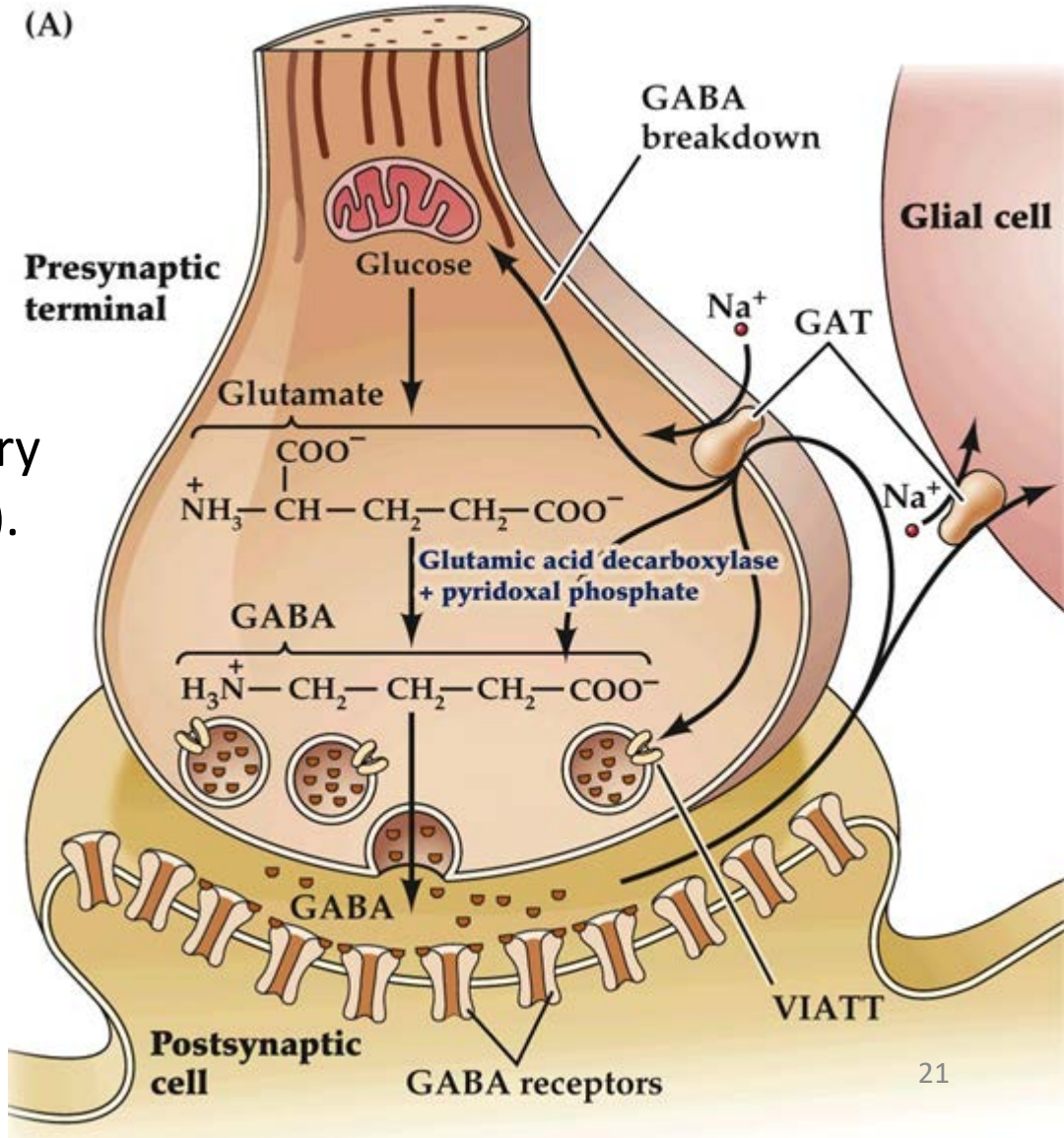
GABA and Glycine

- Most inhibitory synapses in the brain and spinal cord use either γ-aminobutyric acid (GABA) or glycine as neurotransmitters.
- As many as a third of the synapses in the brain use GABA as their inhibitory neurotransmitter, and GABA is most commonly found in local circuit interneurons.
- The predominant precursor for GABA synthesis is glucose, which is metabolized to glutamate by the tricarboxylic acid cycle enzymes.
- The enzyme glutamic acid decarboxylase (GAD), which is found almost exclusively in GABAergic neurons, catalyzes the conversion of glutamate to GABA.



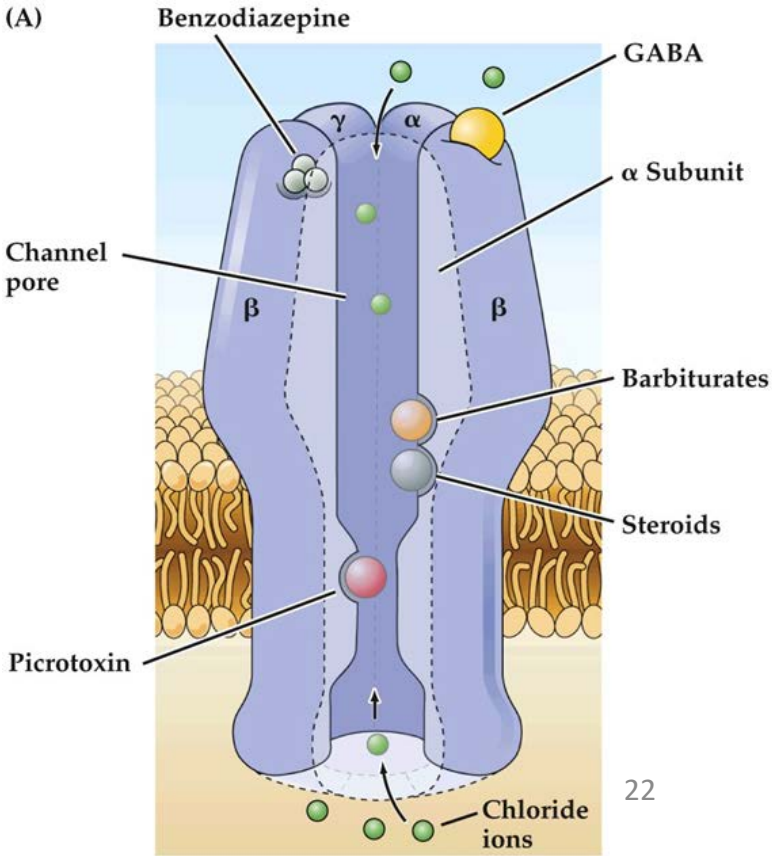
GABA

- GAD requires a co-factor, pyridoxal phosphate, for activity.
  - Because pyridoxal phosphate is derived from vitamin B_6, a deficiency of this vitamin can lead to diminished GABA synthesis.
- Once GABA is synthesized, it is transported into synaptic vesicles via a vesicular inhibitory amino acid transporter (VIAAT).
- The mechanism of GABA removal is similar to that for glutamate: Both neurons and glia contain high-affinity Na^+-dependent co-transporters for GABA which are termed GATs.



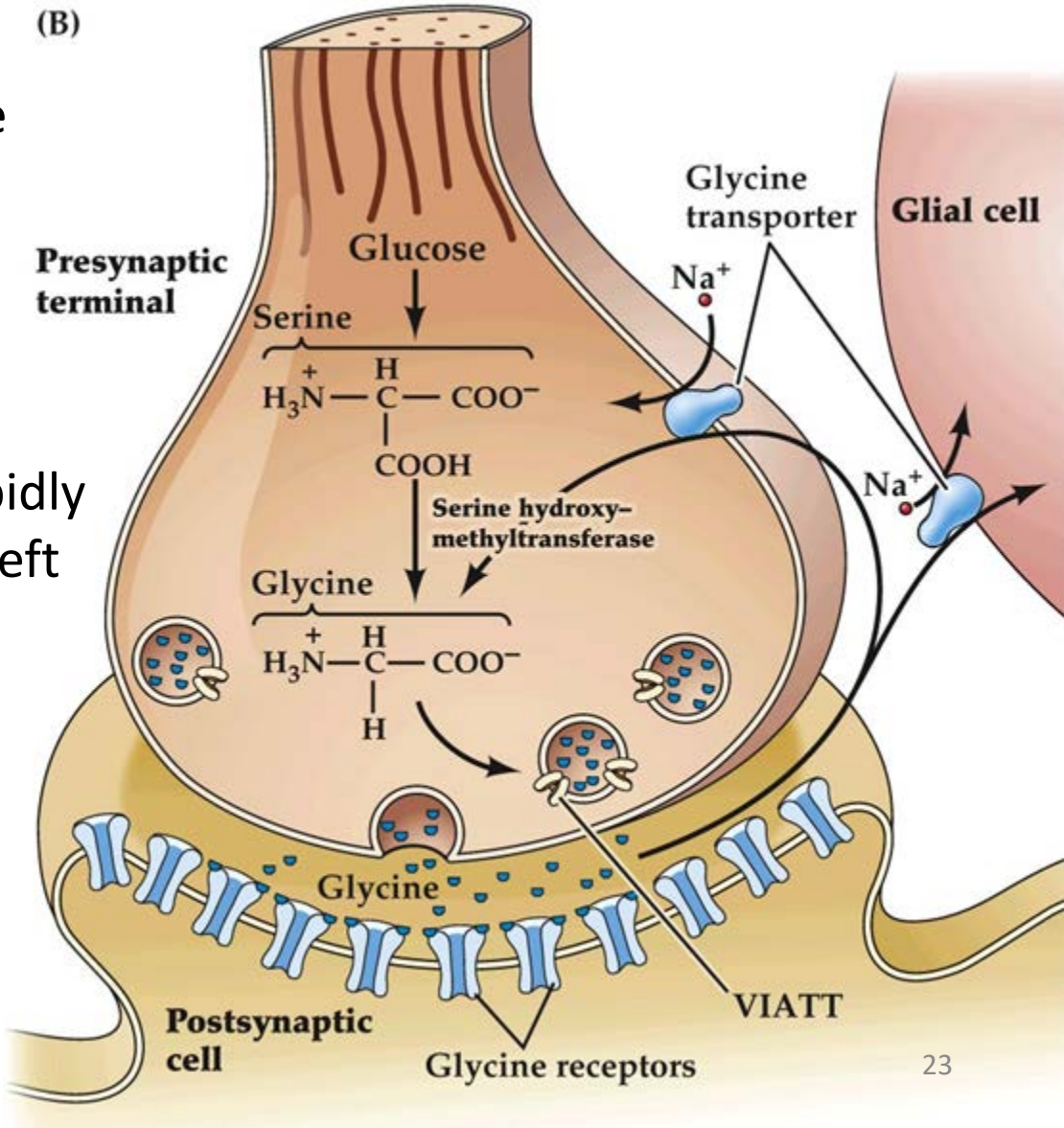
GABA receptors

- GABAergic synapses employ three types of postsynaptic receptors, called $GABA_A$, $GABA_B$ and $GABA_C$.
- $GABA_A$ and $GABA_C$ are ionotropic receptors, while $GABA_B$ are metabotropic receptors.
- Like other ionotropic receptors, $GABA_A$ and $GABA_C$ are pentamers assembled from a combination of numerous types of subunits.
- As a result of this subunit diversity, the composition and function of $GABA_A$ receptors differ widely among neuronal types.
- The ionotropic GABA receptors are GABA-gated anion channels, with Cl^- being the main permeant ion under physiological conditions.
- Ionotropic GABA receptors contain numerous sites at which drugs bind to and modulate these receptors.



Glycine

- Glycine is synthesized from serine by the mitochondrial isoform of serine hydroxymethyltransferase.
- Glycine is transported into synaptic vesicles via the same vesicular inhibitory amino acid transporter that loads GABA into vesicles, VIATT.
- Once released from the presynaptic cell, glycine is rapidly removed from the synaptic cleft by glycine transporters in the plasma membrane.
- The receptors for glycine are also ligand-gated Cl^- channels; their general structure is thought to mirror that of the $GABA_A$ receptors.



The biogenic amines

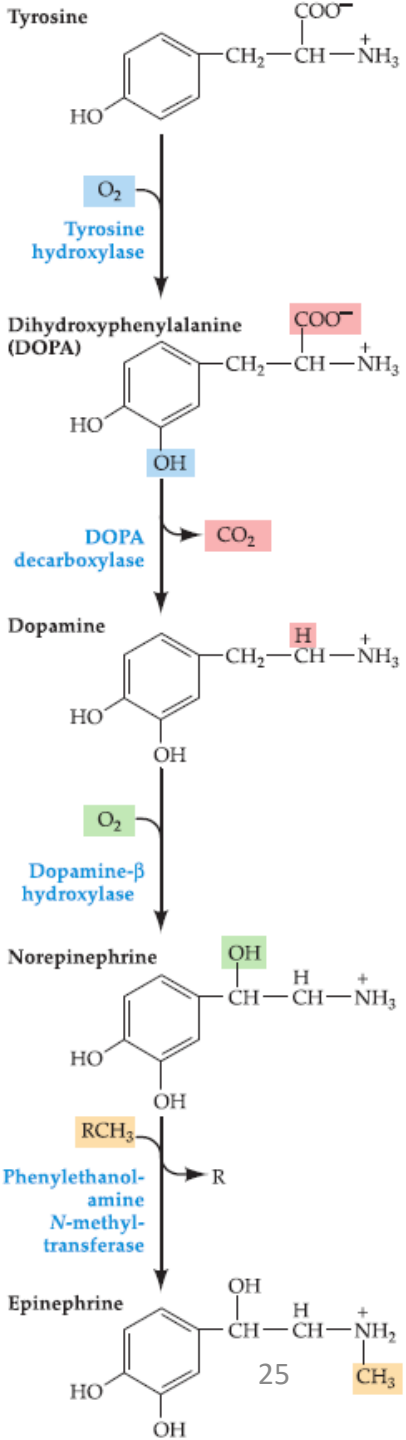
- Biogenic amine transmitters regulate many brain functions and are also active in the peripheral nervous system.

- There are five well-established biogenic amine neurotransmitters: the three **catecholamines**-**dopamine**, **norepinephrine** (**noradrenaline**), and **epinephrine** (**adrenaline**), **histamine** and **serotonin**.

Catecholamines

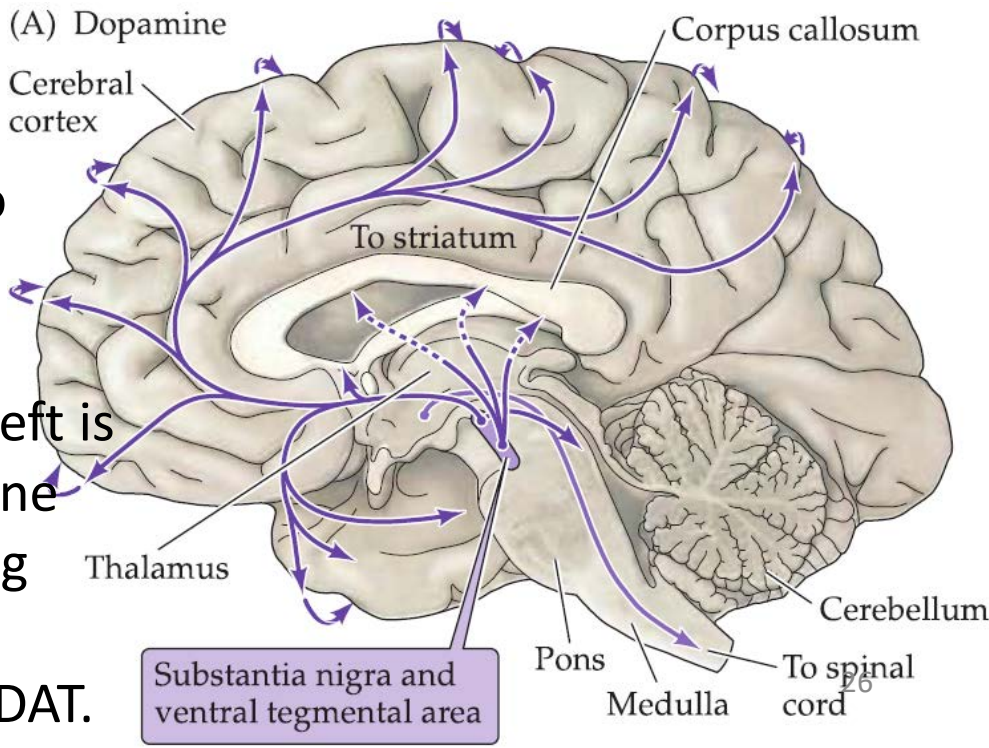
- All the catecholamines (so named because they share the catechol moiety) are derived from a common precursor, the amino acid tyrosine.

- The first step in this reaction pathway, catalyzed by **tyrosine hydroxylase**, is rate-limiting.



Dopamine

- Dopamine is present in several brain regions, although the major dopamine-containing area of the brain is the corpus striatum, which receives major input from the substantia nigra and plays an essential role in the coordination of body movements.
  - In Parkinson's disease, for instance, the dopaminergic neurons of the substantia nigra degenerate, leading to a characteristic motor dysfunction.
  - Dopamine is also believed to be involved in motivation, reward, and reinforcement and many drugs of abuse work by affecting dopaminergic circuitry in the CNS.
- Following its synthesis in the cytoplasm of presynaptic terminals, dopamine is loaded into synaptic vesicles via a vesicular monoamine transporter (VMAT).
- Dopamine action in the synaptic cleft is terminated by reuptake of dopamine into nerve terminals or surrounding glial cells by a Na^+-dependent dopamine co-transporter, termed DAT.



Drugs affecting dopamine pathway

- Cocaine apparently produces its psychotropic effects by inhibiting DAT, thereby increasing dopamine concentrations in the synaptic cleft.
- Amphetamine, another addictive drug, also inhibits DAT as well as the transporter for norepinephrine.

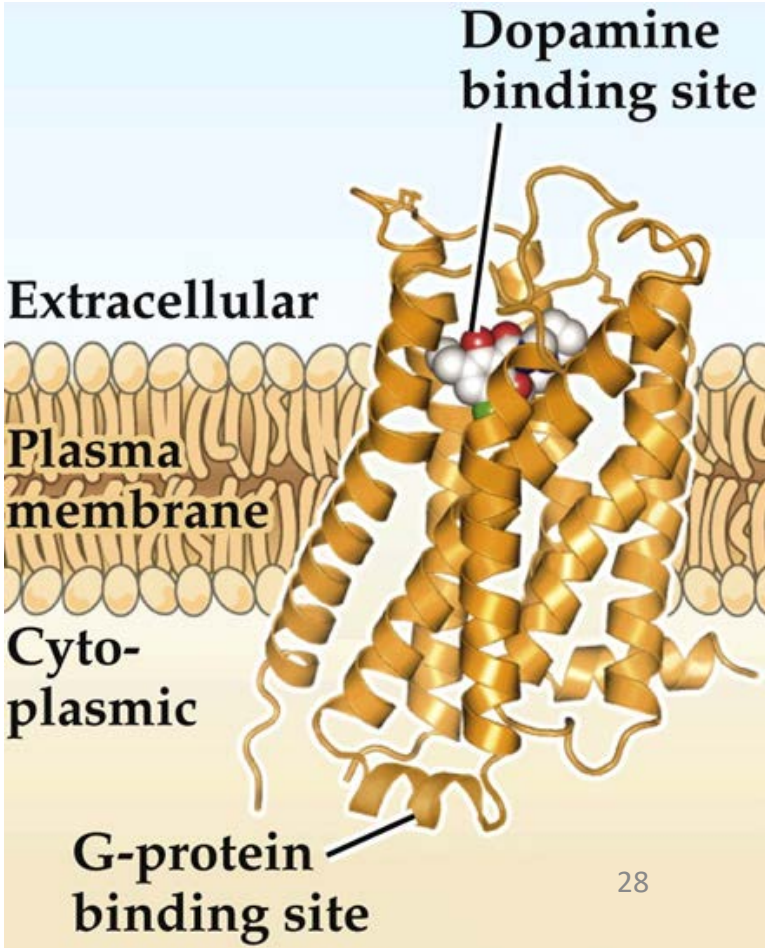
❖ The two major enzymes involved in the catabolism of dopamine are monoamine oxidase (MAO) and catechol *O*-methyltransferase (COMT). Both neurons and glia contain mitochondrial MAO and cytoplasmic COMT.

- Inhibitors of these enzymes, such as phenelzine and tranylcypromine, are used clinically as antidepressants.

Dopamine receptors

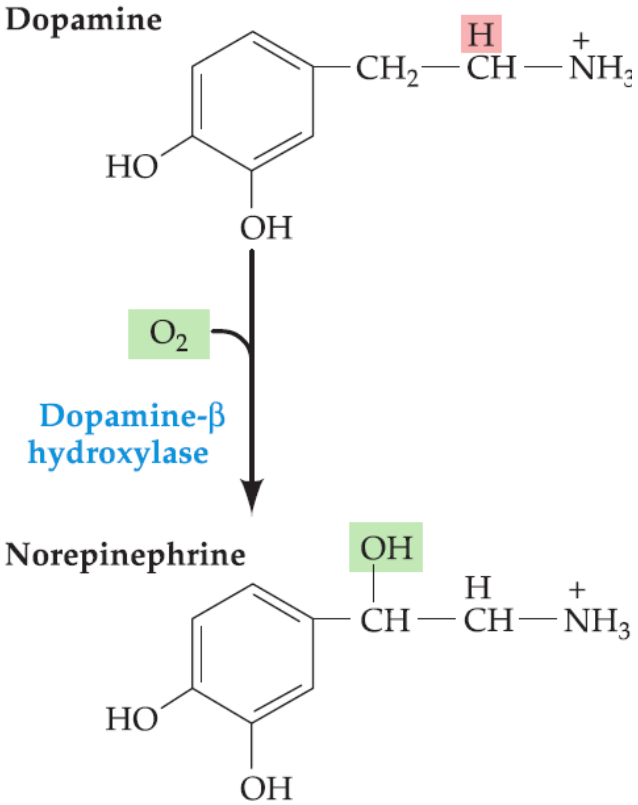
- Once released, dopamine acts exclusively by activating G-protein-coupled receptors.
- The structure of this kind of receptors, such as the D_3 dopamine receptor, closely parallels that of other metabotropic receptors.

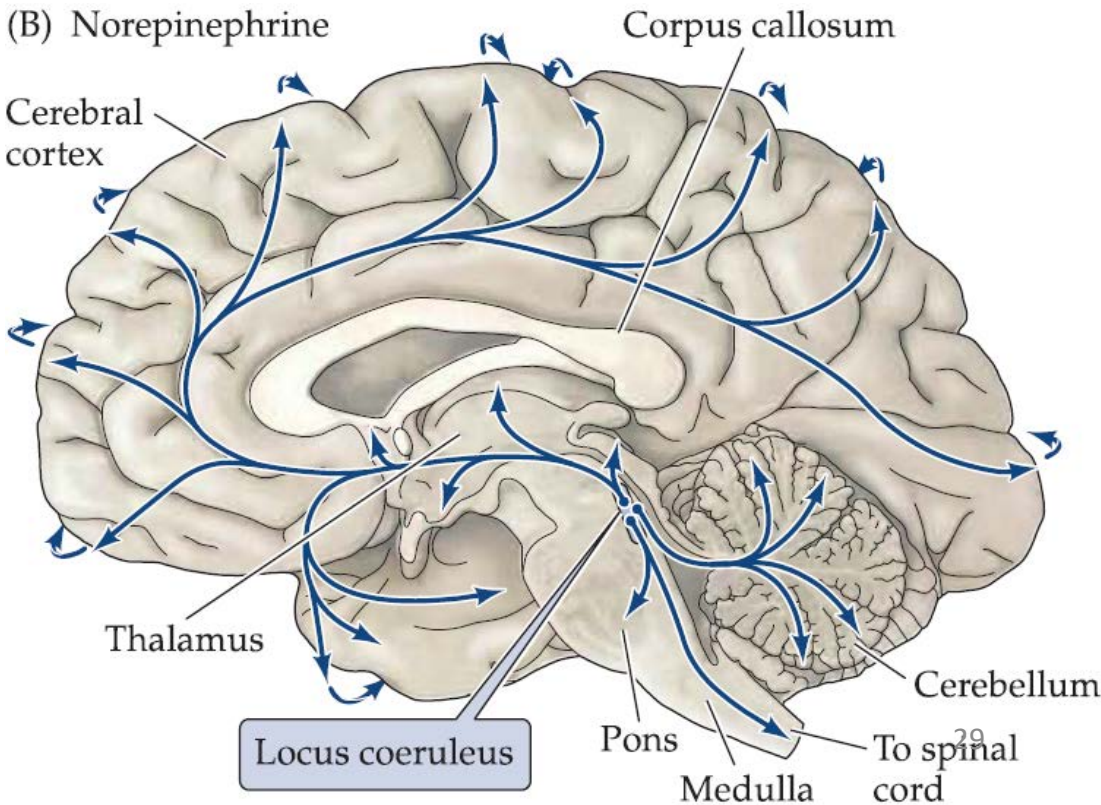
  - Activation of these receptors generally contributes to complex behaviors; for example, administration of dopamine receptor agonists causes hyperactivity and repetitive, stereotyped behavior in laboratory animals.
  - Activation of another type of dopamine receptor in the medulla inhibits vomiting. Thus, antagonists of these receptors are used as emetics to induce vomiting after poisoning or a drug overdose.



Norepinephrine (noradrenaline)

- Norepinephrine is used as a neurotransmitter in the locus coeruleus, a brainstem nucleus that projects diffusely to a variety of forebrain targets and influences sleep and wakefulness, attention, and feeding behavior.
- Norepinephrine synthesis requires dopamine β-hydroxylase, which catalyzes the production of norepinephrine from dopamine.
- Norepinephrine is then loaded into synaptic vesicles via the same VMAT involved in vesicular dopamine transport.



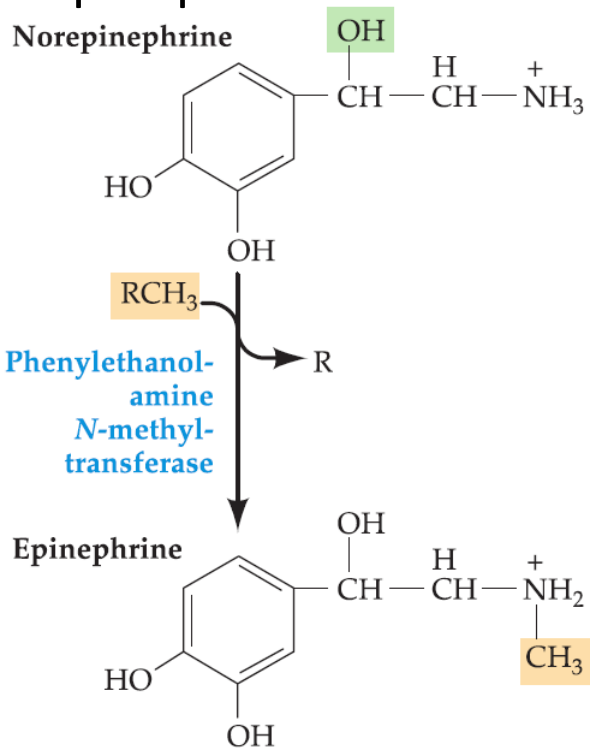


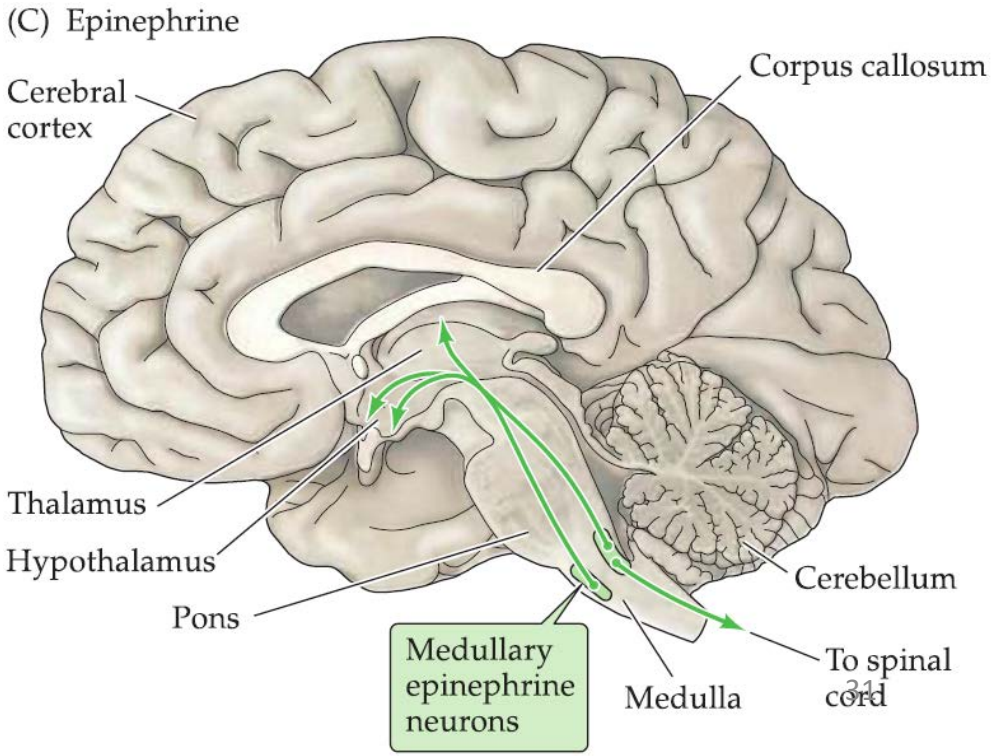
Norepinephrine (noradrenaline)

- Norepinephrine is cleared from the synaptic cleft by the norepinephrine transporter (NET), a Na^+-dependent co-transporter that also is capable of taking up dopamine.
- Norepinephrine acts on α- and β-adrenergic receptors. Both types of receptor are G-protein-coupled.
- Agonists and antagonists of adrenergic receptors, such as the β-blocker propanolol, are used clinically for a variety of conditions ranging from cardiac arrhythmias to migraine headaches.

Epinephrine (adrenaline)

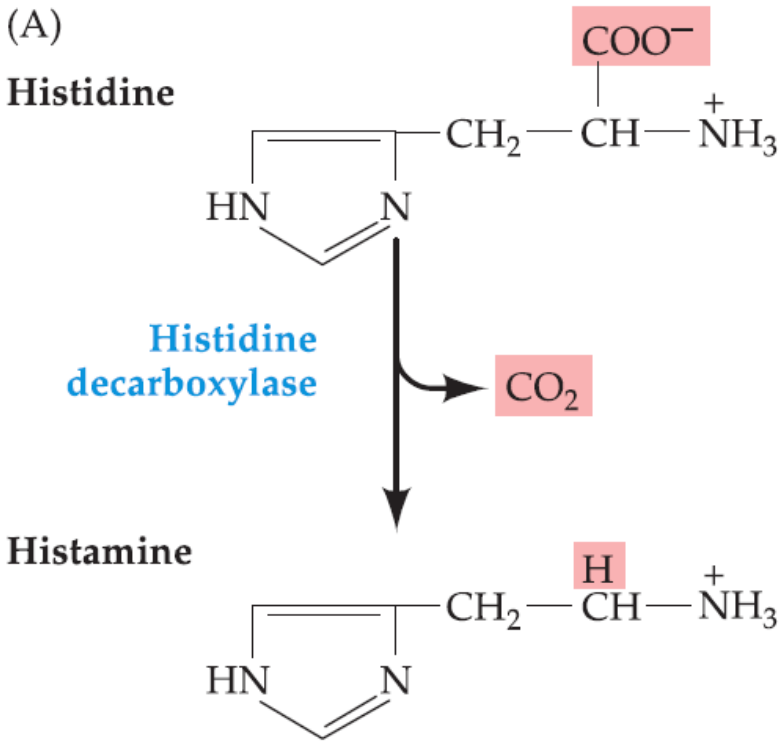
- Epinephrine is present in fewer brain neurons than other catecholamines.
- Epinephrine-containing neurons in CNS are primarily in the lateral tegmental system and in the medulla and project to the hypothalamus and thalamus.
- The enzyme that synthesizes epinephrine, phenylethanolamine-*N*-methyltransferase, is present only in epinephrine-secreting neurons.
- The metabolism and receptors of epinephrine are very similar to those of norepinephrine.

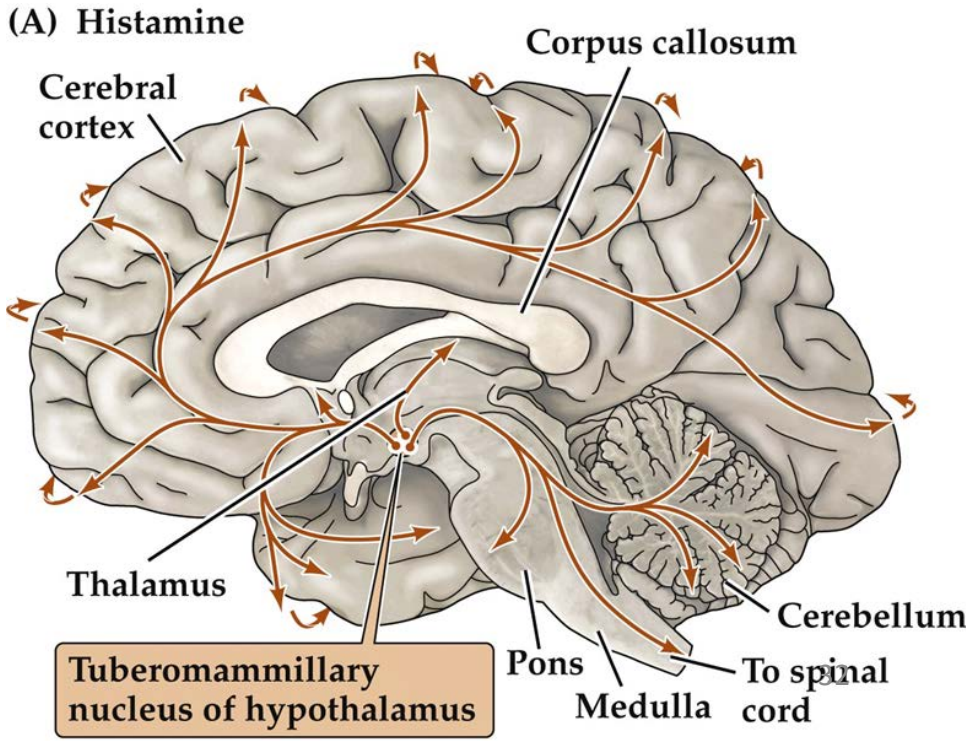




Histamine

- Histamine is found in neurons in the hypothalamus that send sparse but widespread projections to almost all regions of the brain and spinal cord.
- The central histamine projections mediate arousal and attention, similar to central Ach and norepinephrine projections. Histamine also controls the reactivity of the vestibular system.
- Histamine is produced from the amino acid histidine by a histidine decarboxylase and is transported into vesicles via the same VMAT as the catecholamines.



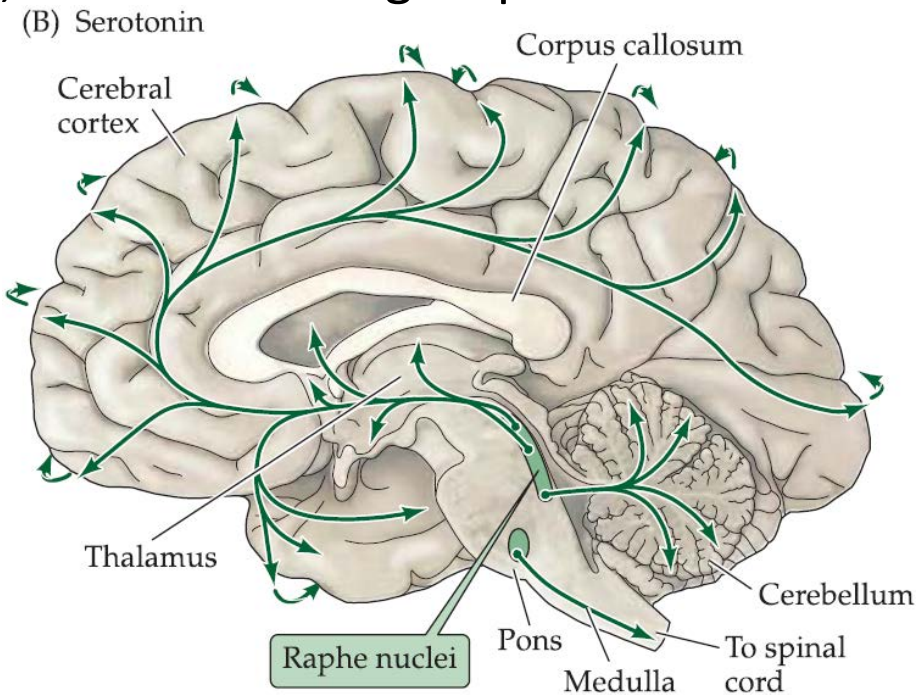


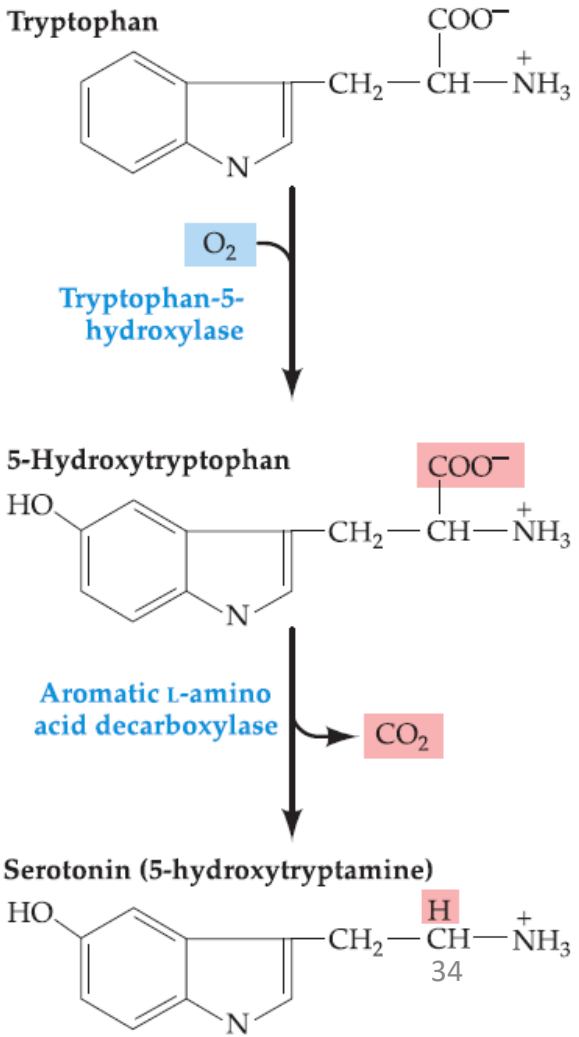
Histamine receptors

- The known histamine receptors are all metabotropic receptors.
- Antihistamines that cross the blood-brain barrier, such as diphenhydramine (Benadryl®), act as sedatives by interfering with the roles of histamine in CNS arousal.
- Antagonists of the H_1 receptor also are used to prevent motion sickness, perhaps because of the role of histamine in controlling vestibular function.
- H_2 receptors control the secretion of gastric acid in the digestive system, allowing H_2 receptor antagonists to be used in the treatment of a variety of upper gastrointestinal disorders (e.g., peptic ulcers).

Serotonin (5-hydroxytryptamine, 5-HT)

- Serotonin is found primarily in groups of neurons in the raphe region of the pons and upper brainstem, which have widespread projections to the forebrain, and regulate sleep and wakefulness.
- 5-HT is synthesized from the amino acid tryptophan, which is an essential dietary requirement.
- Tryptophan is taken up into neurons by a plasma membrane transporter and hydroxylated in a reaction catalyzed by the enzyme tryptophan-5-hydroxylase, the rate-limiting step for 5-HT synthesis.



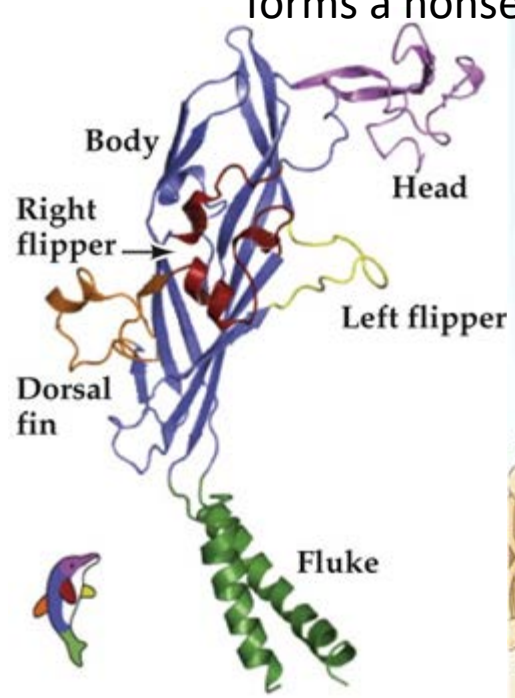


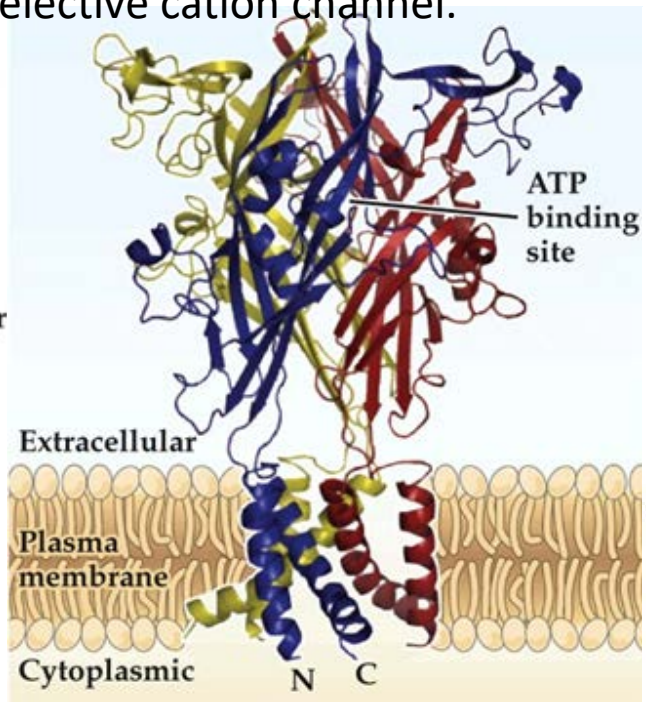
Serotonin (5-hydroxytryptamine, 5-HT)

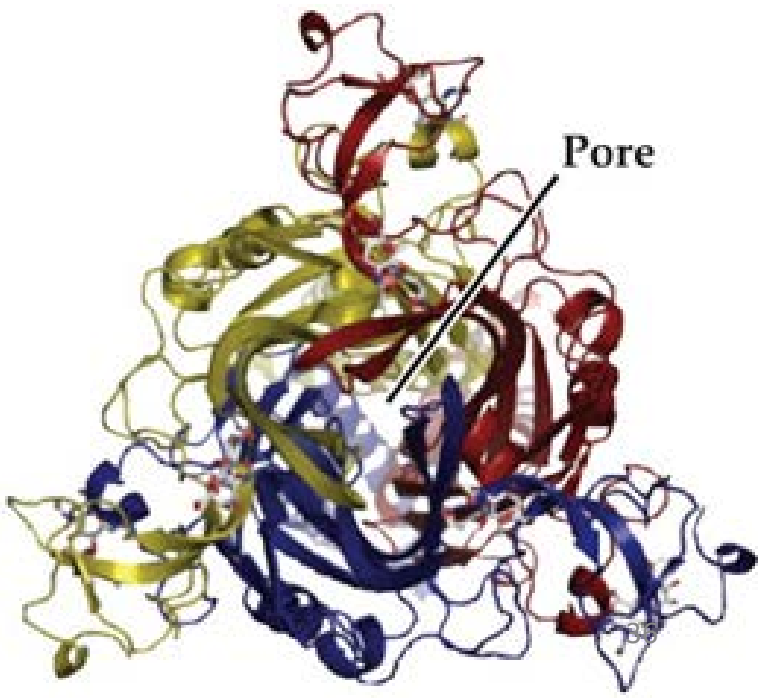
- The synaptic effects of serotonin are terminated by transport back into nerve terminals via a specific serotonin transporter (SERT).
- Many antidepressant drugs are **selective serotonin reuptake inhibitors (SSRIs)** that inhibit transport of 5-HT by SERT.
- Most 5-HT receptors are metabotropic.
- These have been implicated in behaviors, including the emotions, circadian rhythms, motor behaviors, and state of mental arousal.
- Impairments in the function of these receptors have been implicated in numerous psychiatric disorders, such as depression, anxiety disorders, and schizophrenia, and drugs acting on serotonin receptors are effective treatments for a number of these conditions.
- Activation of 5-HT receptors also mediates satiety and decreased food consumption, which is why serotonergic drugs are sometimes useful in treating eating disorders.
- Only one group of serotonin receptors, the 5-HT_3 receptors, are ligand-gated ion channels.

ATP and other purines

- ATP acts as an excitatory neurotransmitter in motor neurons of the spinal cord, as well as in sensory and autonomic ganglia.
- Postsynaptic actions of ATP have also been demonstrated in CNS, specifically for dorsal horn neurons and in a subset of hippocampal neurons.
- Three classes of these purinergic receptors are known.
  - One class consists of ionotropic receptors called **P2X receptors**.
    - The structure of these receptors is somewhat unique among ionotropic receptors because each subunit has only two transmembrane domains.
    - Only three of these subunits are required to form a trimeric receptor.
    - Like all ionotropic receptors, a pore is located in the center of the P2X receptor and forms a nonselective cation channel.

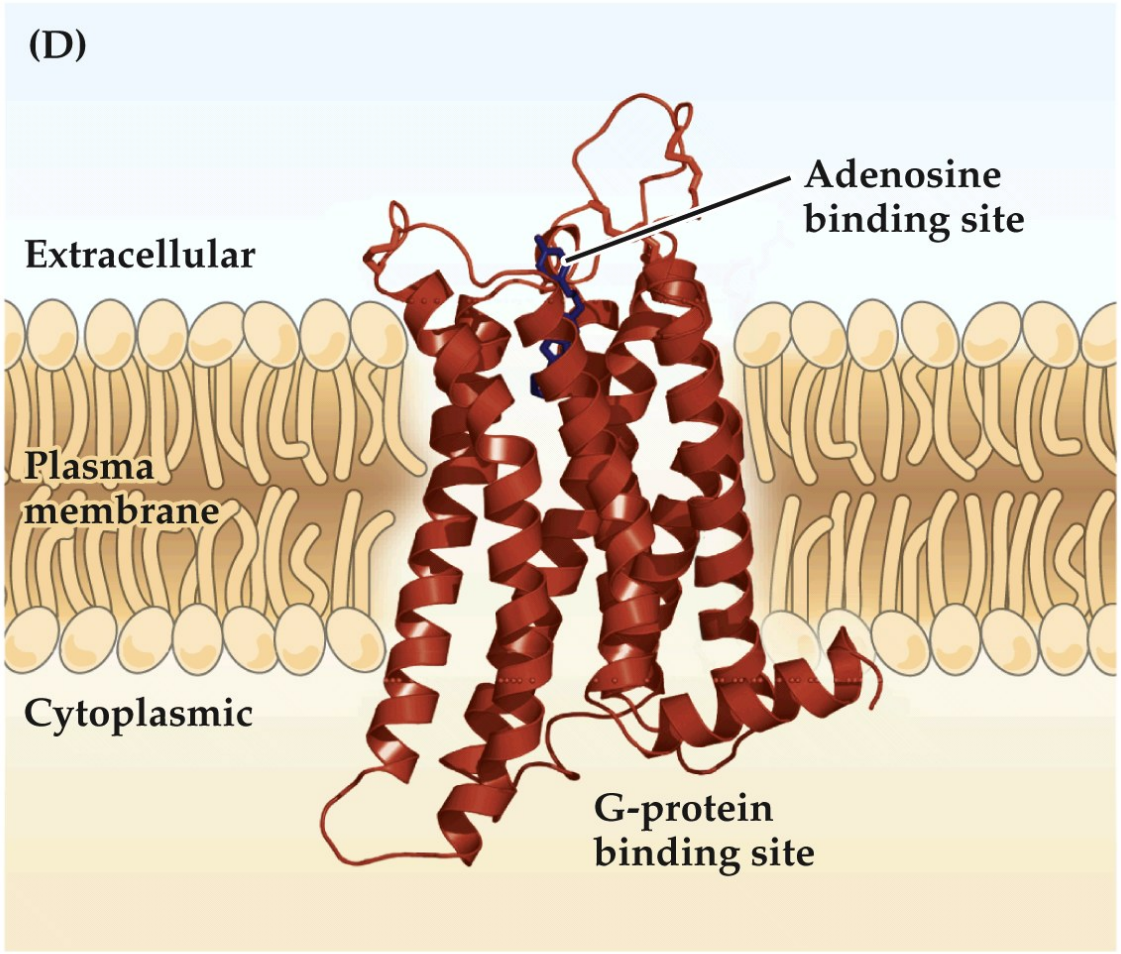






ATP and other purines

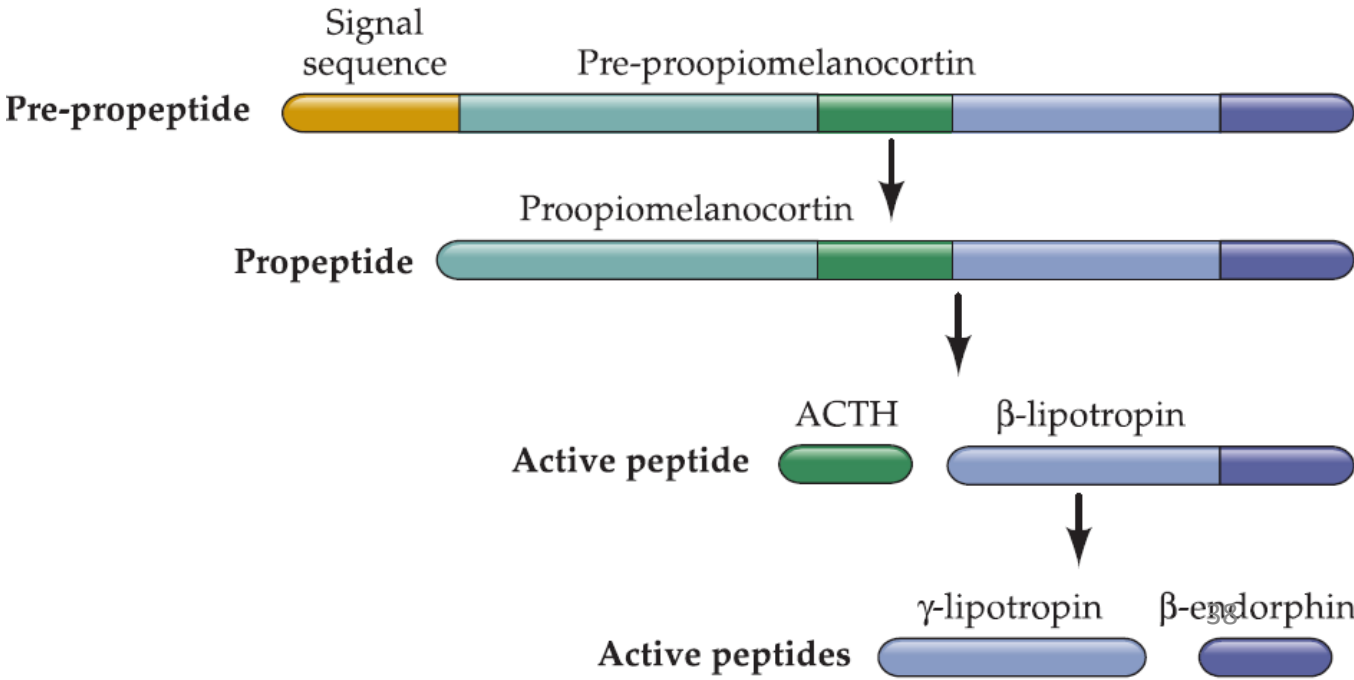
- The other two classes of purinergic receptors are G-protein-coupled metabotropic receptors.
  - The two classes differ in their sensitivity to agonists--one type is preferentially stimulated by adenosine, whereas the other is preferentially activated by ATP.



NEUROSCIENCE 5e, Figure 6.15 (Part 2)

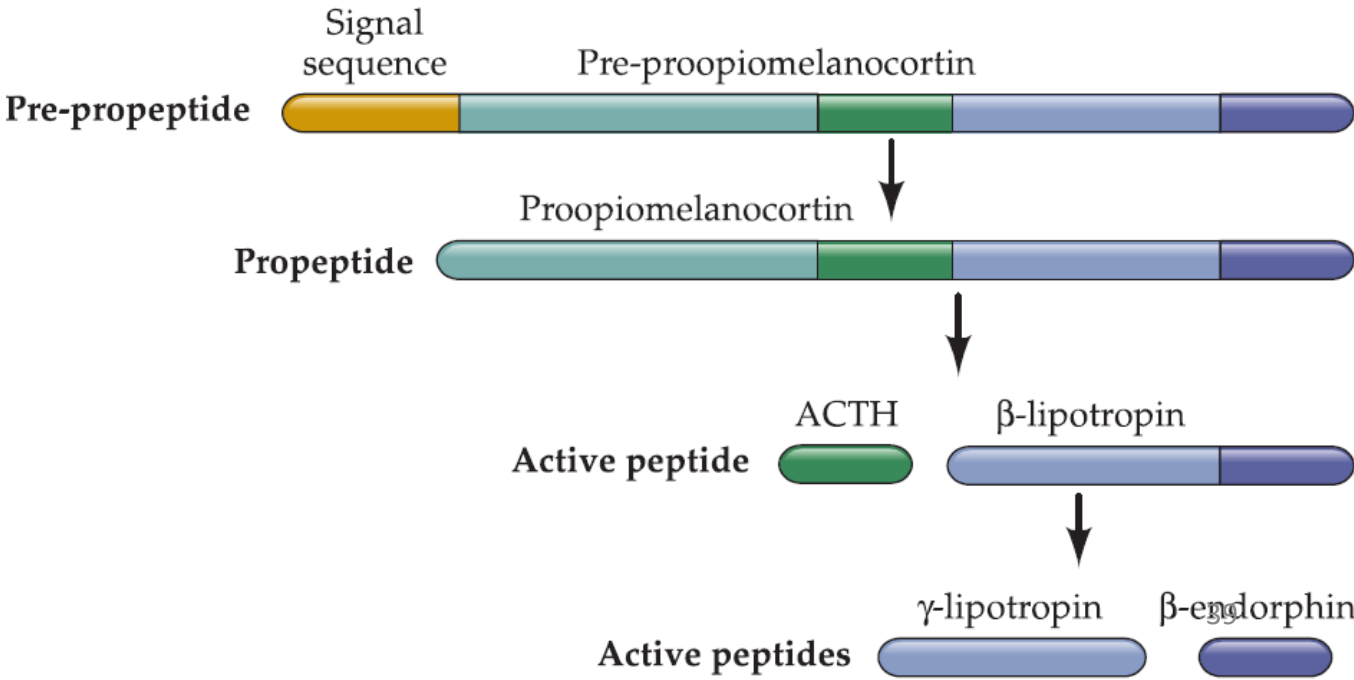
Peptide Neurotransmitters

- The mechanisms responsible for the synthesis and packaging of peptide transmitters are fundamentally different from those used for the small-molecule neurotransmitters and are much like the synthesis of proteins that are secreted from non-neuronal cells.
- Peptide-secreting neurons generally synthesize polypeptides that are much larger than the final, “mature” peptide.
- Processing these polypeptides, which are called **pre-propeptides** (or pre-proproteins), takes place within the neuron's cell body by a sequence of reactions that occur in several intracellular organelles.



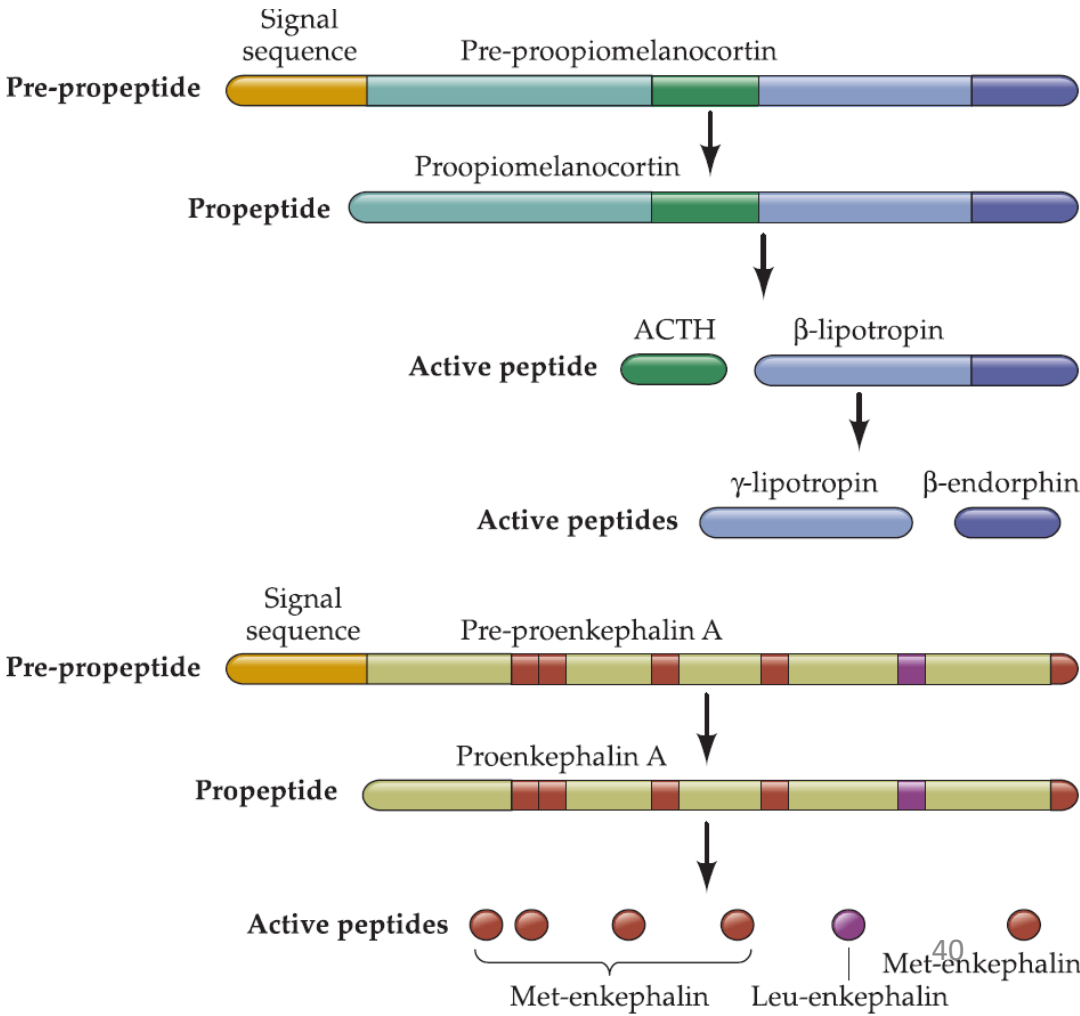
Peptide Neurotransmitters

- Pre-propeptides are synthesized in the rough endoplasmic reticulum, where the signal is removed.
- The remaining polypeptide, called a **propeptide**, then traverses the Golgi apparatus and is packaged into vesicles in the *trans*-Golgi network.
- The final stages of peptide neurotransmitter processing occur after packaging into vesicles and involve proteolytic cleavage, modification of the ends of the peptide, glycosylation, phosphorylation, and disulfide bond formation.



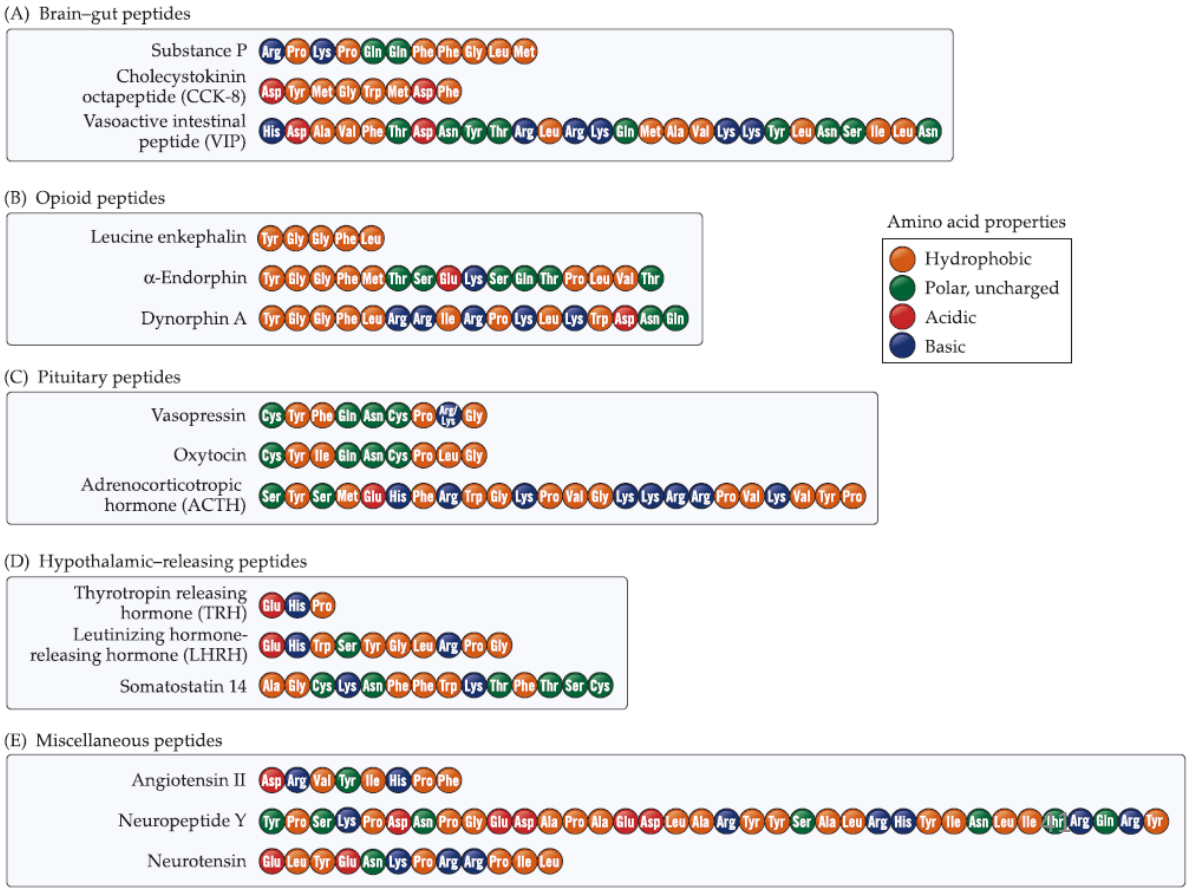
Peptide Neurotransmitters

- Propeptide precursors can give rise to more than one species of neuropeptide, which means that multiple neuroactive peptides can be released from a single vesicle.
- In addition, neuropeptides often are co-released with small-molecule neurotransmitters.
- Thus, peptidergic synapses often elicit complex postsynaptic responses.
- Peptides are catabolized into inactive amino acid fragments by enzymes called peptidases, usually located on the extracellular surface of the plasma membrane.



Peptide Neurotransmitters

- The biological activity of the peptide neurotransmitters depends on their amino acid sequence.
- Based on their sequences, neuropeptide transmitters have been loosely grouped into five categories: the brain/gut peptides; opioid peptides; pituitary peptides; hypothalamic releasing hormones; and a catch-all category containing other, not easily classified, peptides.



Substance P

- The study of neuropeptides began more than 60 years ago with the accidental discovery of **substance P**, a powerful hypotensive agent and an example of the first category of peptide.

- The peculiar name derives from the fact that this molecule was an unidentified component of *p*owder extracts from brain and intestine.
- Substance P is an 11-amino-acid peptide present in high concentrations in the human hippocampus, neocortex, and also in the gastrointestinal tract; hence its classification as a brain/gut peptide.
- It is also released from C fibers, the small-diameter afferents in peripheral nerves that convey information about pain and temperature (as well as postganglionic autonomic signals).
- Substance P is a sensory neurotransmitter in the spinal cord, where its release can be inhibited by opioid peptides released from spinal cord interneurons, resulting in the suppression of pain .

Opioid peptides

- Opioids are an especially important category of peptide neurotransmitters and they so named because they bind to the same postsynaptic receptors that are activated by opium.

(B) Opioid peptides

- The active ingredients in opium are a variety of plant alkaloids, predominantly morphine.
- Morphine, named for Morpheus, the Greek god of dreams, is still in use today and is one of the most effective analgesics, despite its addictive potential.
- The opioid peptides were discovered in the 1970s during a search for **endorphins**--*endo*genous compounds that mimicked the actions of m*orphin*e.

Opioid peptides

- The endogenous ligands of the opioid receptors have now been identified as a family of more than 20 opioid peptides that fall into three classes:

TABLE 6.2 Endogenous Opioid Peptides

NAME	AMINO ACID SEQUENCE[a]
Endorphins	
α-Endorphin	*Tyr-Gly-Gly-Phe*-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr
α-Neoendorphin	*Tyr-Gly-Gly-Phe*-Leu-Arg-Lys-Tyr-Pro-Lys
β-Endorphin	*Tyr-Gly-Gly-Phe*-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Val-Lys-Asn-Ala-His-Lys-Gly-Gln
γ-Endorphin	*Tyr-Gly-Gly-Phe*-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu
Enkephalins	
Leu-enkephalin	*Tyr-Gly-Gly-Phe*-Leu
Met-enkephalin	*Tyr-Gly-Gly-Phe*-Met
Dynorphins	
Dynorphin A	*Tyr-Gly-Gly-Phe*-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln
Dynorphin B	*Tyr-Gly-Gly-Phe*-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr

- Opioid peptides are widely distributed throughout brain and are often co-localized with other small-molecule neurotransmitters, such as GABA, 5-HT.
- In general, the opioids tend to be depressants. When injected intracerebrally in experimental animals, they act as analgesics.
- Opioids are also involved in complex behaviors such as sexual attraction and aggressive/submissive behaviors.

Neuropeptide receptors

- Virtually all neuropeptides initiate their effects by activating G-protein-coupled receptors.
- The study of these metabotropic peptide receptors in the brain has been difficult because few specific agonists and antagonists are known.
- Neuropeptide receptor activation is especially important in regulating the postganglionic output from sympathetic ganglia and the activity of the gut.
- Peptide receptors, particularly the neuropeptide Y receptor, are also implicated in the initiation and maintenance of feeding behavior leading to satiety or obesity.

Unconventional neurotransmitters

- These chemical signals can be considered as neurotransmitters because of their roles in interneuronal signaling and because their release from neurons is regulated by Ca^{2+}.
- However, they are unconventional in comparison to other neurotransmitters because they are not stored in synaptic vesicles and are not released from presynaptic terminals via exocytotic mechanisms.
- In fact, these unconventional neurotransmitters need not be released from presynaptic terminals at all and are often associated with retrograde signaling.
- *Endocannabinoids*; *Nitric oxide* (NO).

Summary

- Glutamate is the major excitatory neurotransmitter in the brain, whereas GABA and glycine are the major inhibitory neurotransmitters.
- The actions of these small-molecule neurotransmitters are typically faster than those of the neuropeptides.
- Two broadly different families of neurotransmitter receptors have evolved to carry out the postsynaptic signaling actions of neurotransmitters.
- Ionotropic or ligand-gated ion channels combine the neurotransmitter receptor and ion channel in one molecular entity, and therefore give rise to rapid postsynaptic electrical responses.
- Metabotropic receptors regulate the activity of postsynaptic ion channels indirectly, usually via G-proteins, and induce slower and longer-lasting electrical responses.
- The postsynaptic response at a given synapse is determined by the combination of receptor subtypes, G-protein subtypes, and ion channels that are expressed in the postsynaptic cell.