Signaling between Neurons

Chapter 5

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5.1 Electrical vs. chemical synapses

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Electrical vs. Chemical synapses

Electrical

- Change in potential is main driver of communication; Carriere of charge is almost always an ion
- Adjacent cells share their cytoplasm; ions, ATP, and larger signaling molecules can move between the two cells
- Physical channel allows for passage of cytoplasm = connexon or hemichannel
- Each hemichannel is made up of 6 proteins called connexins
- When 2 connexons contact each other, the form gap junction (structure that connections neurons electrically
- Neurons are close to each other (~3.5 nanometers)
- Information can be passed bidirectionally
- Detection of several signals at once is possible
- Likely useful for speed (reflex)
- Another advantage: synchronized activity ("go" signal or "shut-down" signal)

Chemical

- Signaling molecule is meals of communication; generally, neurotransmitters
- Neurotransmitters diffuse randomly across the synapse to affect nearby neurons once the chemical binds to a corresponding receptor
- Larger distance between neurons; ~ 20-40 nanometers (a thousand times smaller than the diameter of human hair)
- Allows for a variety of signals, depending on the neurotransmitter and receptor; excitatory (depolarizing) or inhibitory (hyperpolarizing) or more complex (modifying cellular excitability over time)
- Likely useful for complex behaviors and cognition
- Many chemical synapses exist between axon of one neuron and dendrite of another neuron
- One example: neuromuscular junction (NMJ) - acetylcholine (ACh) is released by presynaptic neuron and detected by receptors expressed on muscle; cause contraction of muscle)

Electrical synapse

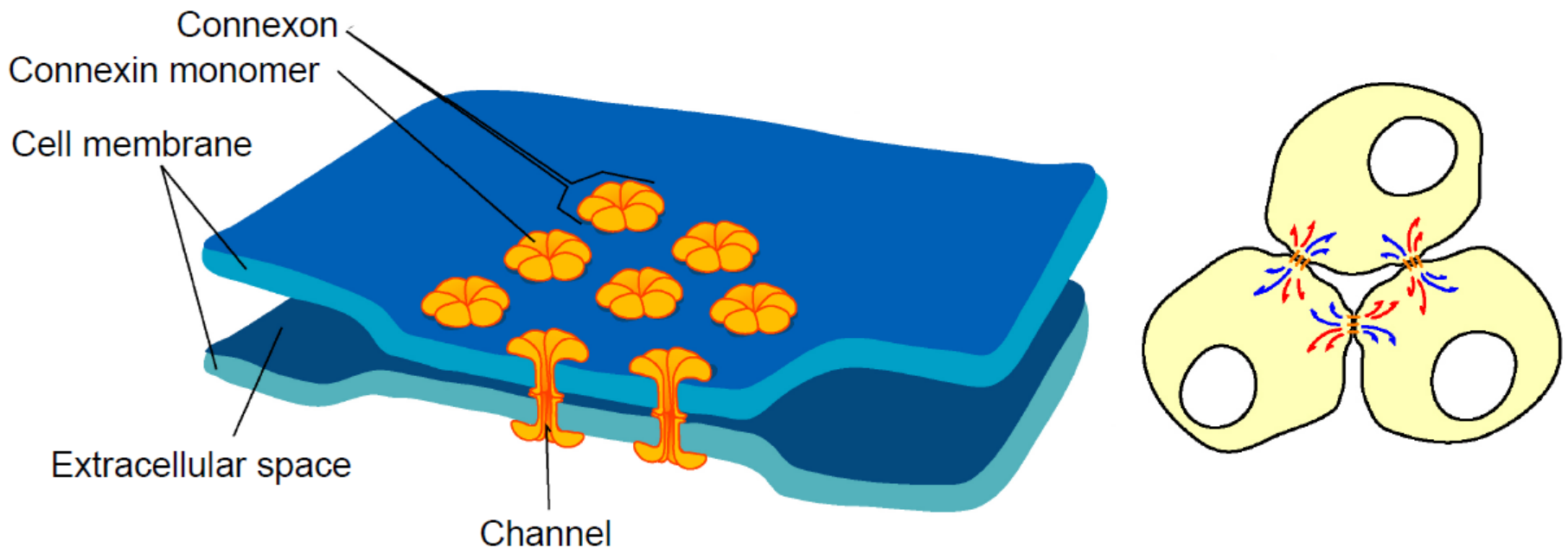


Figure 5.1 An electrical synapse exists between two closely-connected neurons. Cytoplasm passes between the two neurons through a protein complex called a connexon.

Clinical connection: Charcot-Marie-Tooth disease

- Genetic disorder affecting PNS
- Symptoms: muscle weakness, difficulty walking, abnormal sensations (ex. Tingling or pain in extremities)
- Connexin protein, Cx32
  - Mutations to gene that codes for Cx32 are associated with X-linked form of CMT disease
  - Knocking out the gene in experimental mice causes the mice to express similar symptoms as human CMT

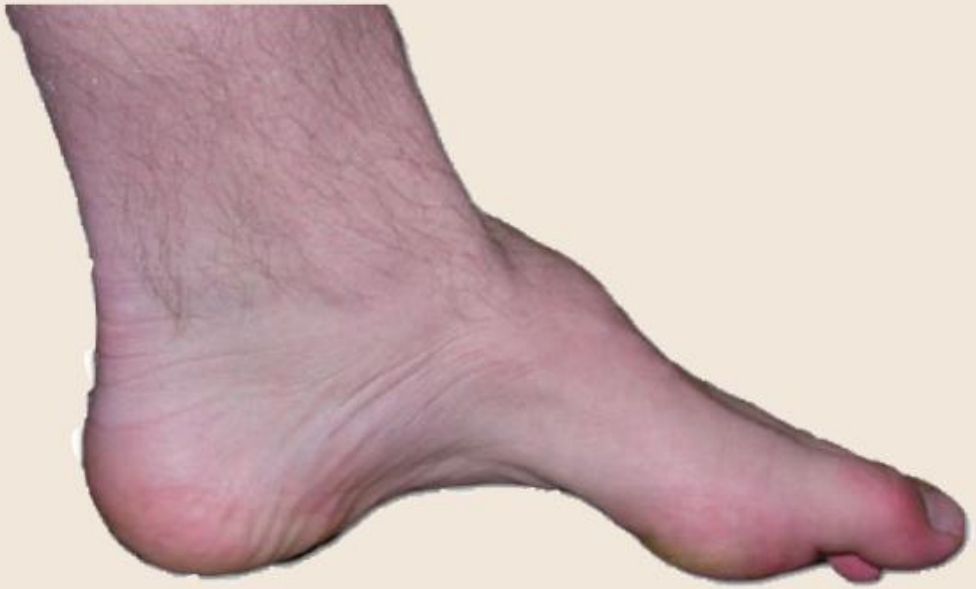


Figure 5.3 People with CMT disease often have abnormally shaped feet.

Chemical synapse

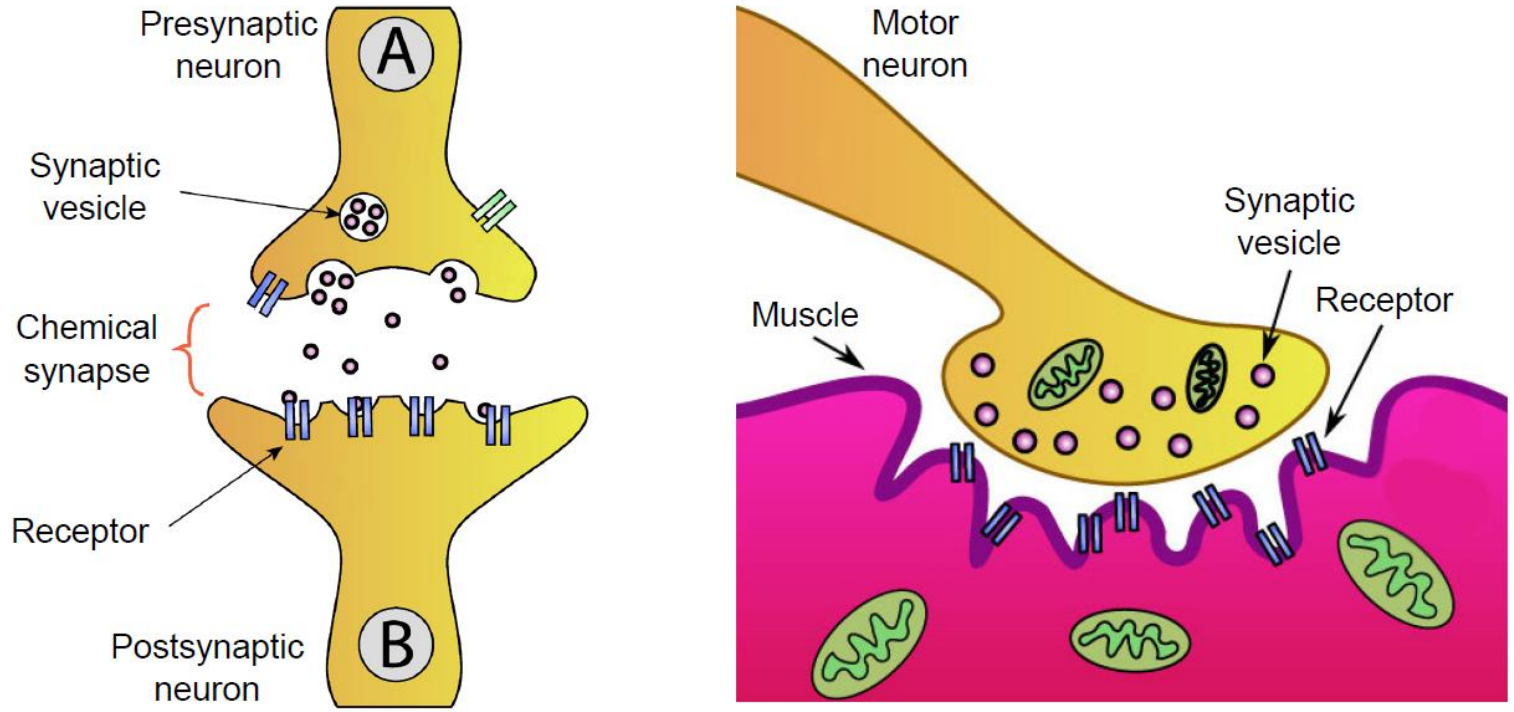


Figure 5.4 Chemical synapses are the site of close interaction between two neurons (left) or a motor neuron and a muscle fiber, which is called the neuromuscular junction (right).

Types of vesicles

Small vesicles

- Diameter of 40 nanometers
- Volume of ~30 cubic microns
- 1000s – 10,000s of neurotransmitters can be stored
- Store common neurotransmitters, including glutamate, GABA, dopamine, and norepinephrine
- Almost always found in axon terminals

Large dense-core vesicles

- Diameter ranges from 100-250 nanometers
- Store peptides such as dynorphin and enkephalin (larger chemical structures than other neurotransmitters)
- Found in the cell bodies, all along the axon, and in axon terminals

Visible with electron microscopy

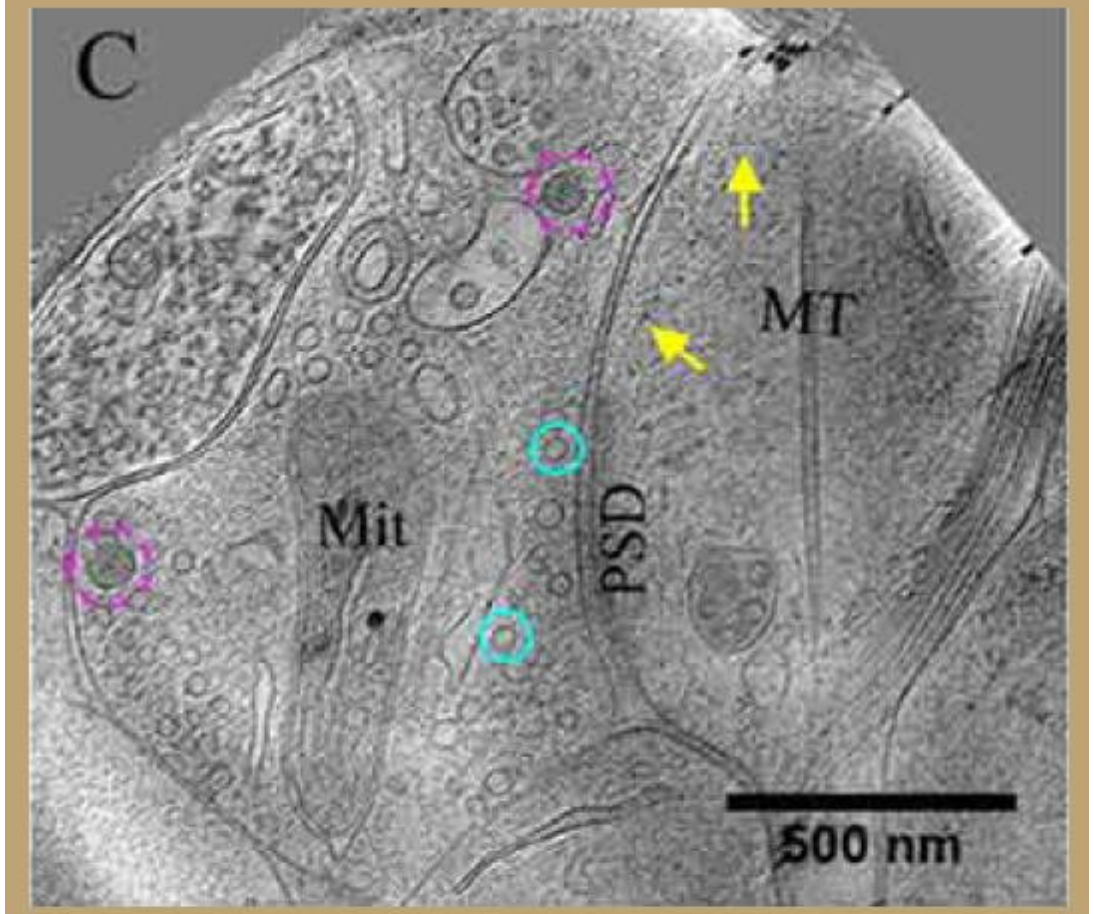


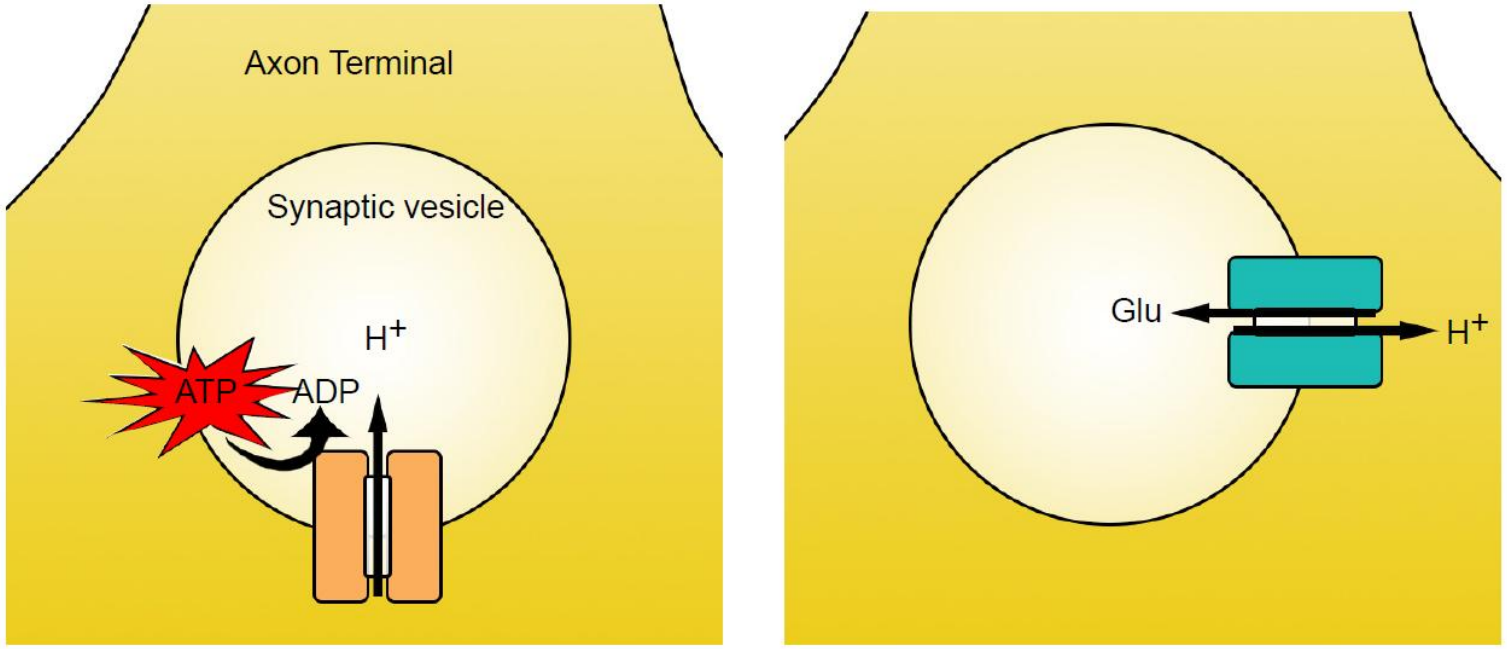
Fig 5.5 Electron microscope image showing small vesicles (cyan) and large dense core vesicles (magenta).

Loading of vesicles

- Small vesicles are filled through action of large transmembrane proteins called vesicular transporters
- Some are specific to a single substrate
  - Vesicular GABA transporter (VGAT)
  - Vesicular glutamate transporter (VGluT)
  - Vesicular acetylcholine transporter (VAChT)
- Some recognize a broad class of neurotransmitters
  - Vesicular monoamine transporters (VMAT) for monoamines such as dopamine and serotonin

Loading depicted

Fig 5.6 Synaptic vesicles in the axon terminal get filled by the action of two different vesicular transporter proteins. The v-ATP-ase uses energy to pump H+ into the vesicle against it's concentration gradient (left). Then, a vesicular transporter such as vGluT use the movement of H+ down it's concentration gradient to increase intravesicular concentration of neurotransmitter (right).



Vesicles have a highly acidic interior

- High concentration of H^+ ions because of transmembrane enzyme vesicular ATP-ase (v-ATP-ase)
- Energy of ATP allows for H^+ concentration in intravesicular space
- For each molecule of ATP used, one H^+ proton gets pumped into the vesicle

Why would it take a lot of energy to move molecules into a vesicle?

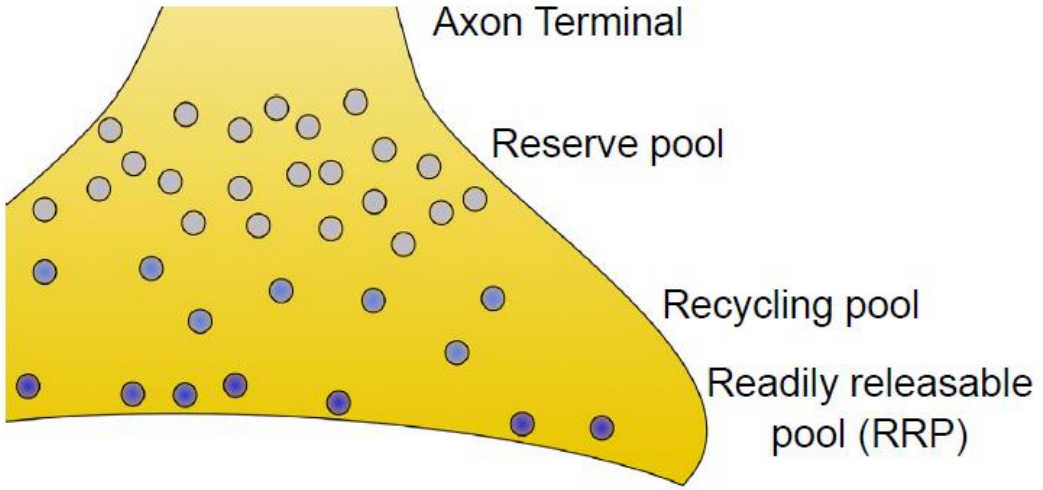
Loading of vesicles continued

- Vesicular transporters pump neurotransmitters against their concentration gradients
- Use high intravesicular concentration of H^+ to help
- When proton moves with concentration gradient, energy is generated
- That energy is used to push neurotransmitter in
- Vesicular transporters are called antiporters because H^+ ions move opposite of neurotransmitters
- Energy required depends on the neurotransmitter (different stoichiometries)
  - 1 H^+ per molecule of GABA
  - 2 H^+ per molecule of dopamine

Location of vesicles

- Readily releasable pool (RRP)
  - Close to cell membrane at terminal
  - Any are already "docked" - i.e. coat proteins are interacting with proteins on inside of cell membrane
  - First to fuse and release contents
- Recycling pool
  - Further from membrane
  - Not primed for release; currently refilling or reloading
  - More intense stimulation required to release contents
- Reserve pool
  - Farthest from membrane
  - Most vesicles are in this pool
  - Very intense stimulation is required

Fig 5.7 Axon terminals contain hundreds of vesicles roughly divided into three categories.

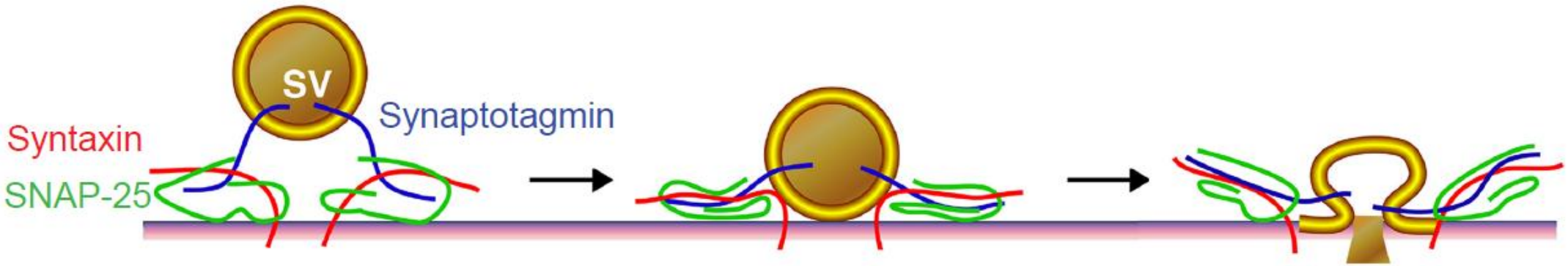


Release of vesicles

- Regulated control of neurotransmitter release is normal and essential
- Depends on several proteins (often embedded within membrane of vesicle or neuronal membrane)
- T-SNAREs
  - Expressed on "target" (inside of cytoplasm)
  - Ex. Syntaxin & SNAP-25
  - Function during vesicular fusion
- V-SNAREs
  - Expressed on vesicles (v for vesicle)
  - Ex. Synaptobrevin & synaptotagmin
  - Involved during synaptic release

Vesicular fusion & neurotransmitter release depicted

Fig 5.8 v-SNARE proteins interact with t-SNARE proteins to allow for vesicular fusion and release of neurotransmitter.



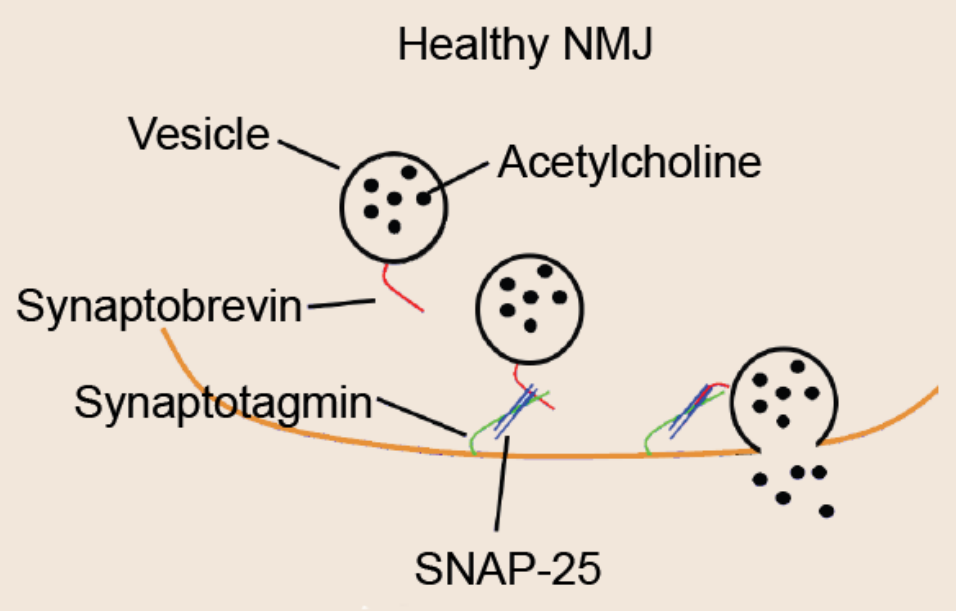


Fig 5.9 Botulinum toxin selectively cleaves vesicular fusion proteins, preventing acetylcholine from being released at the NMJ.

Clinical connection: Botulism

- Note – synaptotagmin is a v-SNARE
- Botulism is a deadly condition resulting from exposure to spores produced by Clostridium botulinum bacteria
- Can be ingested
- One of the most deadly toxins
- "Botox" injections – to reduce appearance of wrinkles by paralyzing muscles
- Toxin is also used medically for conditions resulting from excessive neurotransmitter release (ex. muscle spasms, excessive sweating, or migraine)

Small group activity: Compare and contrast

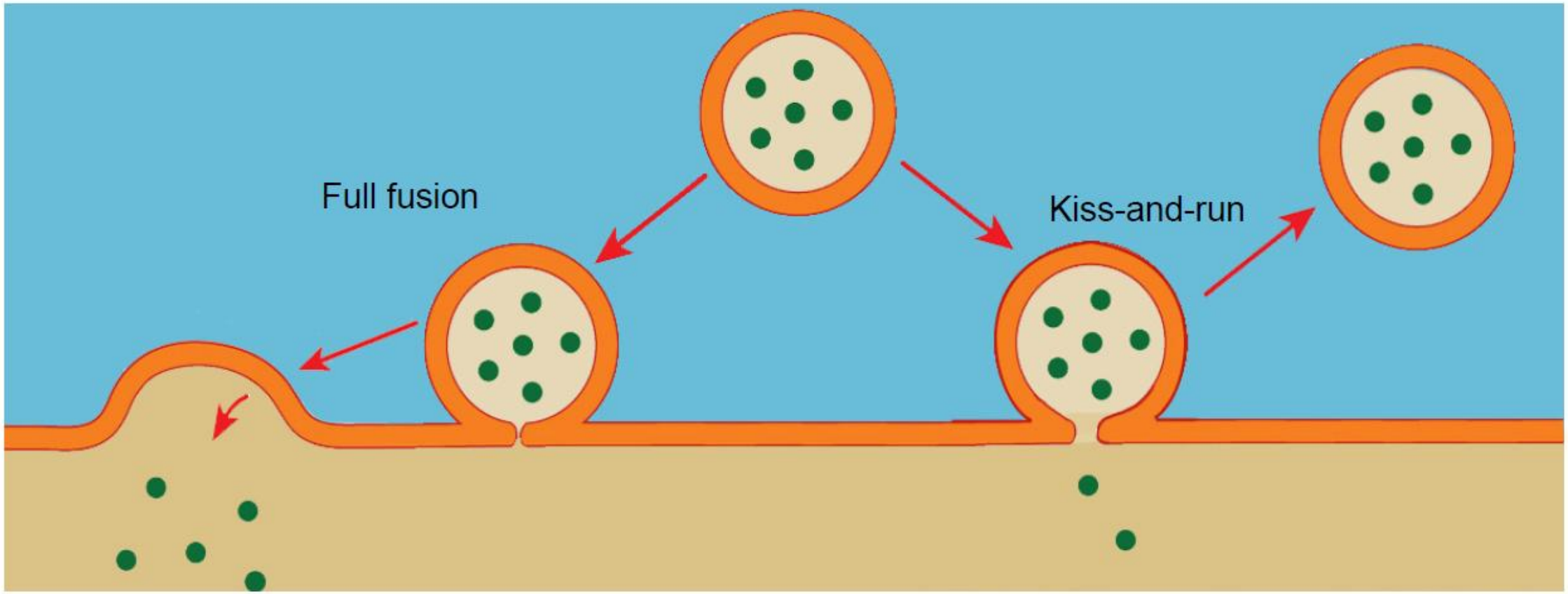
Botulinum

Tetrodotoxin

Fusing of vesicles

- Vesicles must fuse with cell membrane to release chemical contents
- V-SNARE protein synaptotagmin is a key protein required for vesicular fusion; it detects elevated levels of Ca^{2+} - the "go ahead" signal causing neurotransmitter release
- Where does the Ca^{2+} come from?
  - Change in potential travels down axon, causing depolarization at terminal
  - Depolarization at terminal triggers voltage-gated calcium channels (VGCCs) to open and allows Ca^{2+} to enter the cell
  - Ca^{2+} at terminal binds with synaptotagmin
  - V-SNAREs and t-SNAREs interact in presence of Ca^{2+}, forming SNARE complex
  - Twisting of SNARE complex causes vesicle membrane to approach inside of cell membrane, resulting in vesicular fusion

Fig 5.10 Synaptic vesicles either fuse completely (left) or partially in kiss-and-run (right).



All neurotransmitter spills into synapse

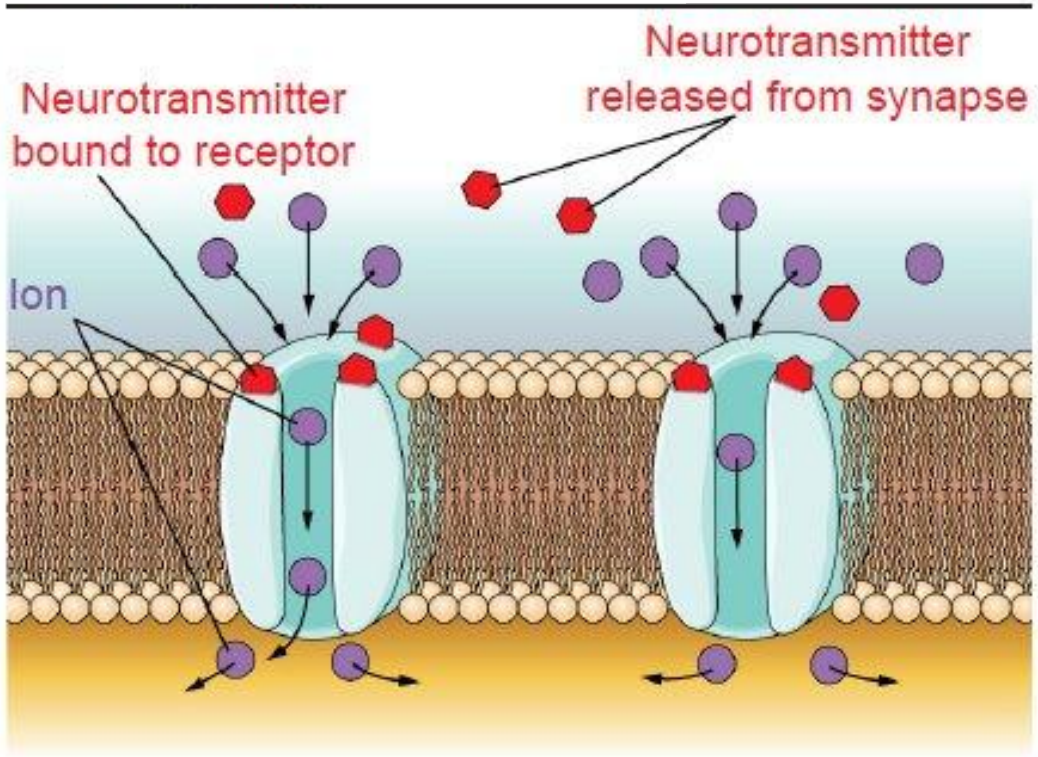
Limited amount of neurotransmitter is released into synapse via diffusion

Receptors

- Proteins that are capable of sending a signal to change the function or activity of a neuron
- Most are large transmembrane proteins
- Active site, AKA orthosteric site, is a series of amino acid residues (on extracellular surface)
  - Shaped to allow molecules of neurotransmitter to bind to receptor
- Two types: ionotropic and metabotropic
- Lots of drugs work on receptors!

Ionotropic receptor

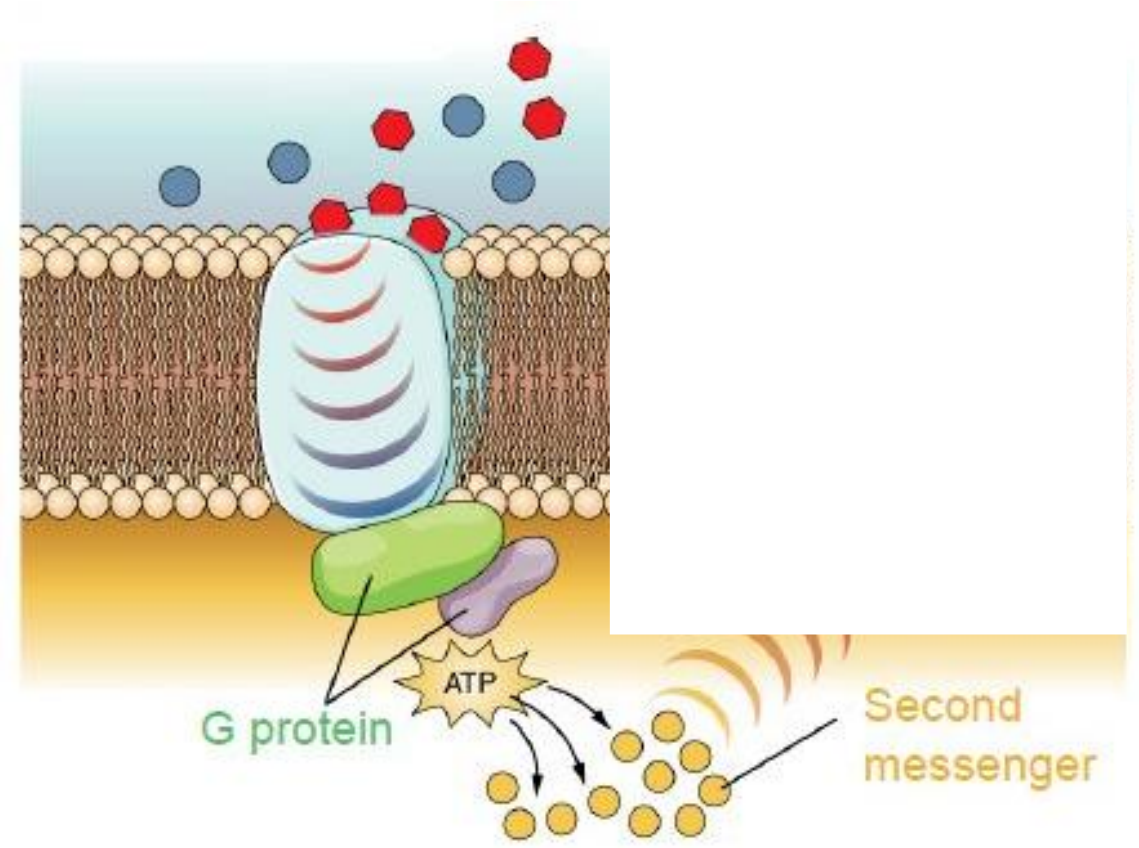
Fig 5.11 Ionotropic receptors allow ion movement after receptor binding



- Large-diameter pore through which ions can pass
- Chemical (ligand) must bind to active site on extracellular side
- Ionotropic receptors are AKA ligand-gated ion channels
- Once activated (opened), ions move with electrochemical gradient and membrane potential will change
- Fast-acting (change in potential in milliseconds)
- Amino acid residues can be very selective for certain ions

Metabotropic receptor

- Receptor complexes that change the cell's metabolism, leading to excitation or inhibition
- No passage of ions
- Instead, actions of G proteins induce changes in excitability through second messenger signaling molecules
- Are transmembrane receptors that contain 7 alpha-helix motifs that pass through the cell membrane
- AKA seven-transmembrane receptors, or 7-TM receptors
- Linked to G proteins on inner surface of cell membrane
- AKA G protein-coupled receptors, or GPCRs
- Slower to affect neuron activity (milliseconds to seconds and possibly longer)



More on metabotropic receptors

- G-proteins can bind to guanosine triphosphate (GTP) or guanosine diphosphate (GDP)
- GTP, like ATP, can be a source of energy
- G-proteins break down GTP to less-energetic GDP
- When GTP is bound to GPCR, the receptor is active; however, when GTP is hydrolyzed to GDP, the receptor becomes inactive
- Some G proteins are made up of different subunits: alpha (α), beta (β), and gamma (γ)
- GTP binding sites are on the alpha subunit (largest of the three)

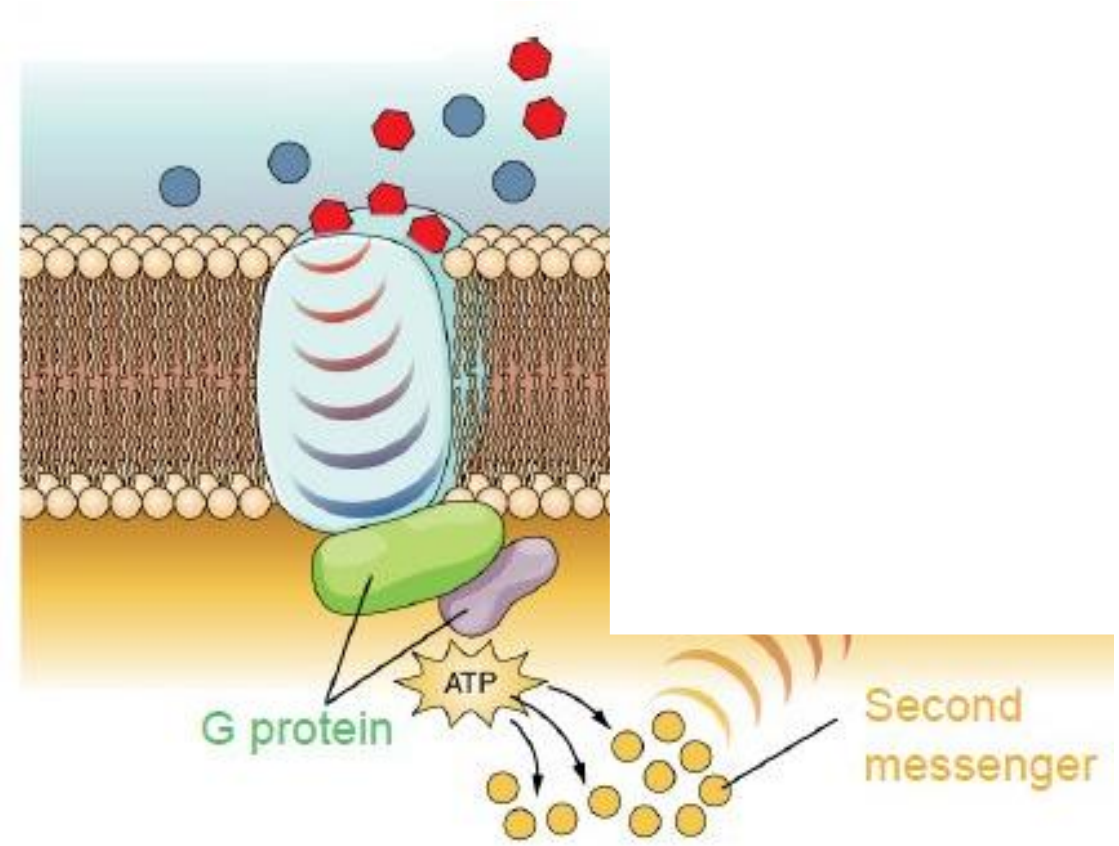
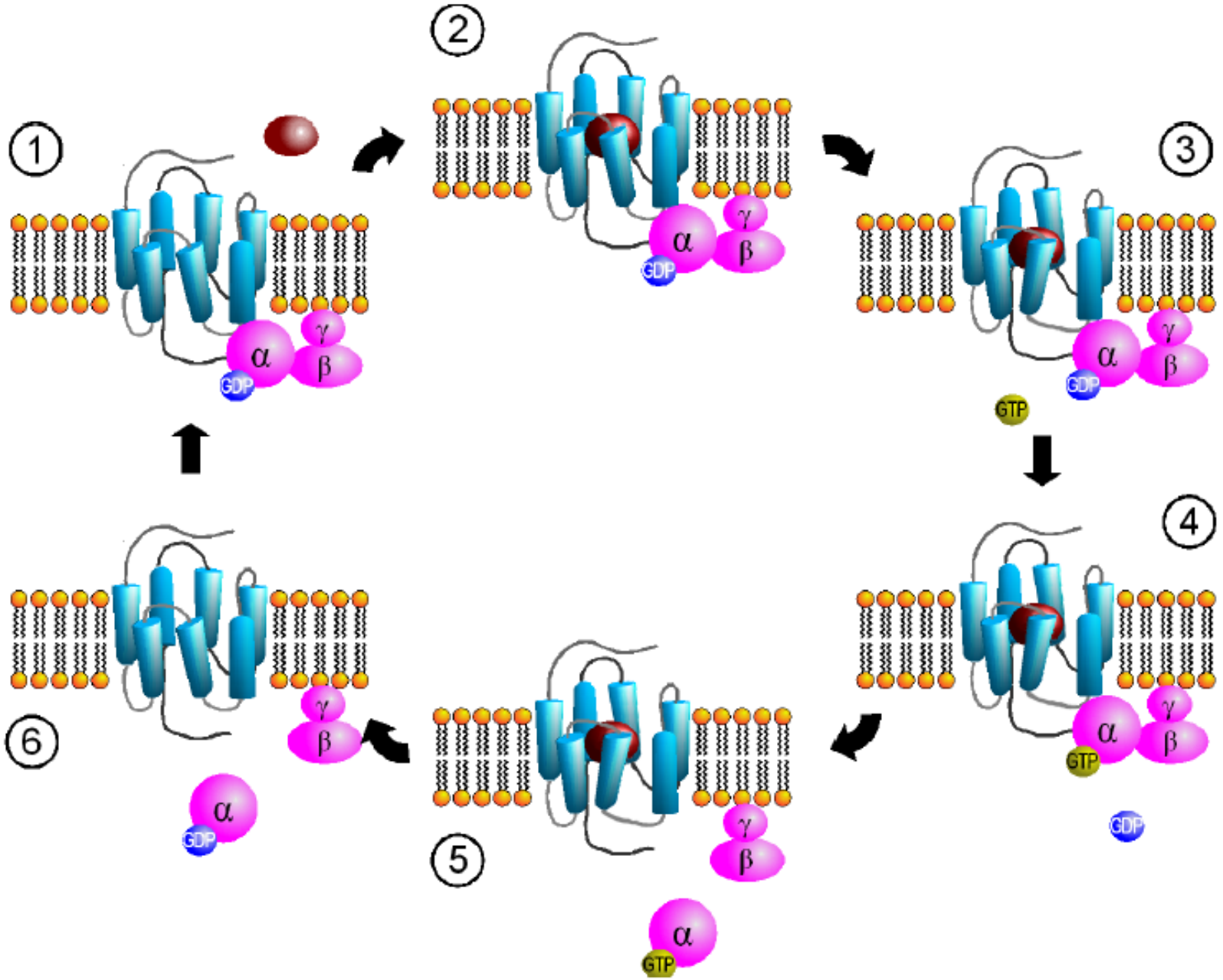
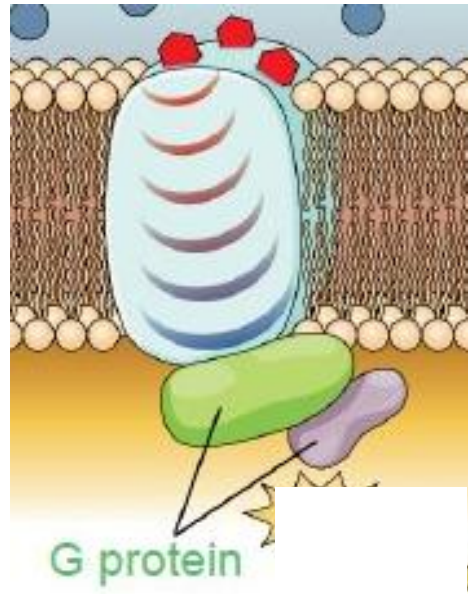


Fig 5.12 GPCRs signal via activation of the G protein attached to the intracellular side of the receptor.





Alpha (α) subunits

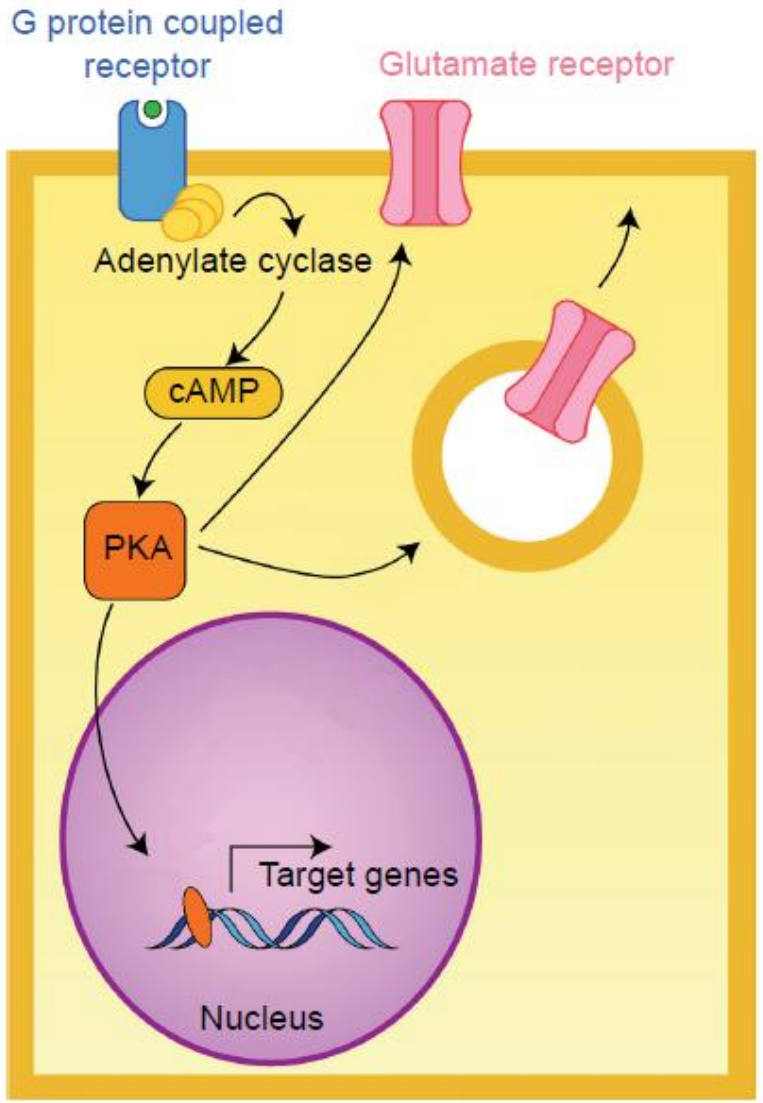
- Usually, alpha subunit becomes soluble after activation, while beta/gamma complex remains embedded in membrane
- G alpha subunit exists in different varieties: $G_{\alpha s}$, $G_{\alpha i}$, and $G_{\alpha q}$

$G_{\alpha s}$

- S stands for stimulatory (excitatory)
- Binding of ligand results in increased activity of adenylate cyclase (AC) enzyme
- AC creates a second messenger, called cyclic AMP (cAMP)
- Increase in cAMP activates protein kinase A (PKA) enzyme
- PKA phosphorylates other proteins, such as
  - glutamate receptors – which will stay open longer
  - internal store of glutamate receptors – which will be trafficked to neuronal membrane and lead to increased excitatory neurotransmission for minutes or hours
- PKA can also lead to change of transcription of various genes which can trigger synthesis of proteins (ex. Actin, important for morphological changes in neuronal structure) or ion channels (which change neuronal responses to neurotransmitter release)

$G_{\alpha s}$

Fig 5.13 GPCRs that are coupled with $G_{\alpha s}$ are excitatory through adenylate cyclase signaling.



$G_{\alpha i}$

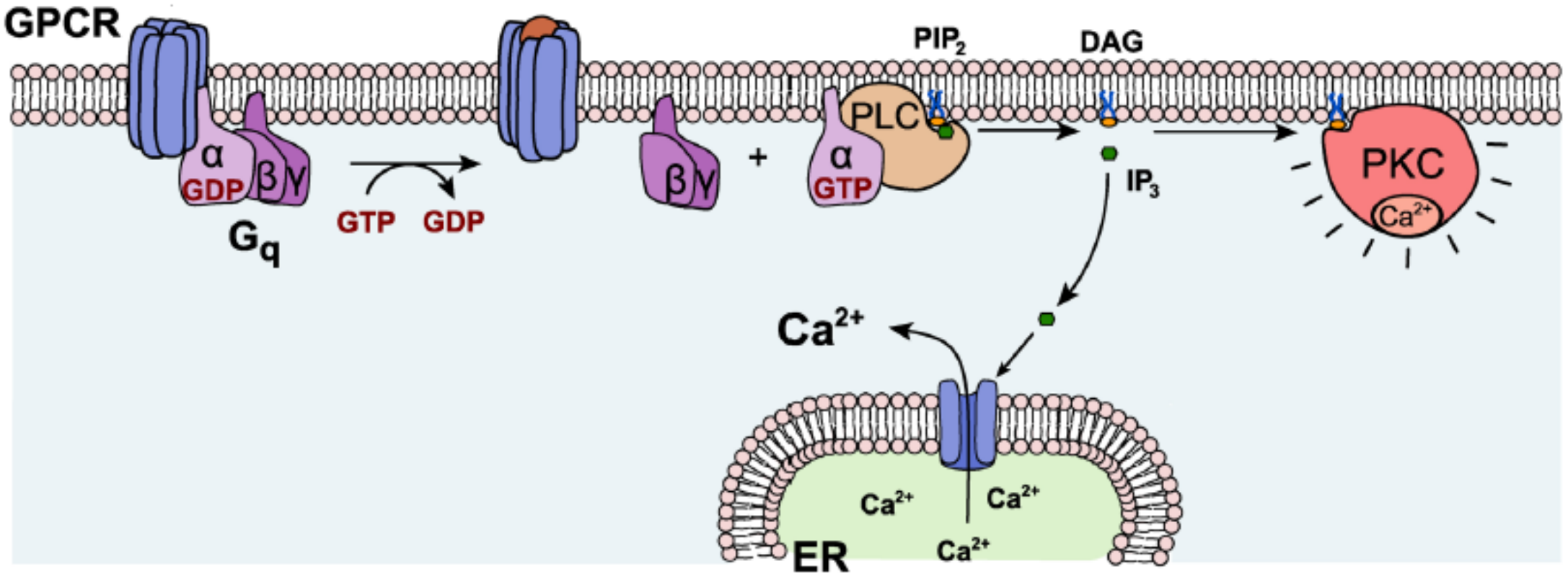
- Opposite function to $G_{\alpha s}$; i stands for inhibitory
- $G_{\alpha i}$ protein activations decrease AC activity, and therefore, intracellular concentration of cAMP, which, in turn, decreases PKA activity
- Decreased PKA activity inhibits / decreases cellular activity
  - Decreased current through glutamate receptors
  - Decreased trafficking of glutamate receptors to presynaptic neuronal membrane
  - Decreased transcription of certain genes

$G_{\alpha q}$

- Generally, an excitatory G protein
- Different pathway compared to the PKA pathway of $G_{\alpha s}$ or $G_{\alpha i}$
- $G_{\alpha q}$ activation leads to activity of phospholipase C (PLC) enzyme
- PLC acts on phospholipid membrane molecule PIP2
    - Breaks PIP2 into 2 separate messenger molecules
        - Soluble inositol triphosphate (IP3)
        - Membrane-embedded diacylglycerol (DAG)
- IP3 liberates Ca^{2+} from intracellular stores, increasing Ca^{2+} levels, depolarizing the cell, and activating calcium-dependent processes, which are often excitatory
- DAG activates protein kinase C (PKC), an enzyme with substrates that increase neurotransmitter release probability or decrease potassium (K) channel conductance

$G_{\alpha q}$ depicted

Fig 5.14 $G_{\alpha q}$ signals using PLC, which then produces two signaling molecules, IP3 and DAG.



Beta and gamma subunits

- Beta and gamma subunits are bound together as a dimer
- Separate from alpha subunit when GPCR (G protein-coupled receptor) becomes activated
- Beta-gamma complex can also function as a signaling molecule

Small group activity: Ionotropic and metabotropic receptors

Similarities

Differences

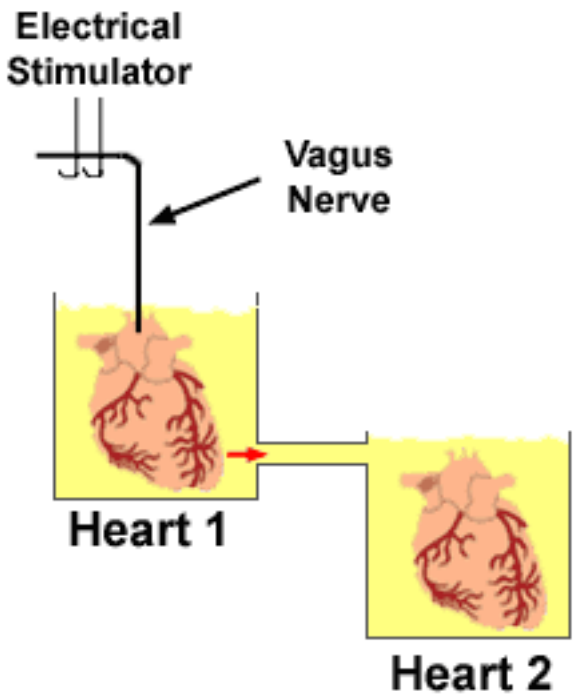
Presynaptic receptors

- Common to think of receptors as expressions in dendrites of postsynaptic cells; however, not all receptors are there
- Can be presynaptic (found at axon terminal)
- Presynaptic receptors are often inhibitory and serve self-regulatory function
- If presynaptic receptors respond to same neurotransmitter as they release, they are called autoreceptors
  - Feedback loop

Neurotransmitters

- Substances released at chemical synapses
- Signaling molecules that allow neurons to communicate with each other
- More than 100 have been identified
- Six common neurotransmitters
  - Glutamate, GABA + glycine, dopamine, serotonin, acetylcholine, & norepinephrine
- Three atypical neurotransmitters
  - Neuropeptides, endocannabinoids, & nitric oxide
- Effect of neurotransmitter depends on receptor (ex. Can excite or inhibit)

Discovering chemical signalling



https://faculty.washington.edu/chudler/chnt.html

- First neurotransmitter discovered and chemically isolated (Nobel Prize in Physiology or Medicine in 1936)
- Vagusstoff (German word meaning Vagus substance)
- Now known as ACh

"In the night of Easter Saturday, 1921, I awoke, turned on the light, and jotted down a few notes on a tiny slip of paper. Then I fell asleep again. It occurred to me at six o'clock in the morning that during the night I had written down something most important, but I was unable to decipher the scrawl. That Sunday was the most desperate day in my whole scientific life. During the next night, however, I awoke again, at three o'clock, and I remembered what it was. This time I did not take any risk; I got up immediately, went to the laboratory, made the experiment on the frog's heart, described above, and at five o' clock the chemical transmission of nervous impulse was conclusively proved."--- quoted from Loewi, O., *From the Workshop of Discoveries*, Lawrence: University of Kansas Press, 1953.

Acetylcholine (ACh)

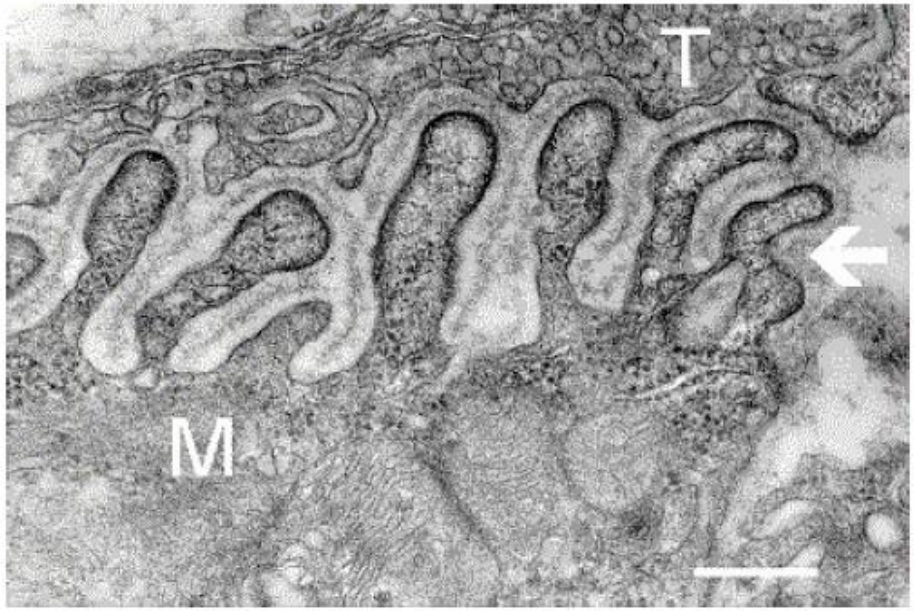
- Small molecule made by choline acetyltransferase (ChAT), which bonds a molecule of acetyl-CoA with a molecule of choline
- ChAT = biomarker for acetylcholine-producing neurons
- ACh acts at ionotropic and metabotropic receptors
  - Nicotinic acetylcholine receptors (nAChRs) are ionotropic (can be activated by nicotine or acetylcholine)
    - Ligand-gated sodium channels, and therefore, excitatory
  - Muscarinic acetylcholine receptors (mAChRs) are metabotropic receptors (can be activated by muscarine found in some mushrooms)
    - Can be coupled with G_s or G_i (excitatory or inhibitory)

ACh continued

- Main neurotransmitter used to communicate with muscles at neuromuscular junction (NMJ)
- At NMJ, ACh is released by motor neurons and activates nicotinic acetylcholine receptors on muscle cells, causing constriction or flexion
- Muscarinic acetylcholine receptors are located in the heart
- Their activation decreases heart rate (as Otto Loewi demonstrated with isolate frog heart)
- In CNS, ACh is involved in a variety of processes, including attention and learning

NMJ

Fig 5.20 An electron microscope image of the neuromuscular junction showing vesicles (T, top) forming a synapse with the muscle cell (M, bottom). Acetylcholine is the main neurotransmitter used in muscle control at the PNS.



Glutamate

- Main excitatory neurotransmitter used by nervous system
- Same as amino acid glutamic acid
- More glutamate per volume of brain tissue than any other neurotransmitter
- Glutamatergic neurons are identified by presence of vesicular glutamate transporter (vGluT)
- Can activate ionotropic and metabotropic receptors

Ionotropic glutamate receptors

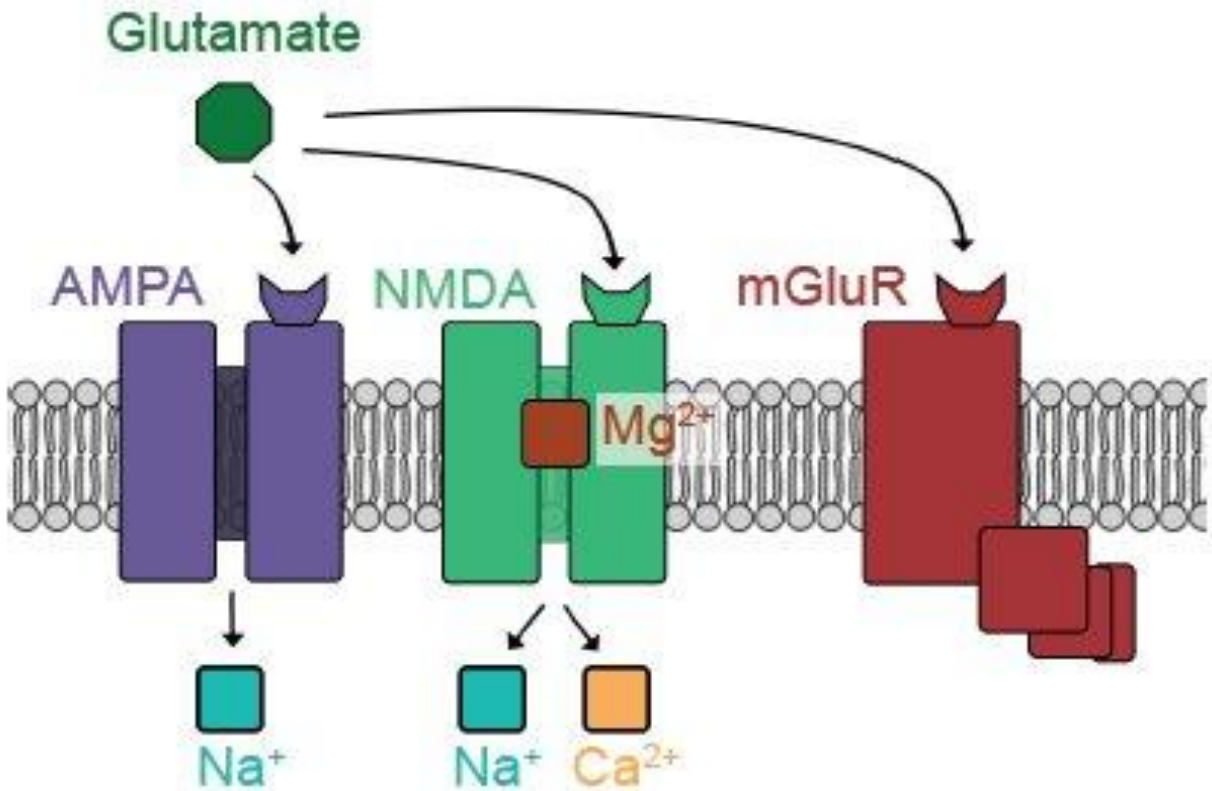
- All ligand-gated cation channels
- Excitatory since they allow Na^+ to move into the cell
- Generally, subdivided into 3 classes, named after exogenous chemicals that activate the receptor:
  - AMPA receptors (Na^+ channels, but some allow Ca^{2+} entry)
  - NMDA receptors – at rest, have a large magnesium ion in the pore that blocks ion movement
  - Kainate receptors (similar to AMPA receptors)

Metabotropic glutamate receptors (mGluRs)

- Signal using different G proteins
- 8 mGluRs, classified into three groups: Group I, Group II, and Group III
- Group I is excitatory GPCRs which signal via G_q
- Groups II and III are inhibitory via the G_i signal transduction pathway

Glutamate receptors

Fig 5.15 Glutamate is the main excitatory neurotransmitter in the nervous system, acting at different categories of receptors, three of which are shown below.



Excitotoxicity

- Theory: excess signaling by glutamate can lead to neuronal death, a phenomenon called excitotoxicity
- NMDA receptor is most strongly indicated
- Uncontrolled elevated levels of calcium can be deadly for neurons
- Excitotoxicity is observed in several disease states, including Parkinson's, Alzheimer's, and multiple sclerosis, and also in injuries, such as concussion or stroke.

GABA

- Gamma-aminobutyric acid (GABA) = main inhibitory neurotransmitter in brain
- Estimated that ~25% of neurons in brain are GABA-ergic
- Similar to glutamate; in fact, synthesized from glutamate in a single step by enzyme glutamic acid decarboxylase (GAD)
- GAD is used as a biomarker for presence of GABA-ergic neurons
- Many interneurons use GABA as signaling molecule

GABA continued

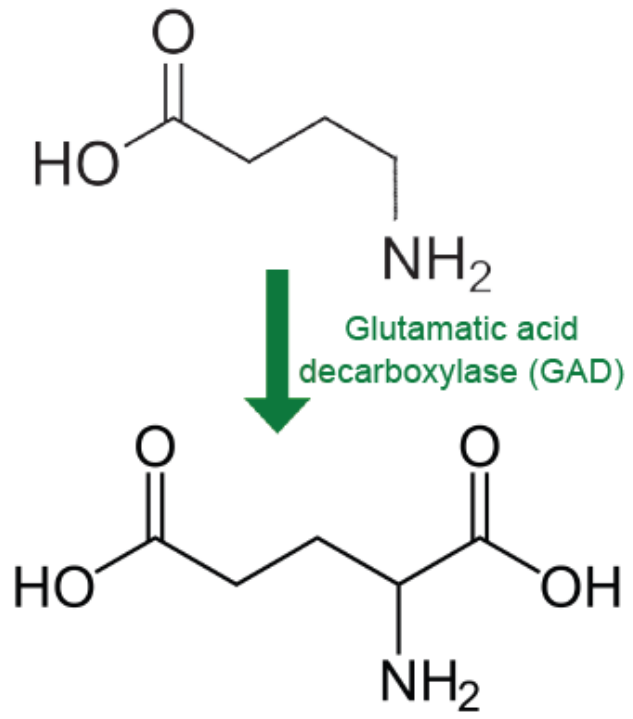
- GABA activates one of 3 main receptors: A, B, and C
- $GABA_A$ receptors are ligand-gated chloride channels; when activated, they cause Cl^- flux which opposes ability of cell to reach action potential threshold
- $GABA_B$ and $GABA_C$ are metabotropic receptors that inhibit activity through action of the G_i protein

Glycine

- Glycine is a neurotransmitter similar to GABA
- Glycine is a small amino acid, used by neurons of spinal cord and brainstem
- Inhibitory
- Opens ligand-gated chloride channels

Synthesis of GABA

Fig 5.16 The inhibitory neurotransmitter GABA is synthesized from glutamate by the action of GAD.



Dopamine (DA)

- Biogenic amine derived from amino acid tyrosine through action of several enzymes, including tyrosine hydroxylase (TH) - marker used to identify dopamine-producing neurons
- Dopamine-producing neurons are not widely abundant in brain
- A few patches of neurons produce dopamine, and most of those are found in the midbrain
- 2 areas of their concentration are the ventral tegmental area and the substantia nigra

DA continued

- Classes of dopamine receptors: D1 through D5, all are metabotropic
- D1 & D5 are generally excitatory, while D2, D3, and D4 are inhibitory
- DA is known as "pleasure neurotransmitter" due to involvement in processing reward and motivation
- More complex than once believe; may serve as a "learning signal" - pay attention to salient stimuli in environment

Dopamine-producing neuron sites

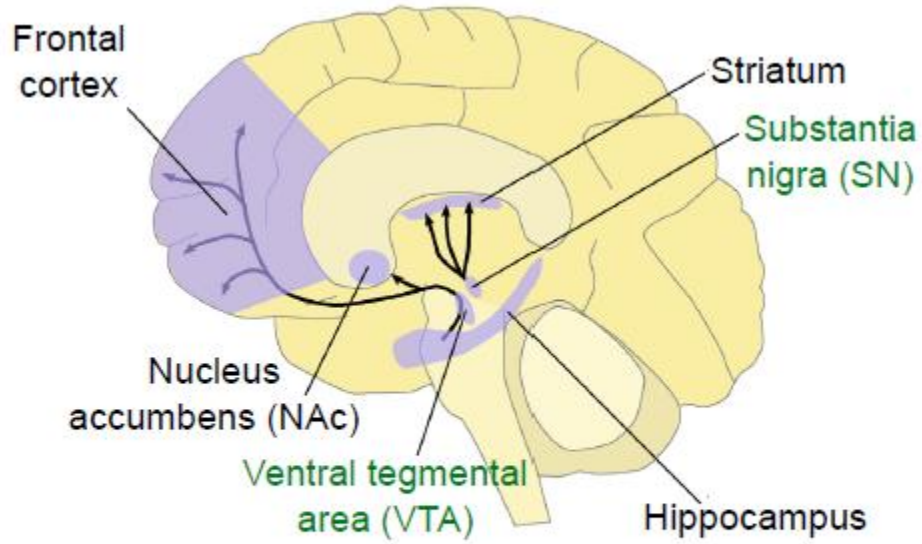


Fig 5.17 Brain dopamine is synthesized in two major midbrain nuclei, the VTA and SN, labeled in green.

Clinical connection: L-DOPA-inducted dyskinesia (LID)

DA is needed for motor control

Degeneration of DA-producing neurons in substantia nigra pars compacta lead to difficulties with motor control, resting tremor, postural instability, & bradykinesia (slowness of movement)

Clinical correlation: Parkinson's disease (PD) and L-DOPA-induced dyskinesia (LID)

Parkinson's disease is a debilitating neurodegenerative disorder that affects as many as 1% of all people aged 60 or older. Generally, PD is lethal within 16 years. By the time a patient presents to the clinic with motor dysfunction, they have already lost almost 60-80% of dopamine-producing neurons in this area!

For decades, clinicians have been using the biochemical precursor to dopamine, L-DOPA, to treat the symptoms. However, after chronic exposure to L-DOPA, the drug becomes less effective and has a shorter duration of therapeutic action. Worse still, frequent treatment can lead patients to develop **hyperkinesias**, an abnormal excess of movements. This iatrogenic disorder is called **L-DOPA induced dyskinesia (LID)**.

Biomedical engineers have developed a promising non-drug approach to treating PD called **deep brain stimulation**. A small stimulating device is surgically implanted into the subthalamic nucleus of the brain. When this brain area is stimulated, neural circuits are recruited which restores normal motor control.

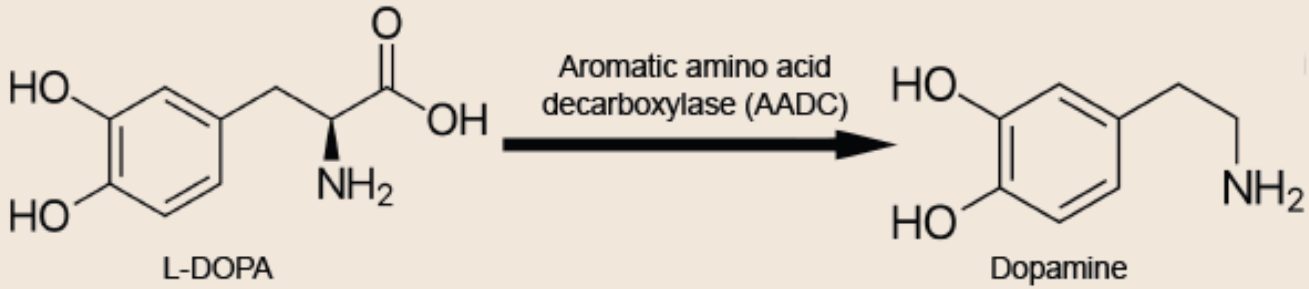


Fig 5.19 Patients with PD have characteristic changes in gait as a result of low dopamine (top). The current best pharmacological therapy is levodopa administration, which is the biochemical precursor to dopamine (bottom).

Deep brain stimulation (DBS)

- https://www.youtube.com/watch?v=34XP72FuvnQ

Serotonin (5-HT)

- Derived from dietary amino acid tryptophan
- Enzyme tryptophan hydroxylase is first step of 5-HT synthesis and is used as a marker to identify serotonergic neurons
- Few areas of the brain synthesize serotonin (like dopamine); major one is Raphe nucleus in brain stem
- Serotonin receptors have a wide variety of actions

5-HT continued

- 7 major families of 5-HT receptors, designated by number, and subclasses, designated by letter
- Most are metabotropic; 5-HT3 receptor is an exception (ionotropic)
- Serotonin is heavily implicated in regulation of mood and complex behavioral conditions
- Drug to treat depression: fluoxetine, acts as a selective-serotonin reuptake inhibitor; prevents reuptake, increasing synaptic levels of serotonin
- Serotonin signaling is also a target for drug to treat anxiety, PTSD, OCD, schizophrenia, and more

Norepinephrine (NE)

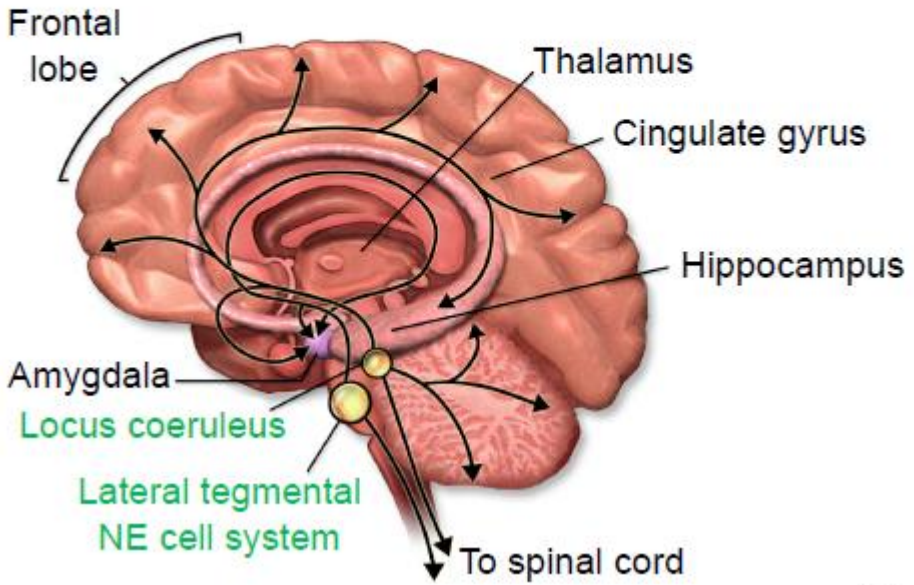
- Synthesized from DA by enzyme dopamine beta-hydroxylase
- Norepinephrine-producing neurons are localized in pons of brain stem, a structure called locus coeruleus (small, but projections are wide throughout brain)
- Outside of brain, NE is responsible for sympathetic nervous system responses, the "fight-or-flight" reaction
  - These NE-producing neuron reside in the sympathetic ganglia, nerve cells running parallel to the spinal cord on each side of the body, projecting to the internal organs

NE continued

- 2 classifications of NE receptors: alpha and beta + subtypes within each category, giving 5 major receptors for NE: alpha-1, alpha-2, beta-1, beta-2, and beta-3 (all metabotropic; some excitatory, and some inhibitory)
  - Beta-blockers are drugs that inhibit beta-adrenergic receptors, resulting in decrease of blood pressure
  - Beta-agonists are used as bronchodilators for asthma
- Functions in brain to modulate behaviors, including alertness and attention

NE-producing brain area

Fig 5.21 Norepinephrine in the brain is synthesized by small populations, but these cell bodies project widely across several other areas.



Neuropeptides

- Large signaling molecules
- Ex. Enkephalin, which has a molecular weight of 570 (compared to monoamines like DA, NE, and 5-HT, with molecular weights of 150-200)
- Ex. Dynorphin (molecular weight > 2000)
- Because of size, packaged in dense-core vesicles very close to production site (near nucleus)
- Agonists at class of receptors called opioid receptors – 3 types (delta [δ], mu [μ], and kappa [κ]) plus nociceptin receptors
    - All inhibitory metabotropic receptors which signal using $G_{\alpha i}$ protein
- Receptors are expressed in several brain areas, but particularly heavily in periaqueductal gray (PAG), a midbrain area that inhibits pain sensation
- Drugs that activate opioid receptors and used to treat pain: oxycontin and fentanyl (lethal in overdose and high risk of substance use disorder)

Enkephalin, a small neuropeptide

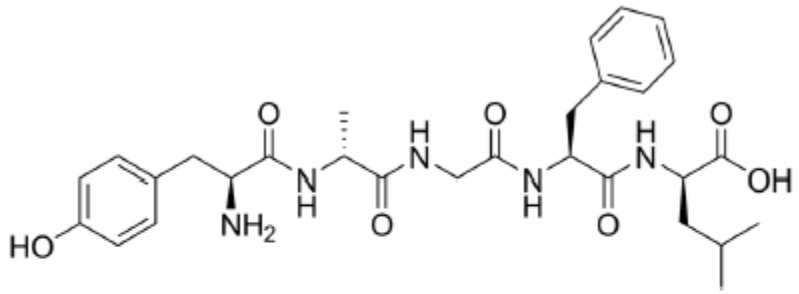


Fig 5.22 Enkephalin, one of the smaller neuropeptides, is very large compared to other neurotransmitters. Enkephalin is an agonist for both δ and μ opioid receptors.

Endocannabinoids (eCBs)

- Class of lipid-based neurotransmitters
- Endogenous chemicals that function similarly to chemicals in cannabis
- Instead of sending information via anterograde signaling, allow retrograde signaling
  - Postsynaptic dendritic component communicates with presynaptic axon terminal
- Not packaged in vesicles; synthesized *de novo* (right when they are needed and used right away)
- 2 most well-characterized eCBs in humans: 2-AG & AEA
- eCBs activate CB1 and CB2 – both inhibitory metabotropic receptors
- CB1 are generally found in nervous system & CB2 elsewhere in body
- Estimated that eCB receptors are most abundant GPCRs in body

Endocannabinoid action depicted

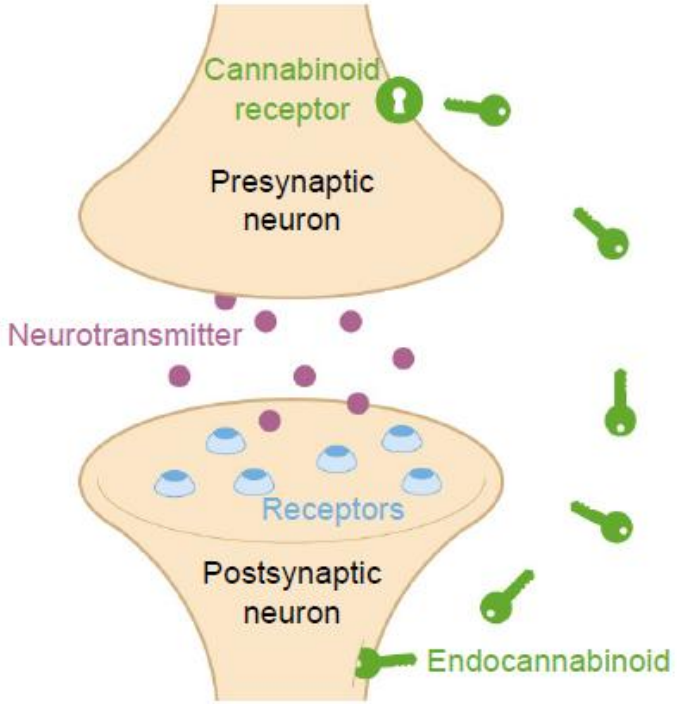


Fig 5.23 ECBs are synthesized from the postsynaptic cell membrane and signal through presynaptic cannabinoid receptors

Nitric oxide (NO)

- Not stored in vesicles
- Synthesized as needed
- NO is formed when amino acid arginine is degraded by enzyme NO synthase (NOS)
- A gas which permeates across cell membrane; no need for transmembrane protein receptors
- Instead, receptor for NO is intracellular and called soluble guanylate cyclase (sGC)
- sGC works differently from metabotropic receptors discussed; linked with signaling molecule cyclic GMP (cGMP)
- CGMP activates protein kinase G (PKG), which can be excitatory or inhibitory depending on intracellular components