Neurotransmitters

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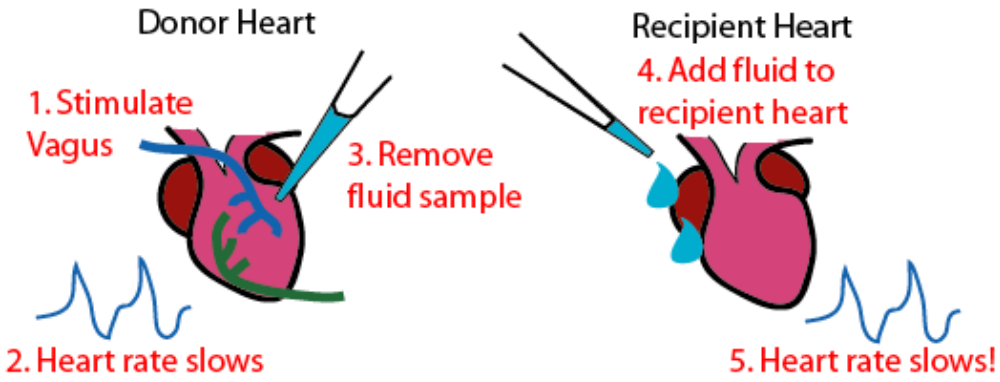
February 2021

Neurotransmitters

- Otto Loewi, 1921

- Synaptic transmission was chemical, at the junction between a branch of the vagus nerve and the heart

- *Vagusstoff (acethylcholine)*



Neurotransmitters

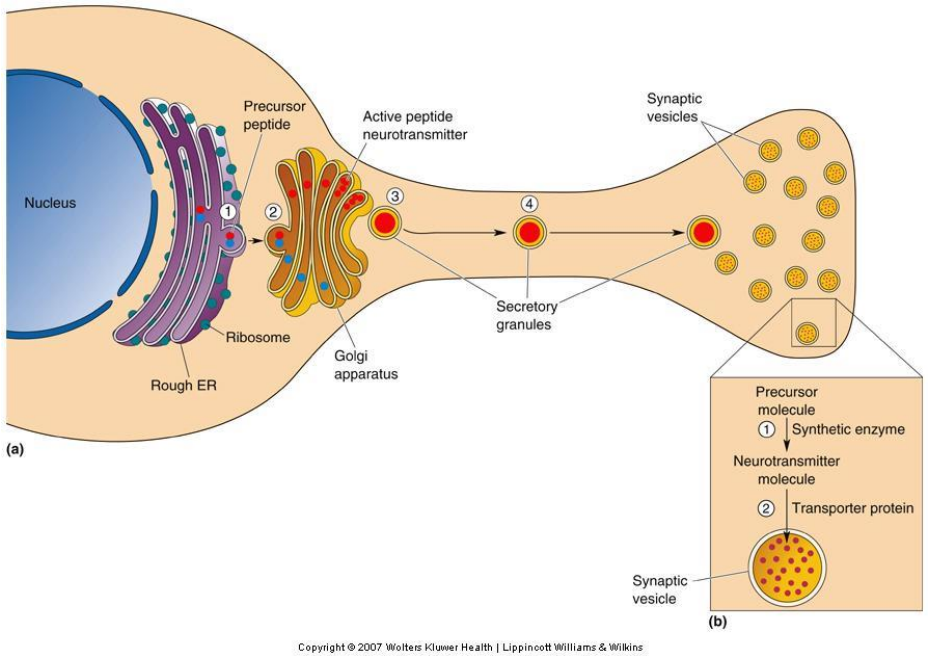
- Neurons mostly release one type of neurotransmitter
  - Amino acid (or amine) and a peptid neurotransmitter is common: *Co-transmitters*
- At most CNS synapses are mediated by the amino acids; glutamate (Glu) , gamma-aminobutyric acid (GABA) , or glycine (Gly)
- The amine acetylcholine (ACh) mediates fast synaptic transmission at all neuromuscular junctions

TABLE 5.1 **The Major Neurotransmitters**

Amino Acids	Amines	Peptides
Gamma-aminobutyric acid (GABA)	Acetylcholine (ACh)	Cholecystokinin (CCK)
Glutamate (Glu)	Dopamine (DA)	Dynorphin
Glycine (Gly)	Epinephrine	Enkephalins (Enk)
	Histamine	*N*-acetylaspartylglutamate (NAAG)
	Norepinephrine (NE)	Neuropeptide Y
	Serotonin (5-HT)	Somatostatin
		Substance P
		Thyrotropin-releasing hormone
		Vasoactive intestinal polypeptide (VIP)

Neurotransmitters

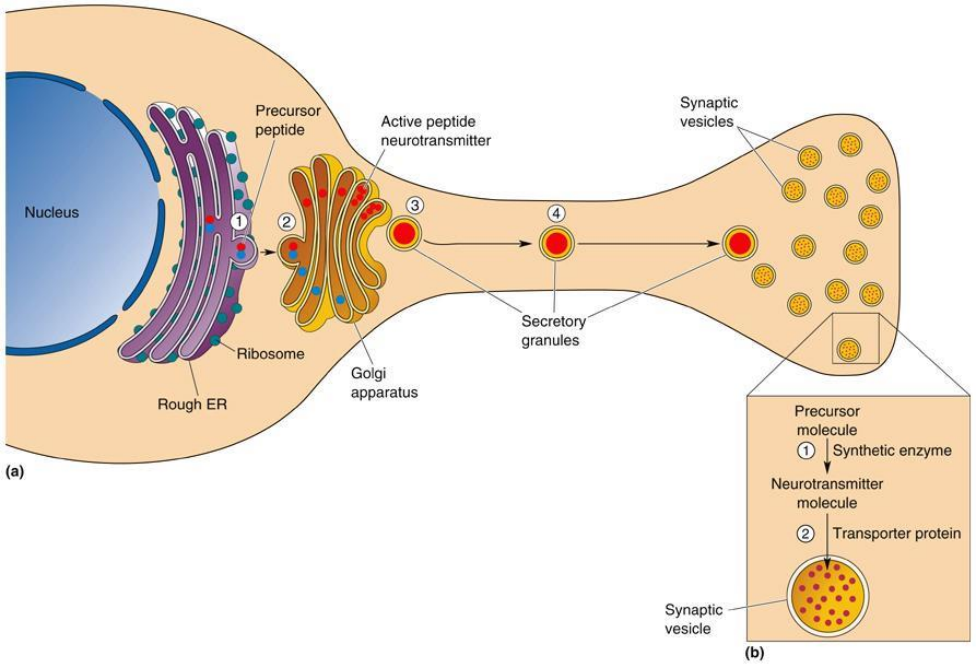
- The amino acid and amine neurotransmitters
  - small organic molecules containing at least one nitrogen atom
  - stored in and released from *synaptic vesicles*
- Peptide neurotransmitters are large molecules—chains of amino acids—
  - stored in and released from *secretory granules*
- Secretory granules and synaptic vesicles are frequently observed in the same axon terminals



Neurotransmitters

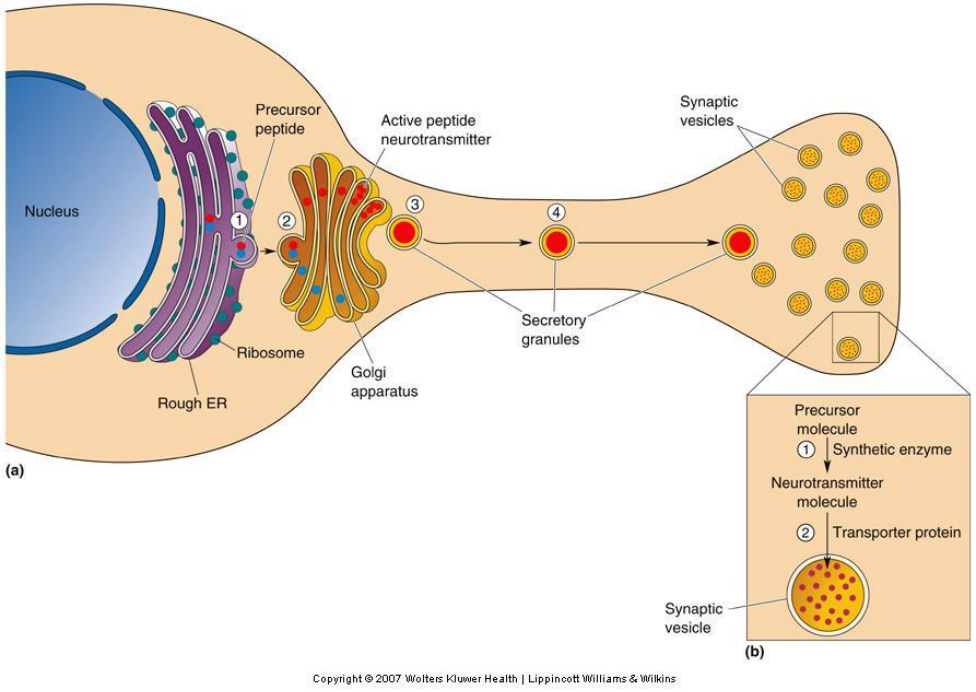
- The synthesizing enzymes for both amino acid and amine neurotransmitters are transported to the axon terminal, where they locally and rapidly direct transmitter synthesis

- Once synthesized in the cytosol of the axon terminal, the amino acid and amine neurotransmitters are taken up by the synaptic vesicles (transporters embedded in the vesicle membrane)



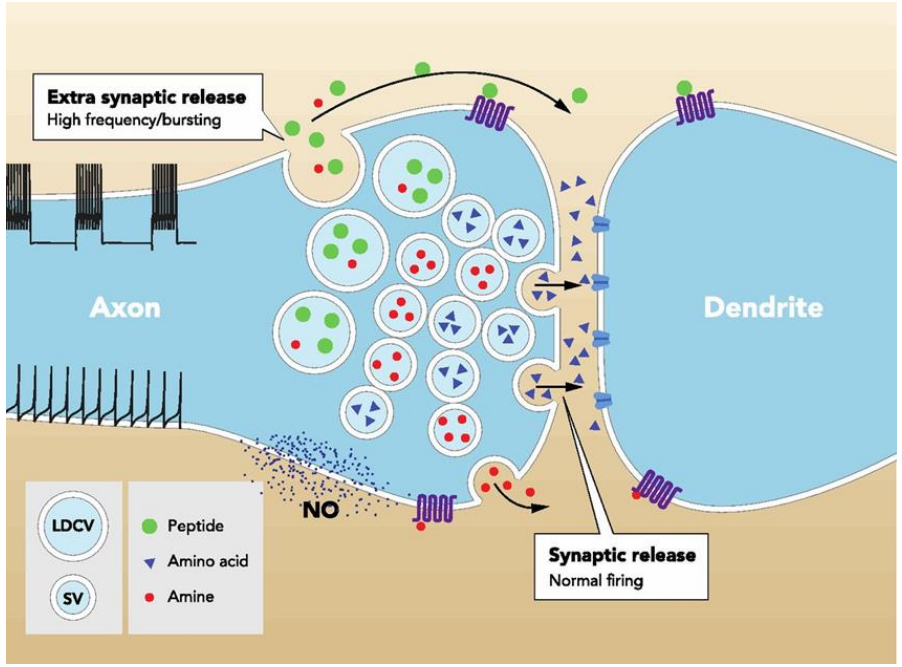
Neurotransmitters

- Peptides;
  - Synthesized in the rough ER
  - Split to the active neurotransmitter in the golgi aparatus
  - Secretory granules containing the neurotransmitter bud off from the golgi aparatus
  - Carried to the axon terminal by axoplasmic transport



Peptide Neurotransmitters

- Peptides are often cotransmitters (released together with a small transmitter)
- Release of peptides typically requires a high-frequency train of stimuli
- Peptides act on slow metabotropic receptors (There are not peptide-gated ion channels)
- There are a great diversity of peptides
  - Examples:
    - Opioid peptides
      - Endorphin, enkephalin, dynorphin
    - Substance P
    - Orexin
- The functions of peptides are generally not well understood
  - excitatory or inhibitory effects → modulatory



Naming of neurotransmitter systems

- ACh and all the molecular machinery associated with it are collectively called the *cholinergic system*

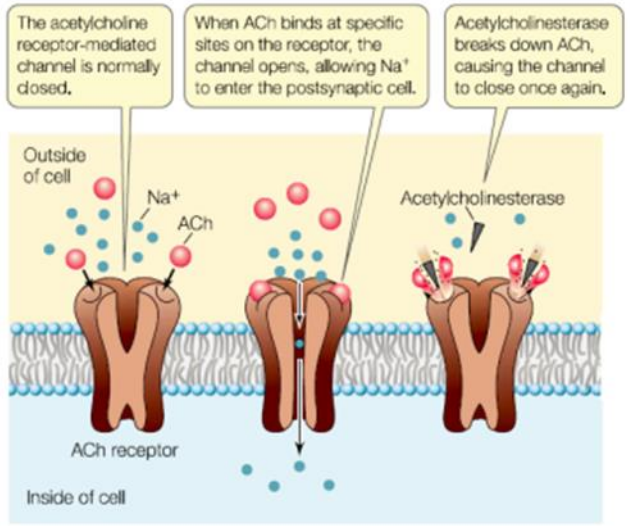
- GABAergic synapses

- Dopaminergic neurons

Neurotransmitter Receptors

- All receptors for chemical transmitters have two biochemical features in common:
  1. They are membrane-spanning proteins. The region exposed to the external environment of the cell recognizes and binds the transmitter from the presynaptic cell.

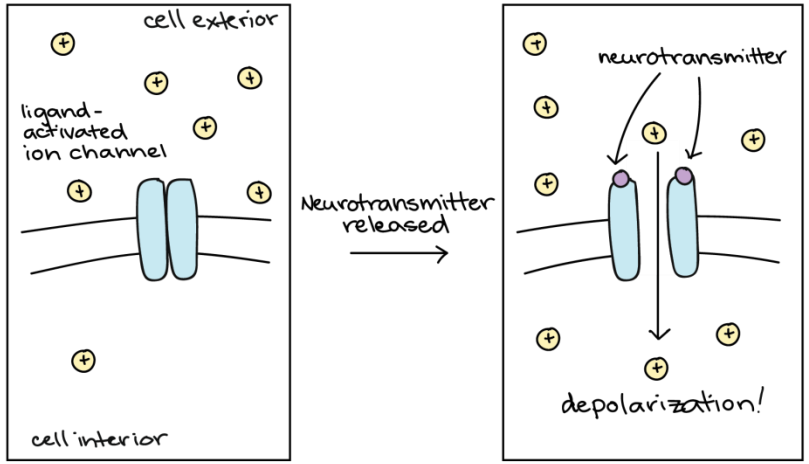
  2. They carry out an effector function within the target cell. The receptors typically influence the opening or closing of ion channels.



Neurotransmitter Receptor Types

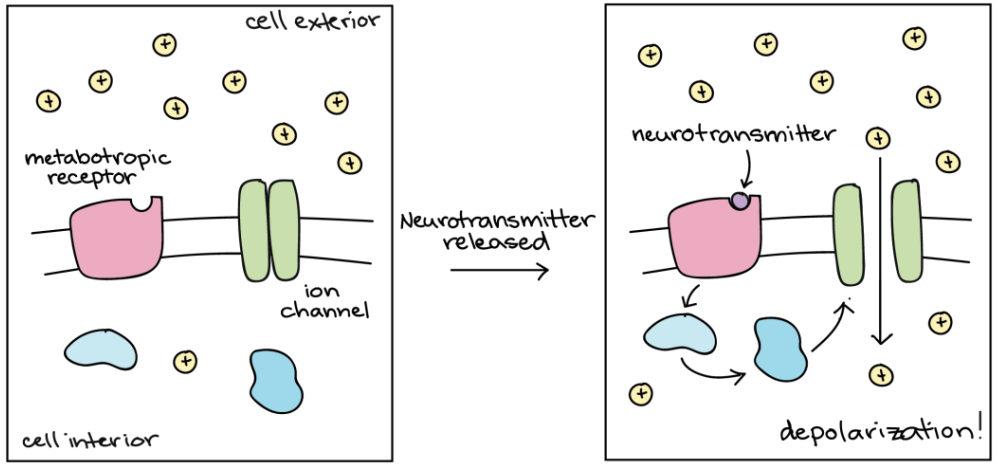
Ionotropic receptors

- Ion channels
- Direct change in ion movement across the plasma membrane of postsynaptic cell
- Fast, short-lived responses



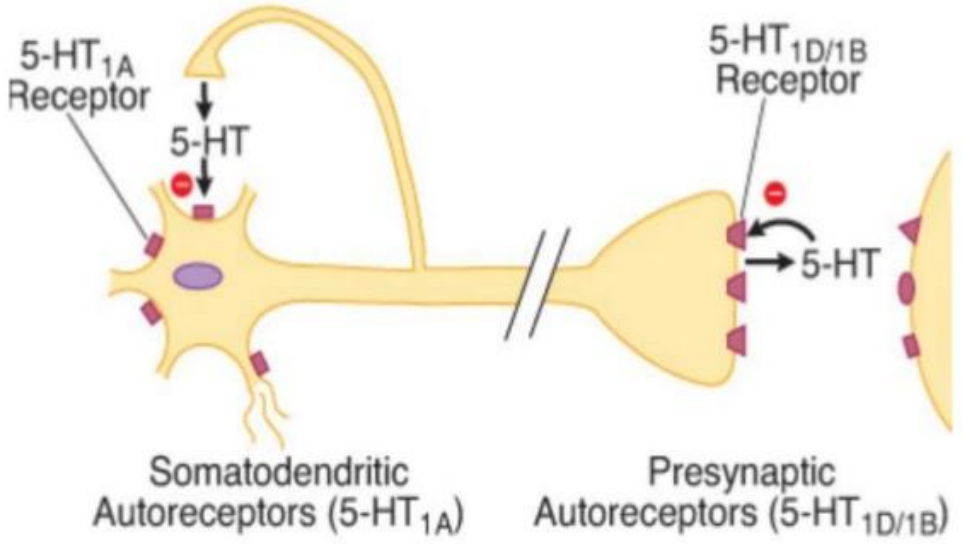
Metabotropic receptors

- Not ion channel
- Induce signalling cascade in the postsynaptic cell that leads to changes in ion channels
- Slow and longer-lived responses



Autoreceptors and Presynaptic Inhibition

- Receptors are sometimes found on the presynaptic terminal.
- Activation leads to:
  - Inhibition of neurotransmitter release
  - Neurotransmitter synthesis.
- Autoreceptors may act as a brake on the release of neurotransmitters

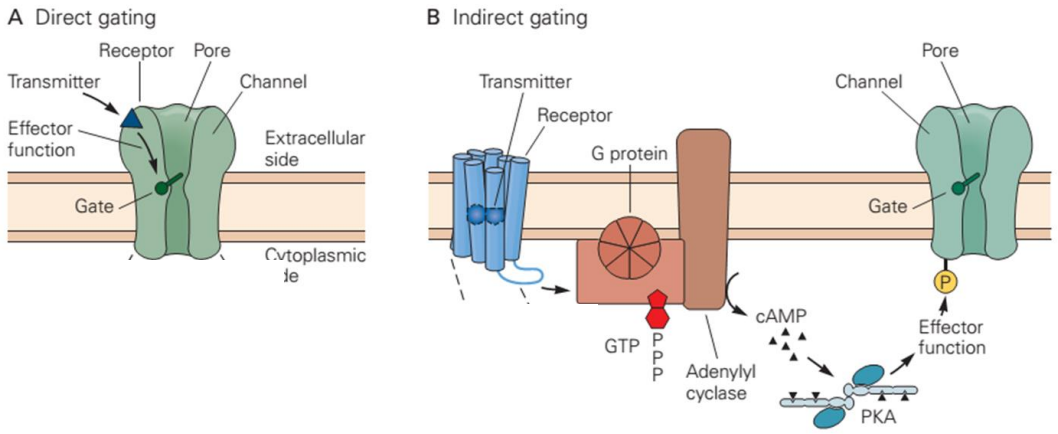


Neurotransmitter Receptors

Postsynaptic Receptors Gate Ion Channels Either Directly or Indirectly

- *Ionotropic receptors:* the receptor undergoes a conformational change that opens the channel.

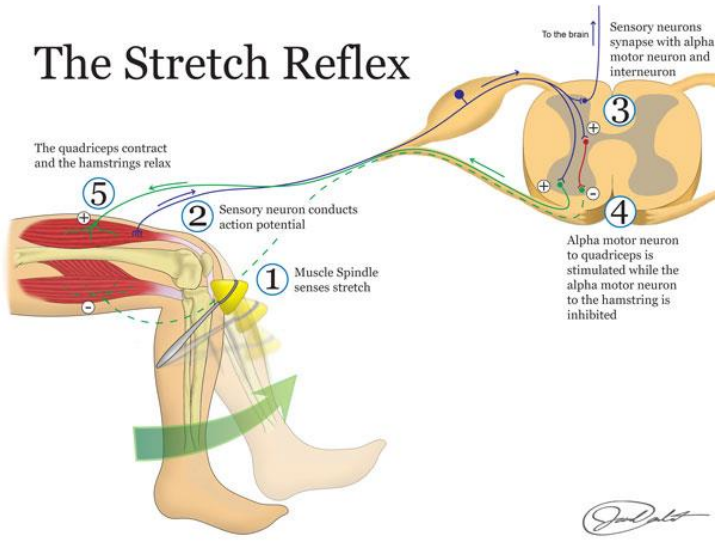
- *Metabotrobic receptors:* alter intracellular metabolic reactions. Production of second messengers (cAMP, DAG), activates protein kinases (PKA) that phosphorylates ion channels, leading to their opening or closing



Neurotransmitter Receptors

- Ionotropic receptors
  - produce relatively fast synaptic actions lasting only milliseconds
  - found at synapses in neural circuits that mediate rapid behaviors, (e.g., stretch receptor reflex)

- Metabotropic receptors
  - produce slower synaptic actions lasting seconds to minutes
  - can modulate behavior by altering the excitability of neurons and the strength of the synaptic connections of the neural circuitry mediating behavior, (e.g., learning)



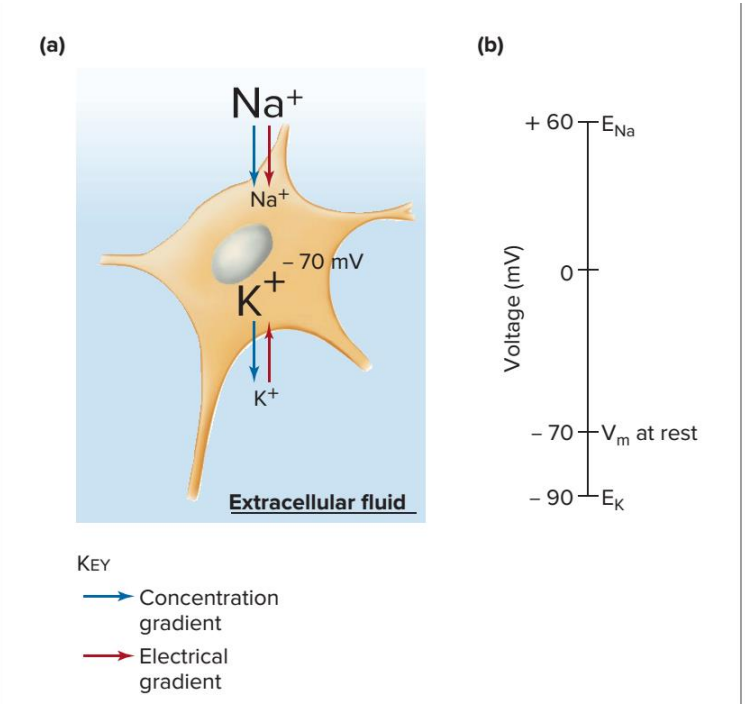
Neurotransmitter Receptors

- For ions, transmitter-gated channels are not as selective as voltage-gated channels.
  - ACh-gated ion channels at the neuromuscular junction are permeable to both Na^+ and K^+

- If the open channels are permeable to Na^+, the net effect will be to depolarize the postsynaptic cell from the resting membrane potential

Neurotransmitter Receptors

- Both electrical and concentration gradients drive Na+ into the cell, whereas for K+ , the electrical gradient opposes the concentration gradient
- Opening channels that are permeable to both ions results in the simultaneous movement of a relatively small number of potassium ions out of the cell and a larger number of sodium ions into the cell
- The net movement of positive ions is into the postsynaptic cell, causing a slight depolarization.



Criteria for a neurotransmitter

- Criteria that must be met for a molecule to be considered a neurotransmitter:

1. The molecule must be synthesized and stored in the presynaptic neuron.
2. The molecule must be released by the presynaptic axon terminal upon stimulation.
3. The molecule, when experimentally applied, must produce a response in the postsynaptic cell that mimics the response produced by the release of neurotransmitter from the presynaptic neuron.

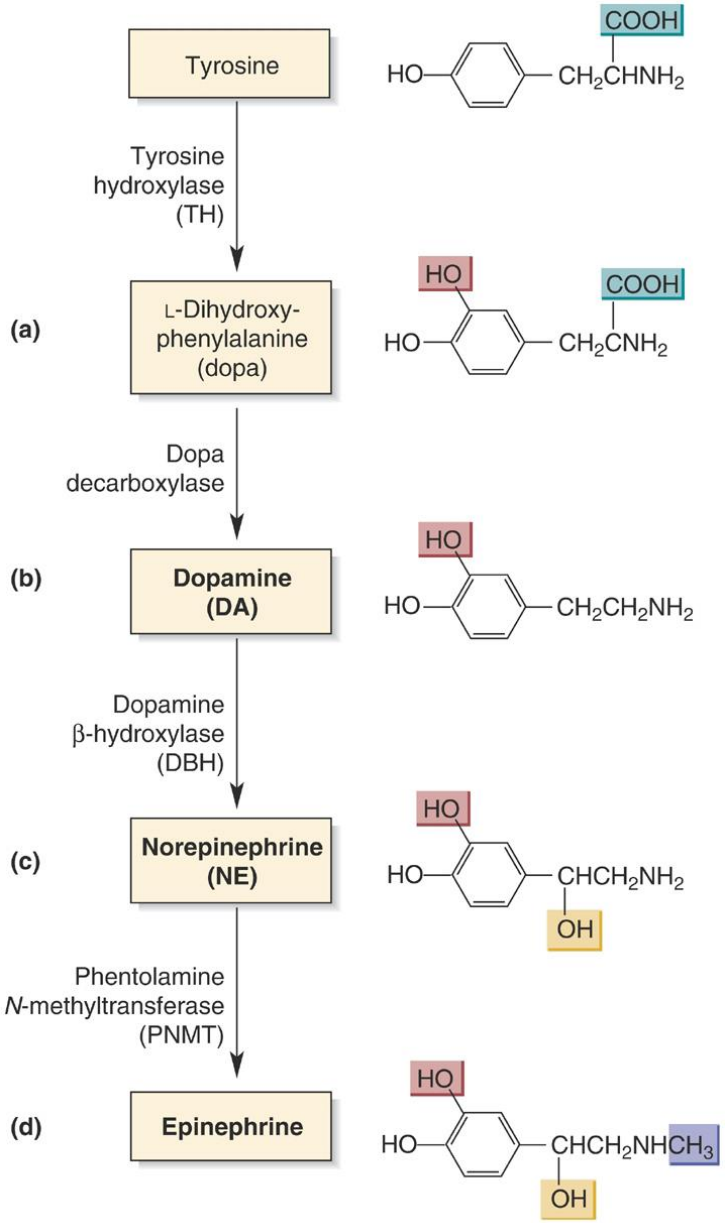
Neurotransmitters

- Conventional transmitters
  - The basic excitatory and inhibitory transmitters
    - Glutamate, GABA, glycine
  - Modulatory transmitters
    - acetylcholine, norepinephrine, dopamine, serotonin, histamine
  - Peptides
    - Many types, example: endorphin
- Unconventional transmitters
  - Membrane permeable; not released from vesicles
  - May not have specific, dedicated receptors
  - Examples:
    - Endocannabinoids
    - Nitric Oxide
    - Retrograde transmission
    - “inter-cellular messengers” rather than “neurotransmitters”

Synthesis of Neurotransmitters

- Each neurotransmitter has its own specific synthetic enzyme or enzymes

1. the synthetic enzyme is found exclusively in neurons that release that neurotransmitter
   - serves as a marker for those neurons
   - Tyrosine hydroxylase for norepinephrine and dopamine containing neurons
2. the enzymes are found in all cells, but are expressed at higher levels in neurons that use that neurotransmitter
   - glutamate



Amino Acid Neurotransmitters

- *Glutamate, Aspartate, GABA, Glycine*
- High concentration in brain circuits
  - Cortico-cortical
  - Sensory-motor
- Point-to-point communication
- Consistently excitatory or inhibitory
  - Mainly ionotropic receptors but do have metabotropic receptors
- Fast acting, short duration (1-5 ms)

Glutamate

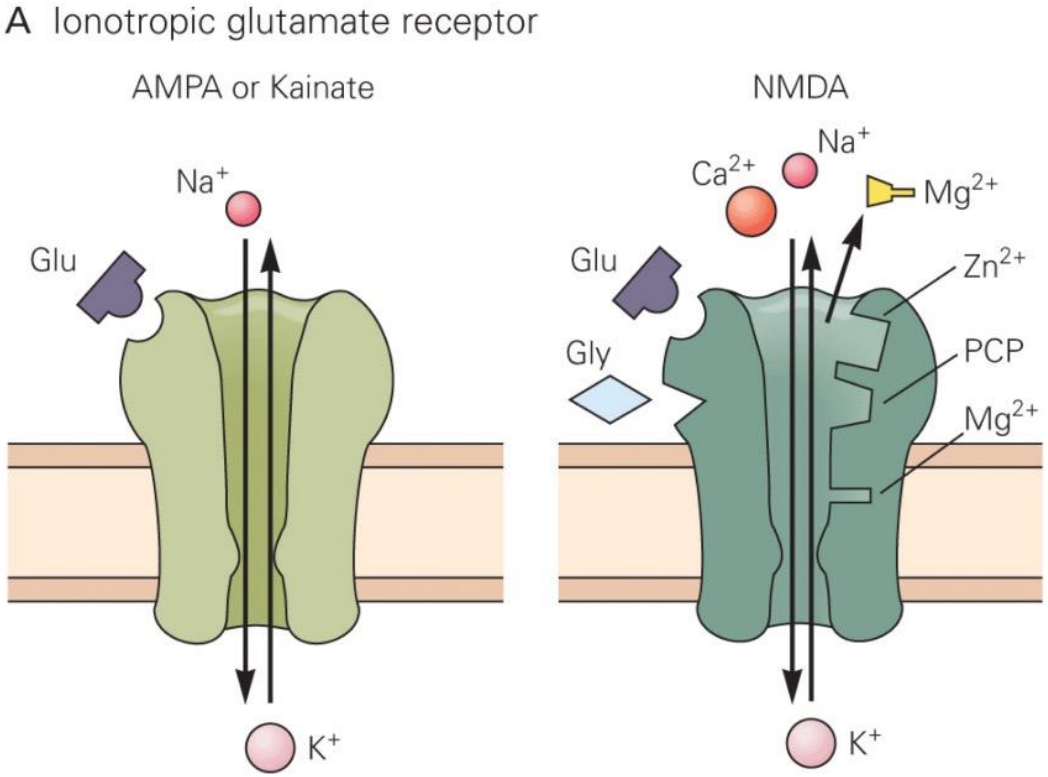
- Principal excitatory Neurotransmitter
- Biosynthesized as byproduct of cell metabolism
- Removed by reuptake
- Elevated levels → neurotoxic
- 4 receptor types
  - NMDA
  - AMPA
  - Kainate
  - mGluR - Metabotropic

Ionotropic

Glutamate Receptor

- NMDA
  - Mg^{2+} block
    - Released with depolarization
  - Ca^{2+}, Na^{2+}, K^{+}

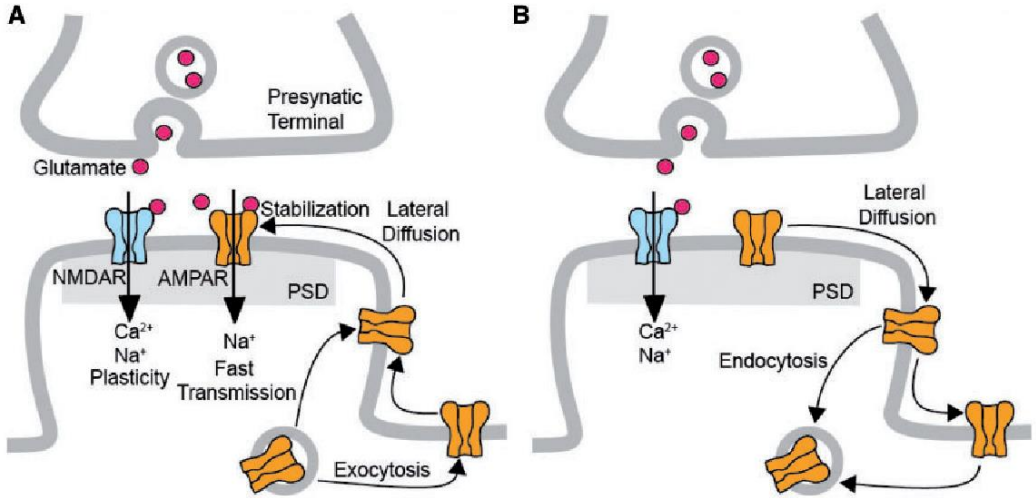
- AMPA or Kainate
  - Na^{2+}, K^{+}
  - Actively recyled (endo, exocytosis)



AMPA receptor traficking

- Ca^{2+} → Activation of Protein Kinases → AMPA vesicle exocytosis

- Less Ca^{2+} → Activation of Phosphatases → AMPA vesicle endocytosis (desensitization)



GABA

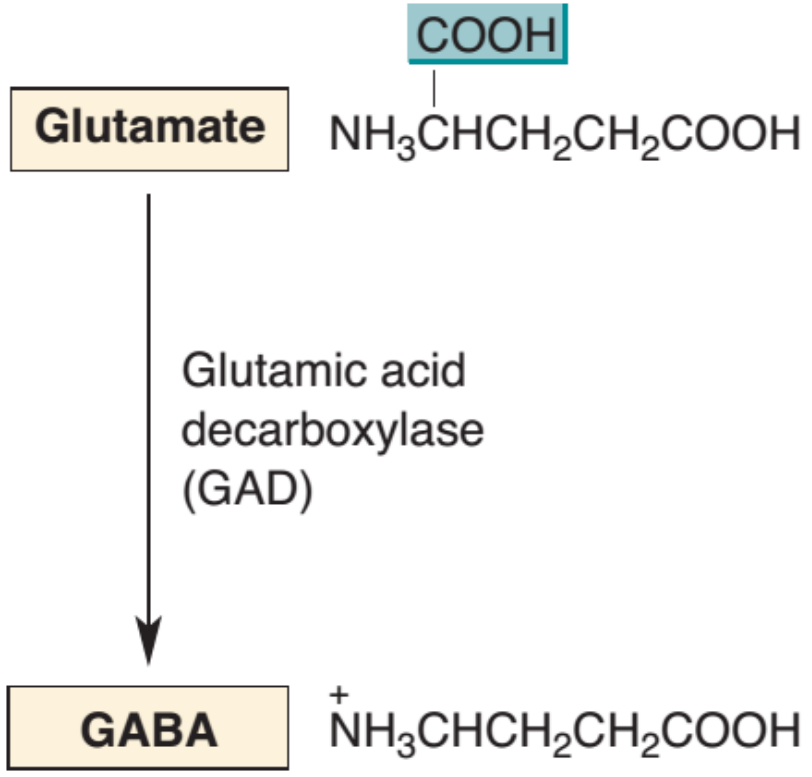
1. GABA is formed by removal of carboxyl group of glutamate, by the enzyme GAD

2. packaged into synaptic vesicles and released by depolarization

3. a. taken up by nerve terminal for repackaging into synaptic vesicles

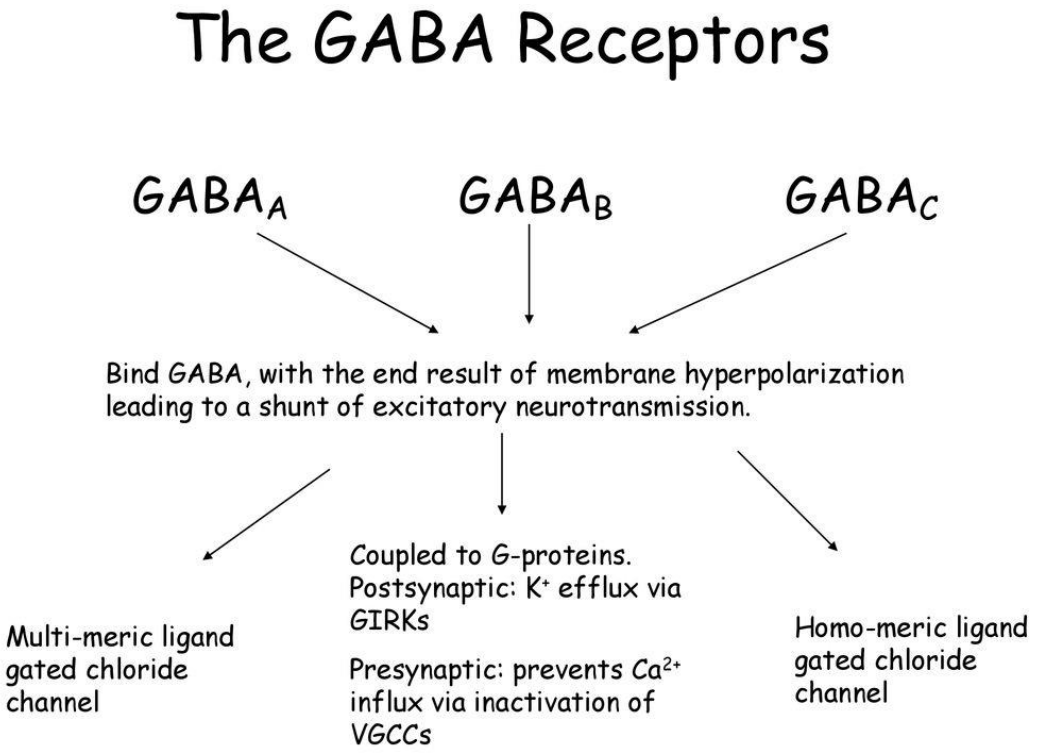
   b. taken up by glial cells, where it undergoes reconversion to glutamate

Glutamate is transported back into nerve terminal, where it serves as precursor for new GABA synthesis



GABA receptors:

- $GABA_A$
  - Fast GABA transmission
  - ligand-activated chloride channels
- $GABA_B$
  - Slow transmission
  - metabotropic receptor
  - Opening of G-protein coupled K+ channels
  - Inactivation of voltage gated Ca2+ channels
- $GABA_C$
  - Fast GABA transmission
  - ligand-activated chloride channels



Biogenic Amines

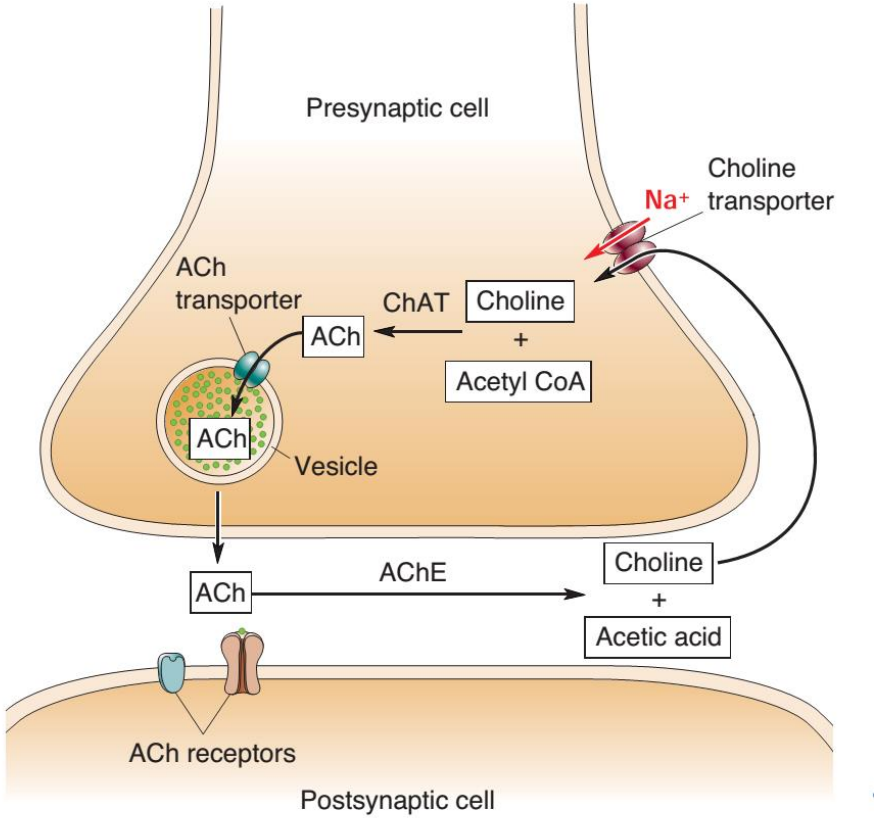
- *Acetylcholine, Dopamine, Norepinephrine, Epinephrine, Serotonin*

Catecholamines

- Medium concentration in brain
- Circuits
  - Single-source divergent projections
  - Mainly midbrain to cortex
- Modulatory functions
  - Excitatory or inhibitory as a function of receptor
- More metabotropic receptors than ionotropic
- Slow acting, long duration

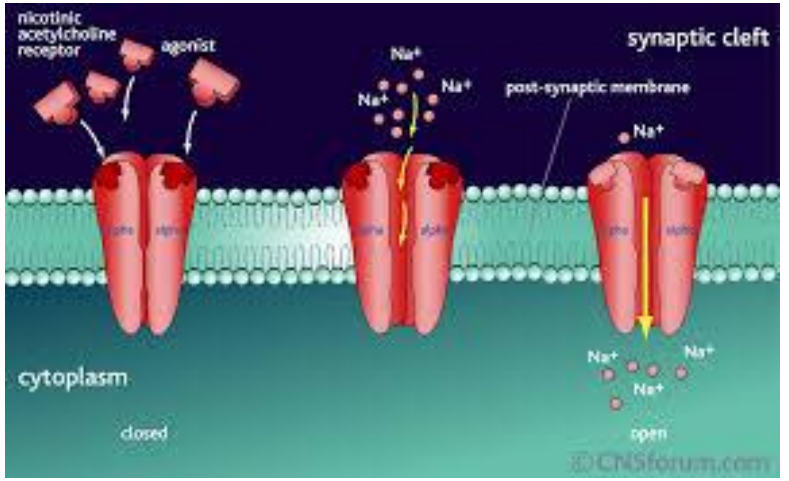
Acetylcholine

- Major neurotransmitter in the peripheral nervous system at the neuromuscular junction
- Acetylcholine is synthesized from choline (a common nutrient found in many foods) and acetyl coenzyme A in the cytoplasm of synaptic terminals and stored in synaptic vesicles.
- After it is released and activates receptors on the postsynaptic membrane, degredaded by acetylcholinesterase (located on the presynaptic and postsynaptic membranes) to choline and acetate.
- Choline is transported back into the presynaptic axon terminals where it is reused in the synthesis of new ACh.

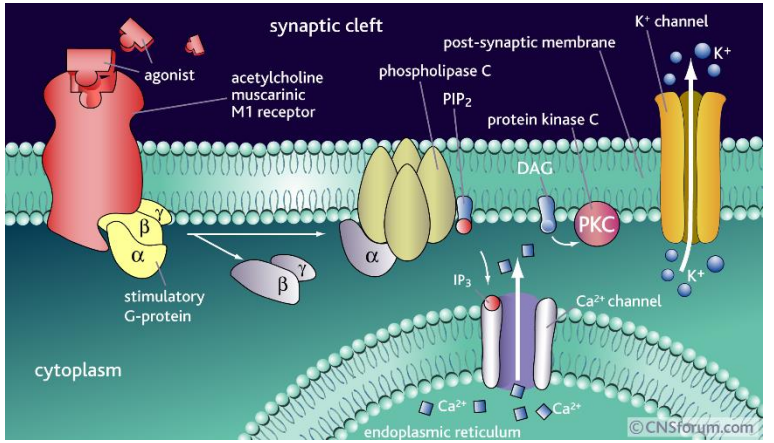


Acetycholine Receptors

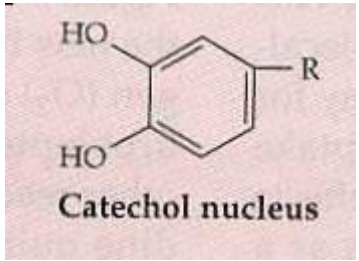
- Nicotinic Receptors:
  - Opens a Na+ channel
  - Causes a depolarization, and results in an EPSP
  - The electrical response is fast, and short-lived
  - Skeletal muscles

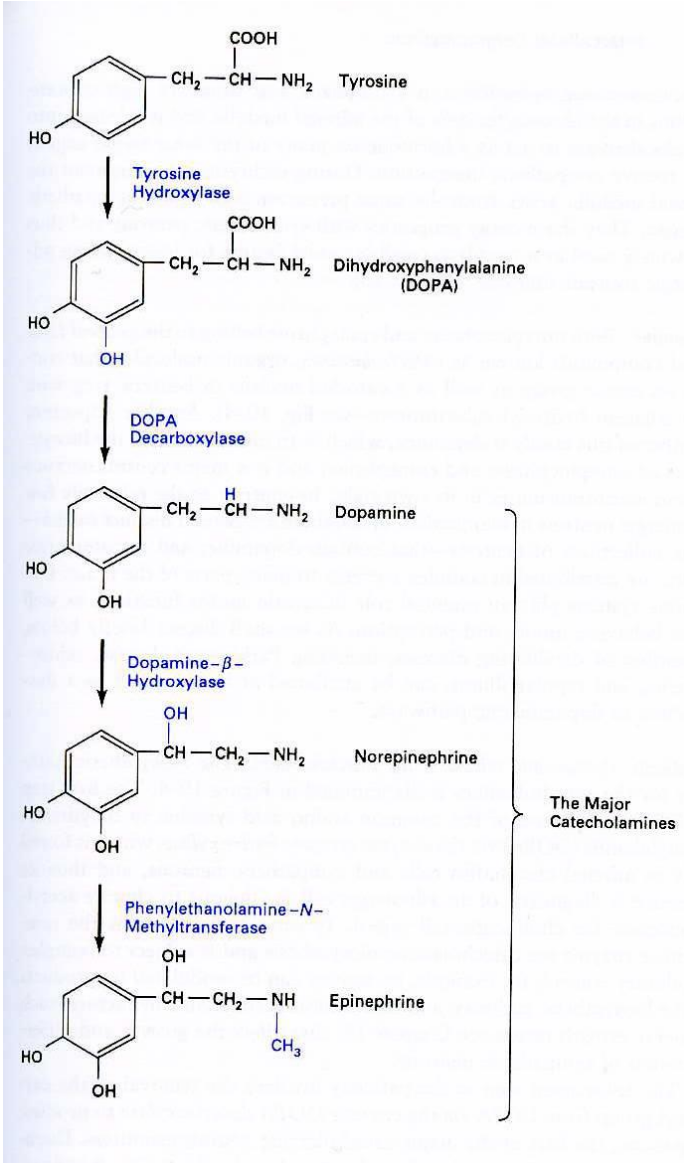


- Muscarinic Receptors
  - Receptor is linked to a G-protein – The G-protein activates channels or enzymes indirectly –
  - Responses are diverse, slower, and longer-lived
  - Control peristalsis, glandular secretion, pupil constriction, vasodilation and heart rate reduction



The catecholamin neurotransmitters

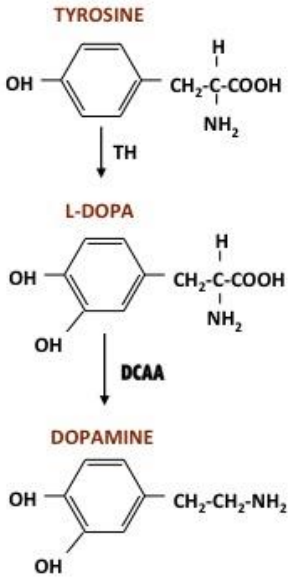


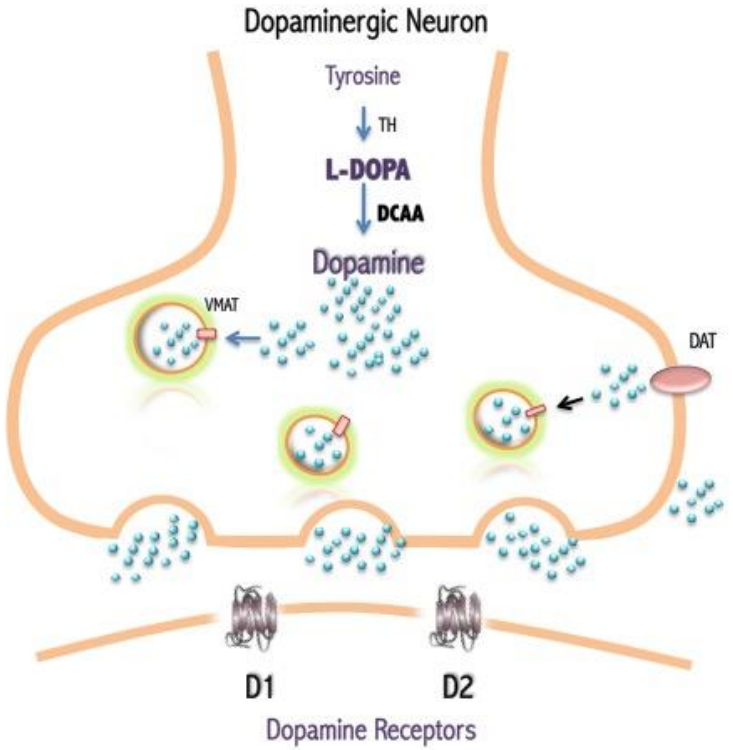


Dopamine

- Concantrated at the substantia nigra and ventral tegmental area of midbrain
- G-protein coupled receptors: D1 like (D1, D5, stimulatory), D2 like (D2, D3, D4, inhibitory)
- Removed from the synaptic cleft by dopamine transporter (DAT)

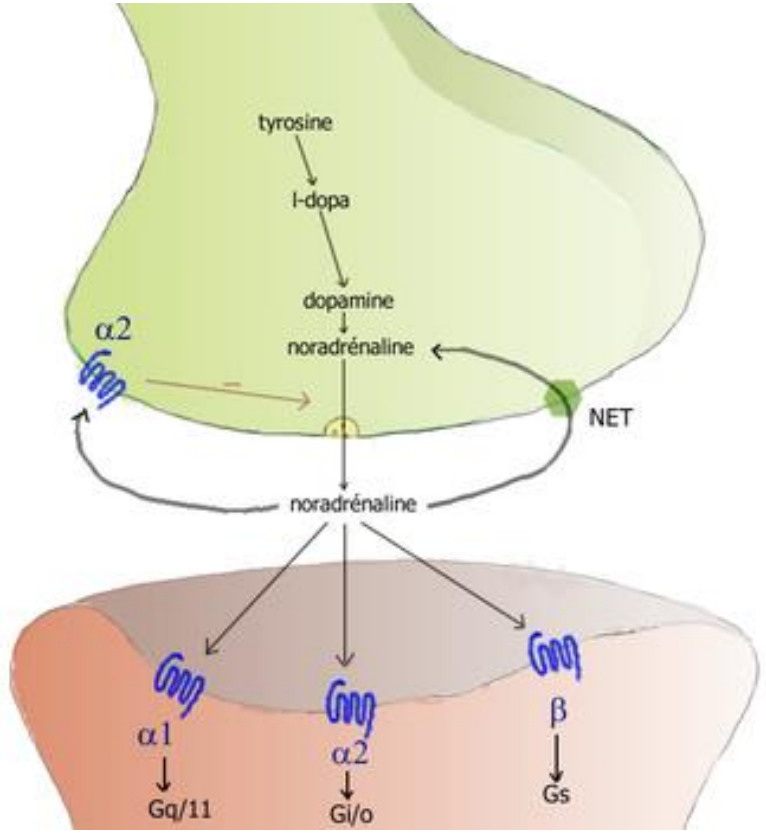
- Movement – Parkinson disease
- Processing of rewarding experiences – addiction
- Memory
- Sleep regulation
- Motivation





Norepinephrine (Noradrenaline)

- Hormone (adrenal glands) and neurotransmitter
- First discovered in the sympathetic branch of the autonomic nervous system
- Locus coerulus of pons
  - Wide projections to the brain
- Adrenergic receptors
  - G-coupled α- and β-adrenergic receptors
- Removed from the synaptic cleft by norepinephrine transporter (NET)
- CNS
  - Sleep-wake cycle
  - Attention
  - Vigilance
- PNS
  - Responses that involve increased activity (e.g., elevated blood pressure)

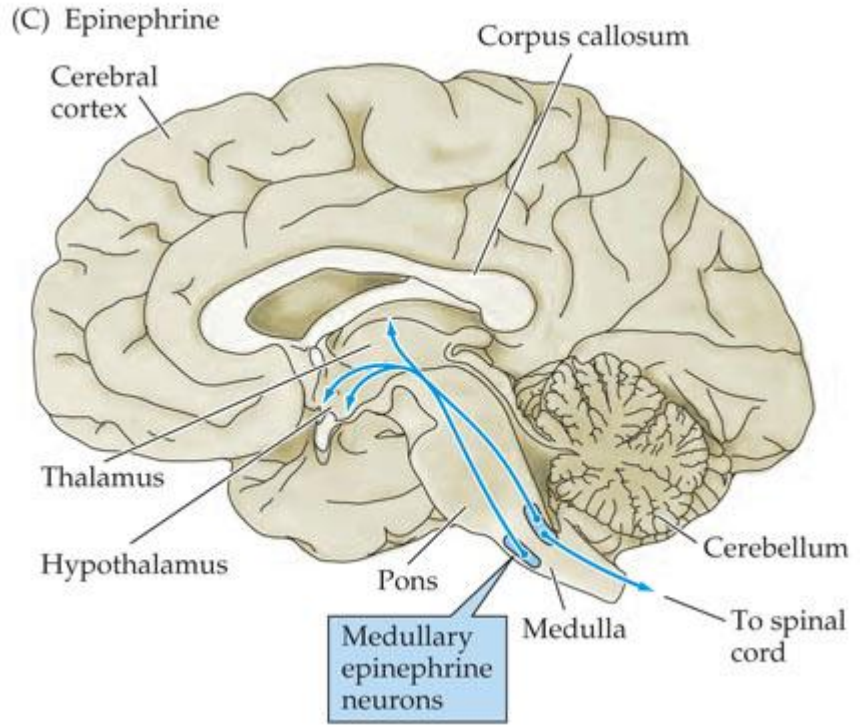


Epinephrine (Adrenaline)

- Epinephrine does not have its own receptors. Instead, since its chemical composition resembles norepinephrine very closely, epinephrine stimulates norepinephrine receptors both in the brain as well as peripherally

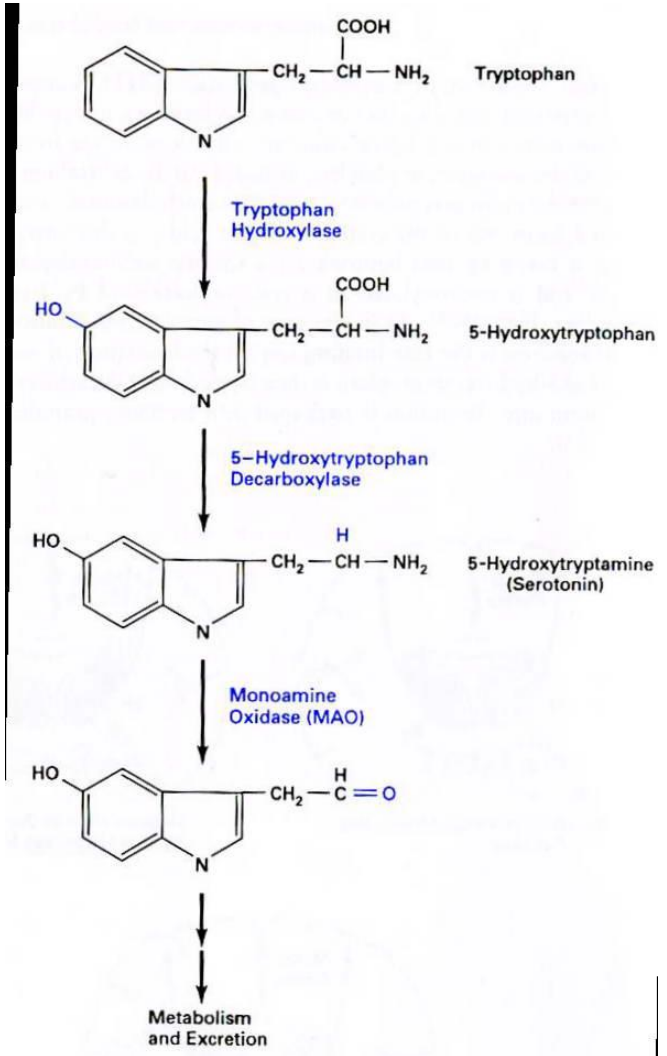
- Brain: medullary epinephrine neurons
  - Project to thalamus, hypothalamus and medulla

- While norepinephrine is primarily a neurotransmitter, epinephrine is primarily a hormone
  - mainly produced by the adrenal glands and has functions peripherally



Serotonin (5HT)

- First identified as an element found in the blood that aided clotting and produced vasoconstriction
- Raphe nuclei (brain stem)
  - Project throughout the brainstem and brain
- 7 different receptor families
  - 6 families G-protein coupled receptors
  - 1 family ligand gated ion channels
- Removed from synaptic cleft via reuptake by Serotonin Transporter (SERT)
- Important for food intake, aggression, mood.

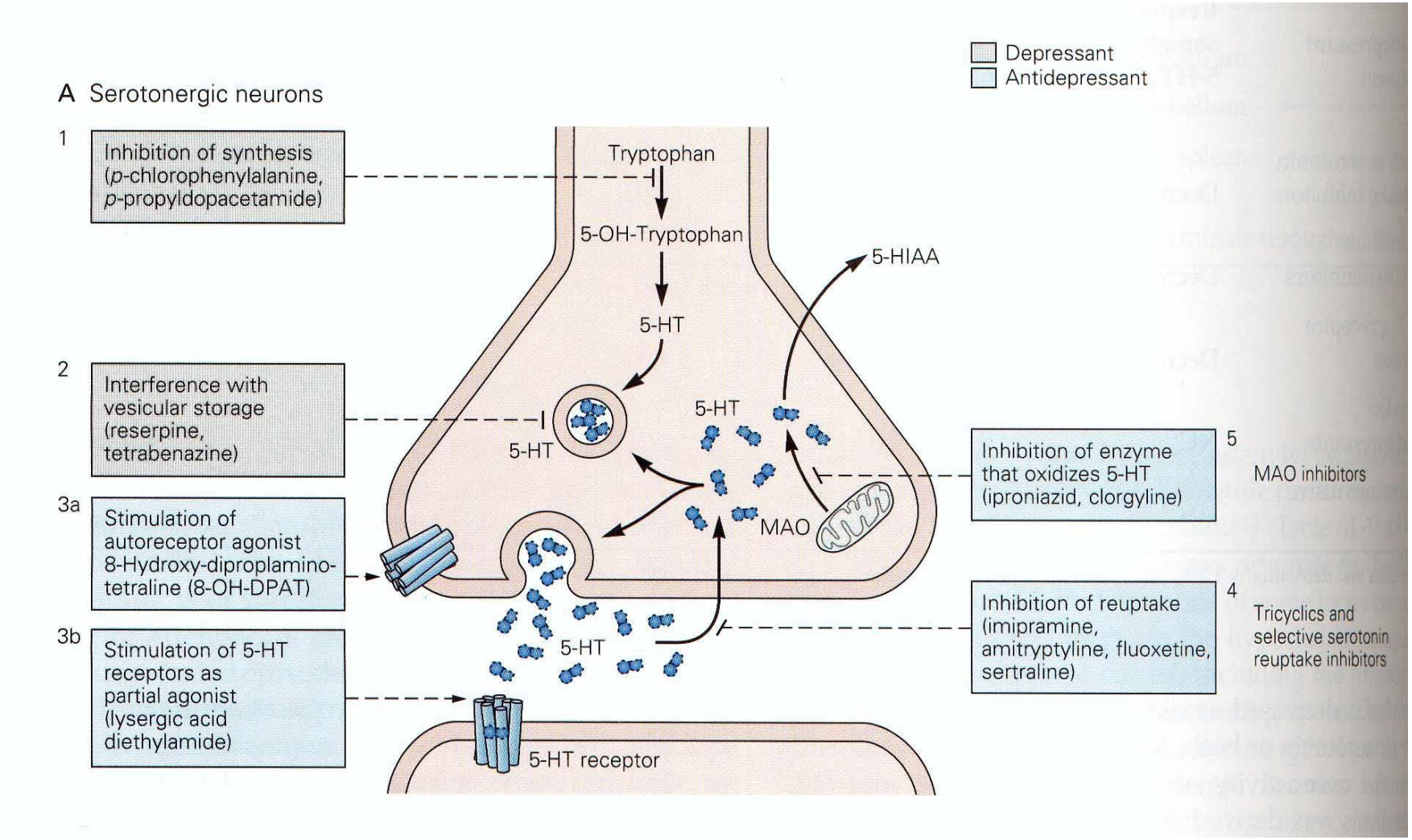


Synthesis and metabolism of serotonin (5-hydroxytryptamine, or 5-HT).

Monoamin Oxidase (MAO)

- Breakdown of monoamines
  - Dopamine, Norepinephrine, Epinephrine, Serotonin
- Bound to the outer membrane of mitochondria
- MAO-A and MAO-B
  - Both are found in neurons and astroglia.
  - Outside the central nervous system:
    - MAO-A is also found in the liver, pulmonary vascular endothelium, gastrointestinal tract, and placenta
    - MAO-B is mostly found in blood platelets

Action of antidepressants and other drugs at serotonergic synapses



Neuropeptides

- Low concentration in brain
- Large vesicles
- Co-localized with other transmitters
- Modulatory functions
- Mostly inhibitory
- Virtually all metabotropic
- Slow acting, long duration (10-1000 ms)
- Examples: Enkephalins, Endorphins, Oxytocin, Vasopressin, Opioids

Nitric Oxide

- Produced by enzymes in axon terminals (in response to Ca^{2+} entry) and simply diffuse from their sites of origin in one cell into the intracellular fluid of other neurons or effector cells, where they bind to and activate proteins

- Nitric oxide released from neurons activates guanylyl cyclase in recipient cells. This enzyme increases the concentration of the second-messenger cyclic GMP, which in turn can alter ion channel activity in the postsynaptic cell