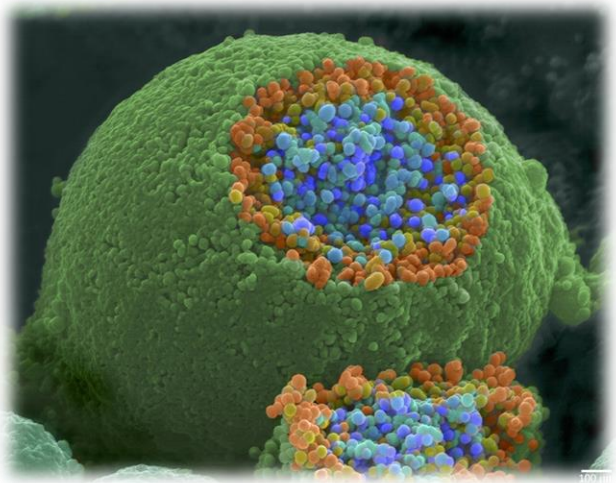

NEUROTRANSMITTERS

Faculty of Dentistry

Nervous System

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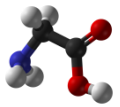
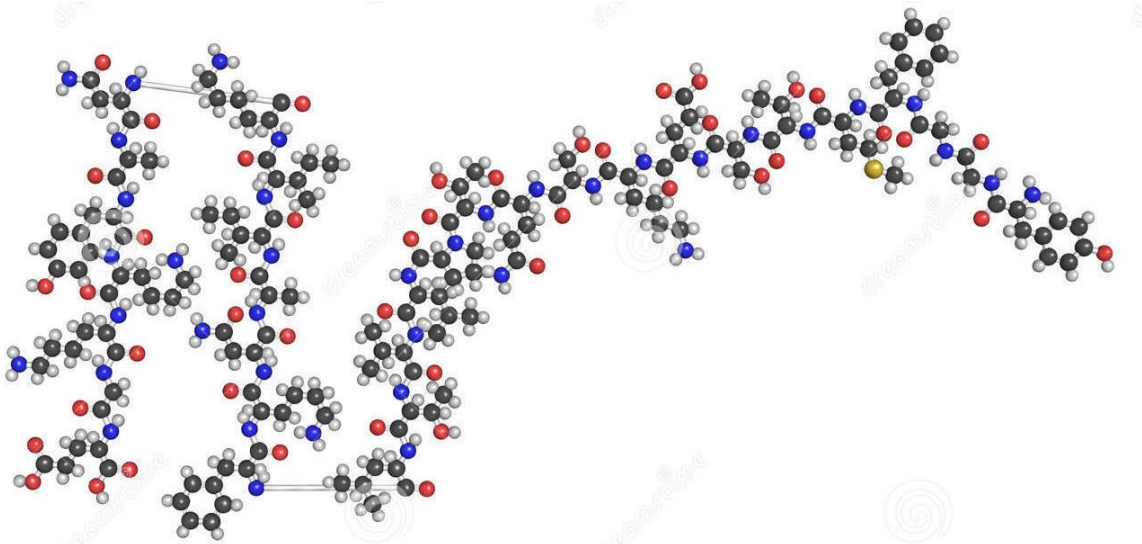
Neurotransmitters (NTs)

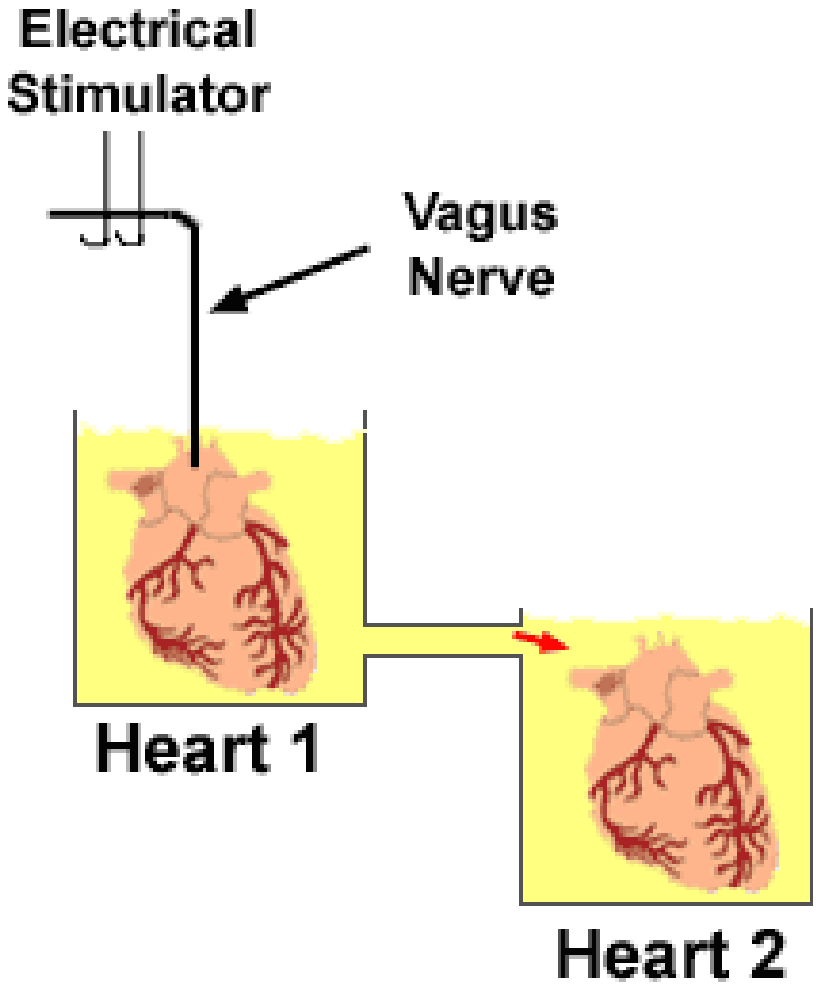
- Molecules that act as messengers in the nervous system
- Their structures are extremely diverse
- 2C Gly →Large peptides





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

Otto Loewi (1873-1961)



For a molecule to be NT, the following conditions must be met

- ✓Must be synthesized or found in the neuron.
- ✓ It must be released when the neuron is stimulated and produce a response at the target.
- ✓The same response should be obtained as the molecule is applied to the target in the experimental setting.
- ✓After performing its function, it should be removed.

Classification of NTs

Neurotransmitter		Example
Ester		Acetylcholine
Amino acids		Glycin
		GABA
		Glutamate
		Aspartate
Amines	Chatecholamines	Epinephrine (Adrenalin)
		Norepinephrine (Noradrenalin)
		Dopamine
	Indolamines	Serotonin
		Histamine
		Torin
Peptides		Endorphin, Enkephaline, Substance P, Cholecystokinin
Others		ATP, NO, CO

The first step in synaptic transmission is the synthesis of NTs.

Small-molecule NTs

- They are synthesized locally at the axon terminal
- The precursor molecules required for their synthesis are taken to the axon terminal by selective transporters on the membrane.
- A group of precursor molecules are the intermediate products of metabolic events already occurring in the neuron.
- The enzymes that will catalyze these processes are produced in the cell body and delivered to the axon terminal by slow axonal transport.

Peptide NTs

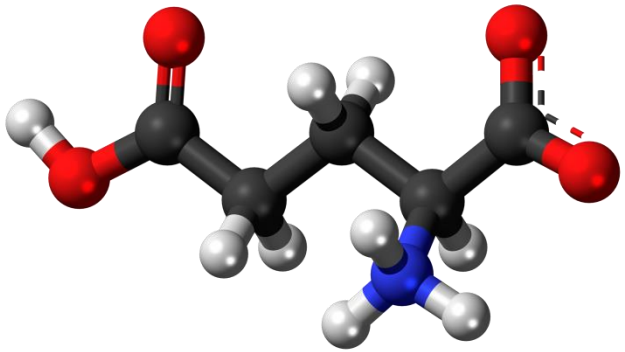
- They differ from other NTs in size and where they are synthesized.
- 3-36 aa long
- They are synthesized in ribosomes in the cell body.
- Synthesis processes are more complex, similar to secretory protein synthesis.

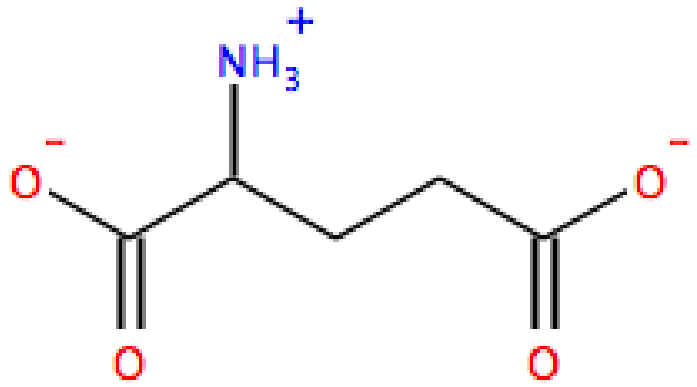
Peptide NTs

- 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

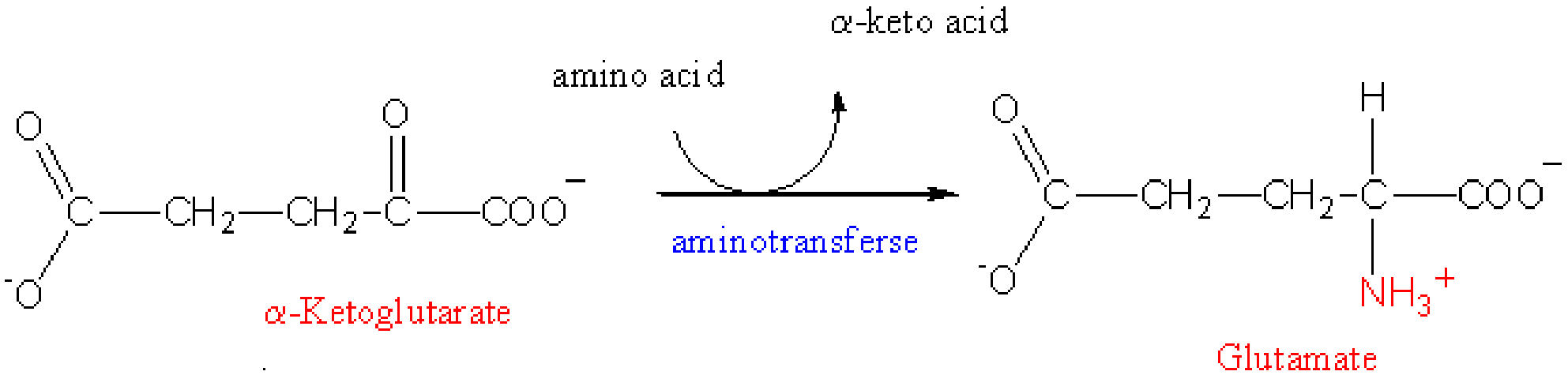
Glutamate (Glu)

- Principal excitatory NT
- Plays a role in many different brain functions such as perception, memory and learning.
- Synthesized from α-ketoglutarate, which is an intermediate of the Krebs cycle.

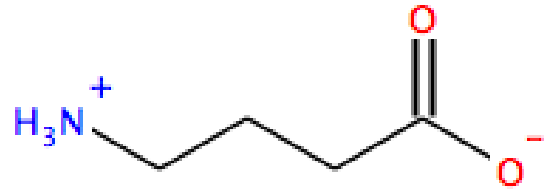




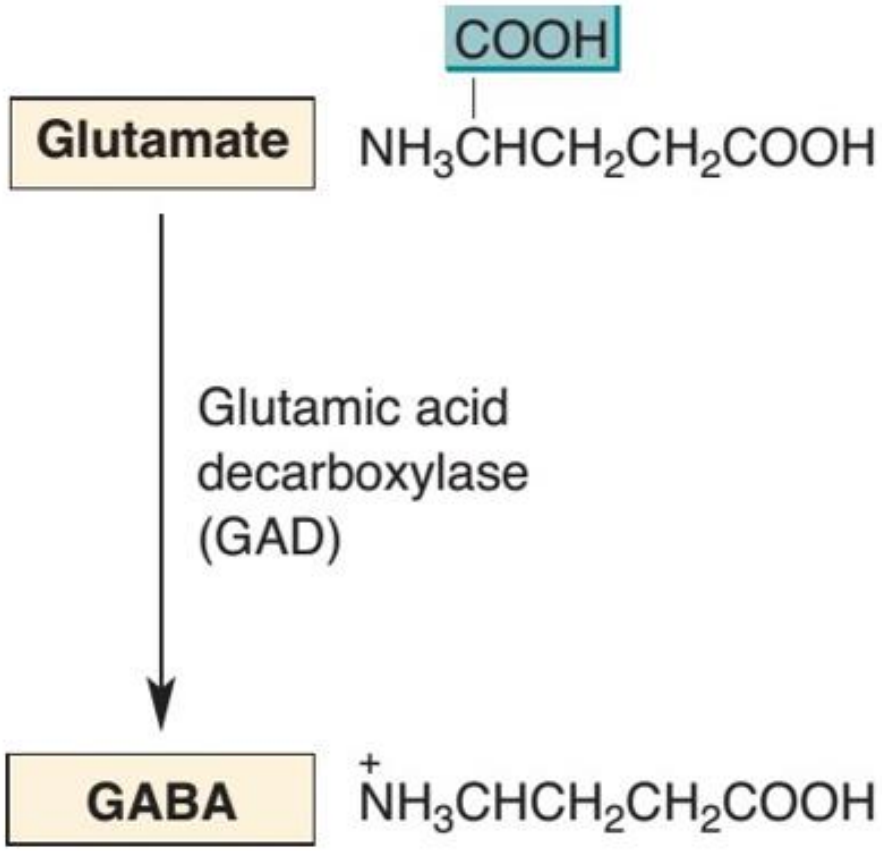
Glutamate (Glu)



GABA (ɣ-amino butiric acid)



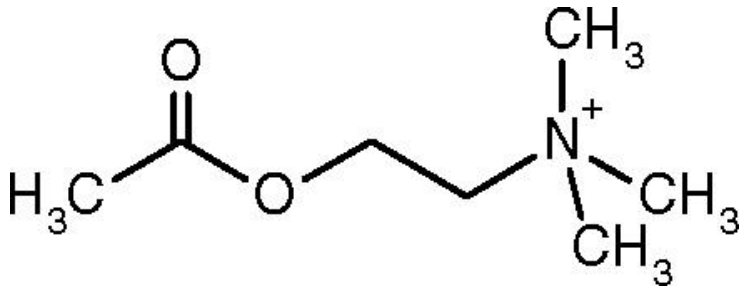
- The most important inhibitory NT
- Found in high concentration in the CNS
- Synthesized from glutamate
- formed by removal of carboxyl group of glutamate, by the enzyme GAD



Acetylcholine (ACh)

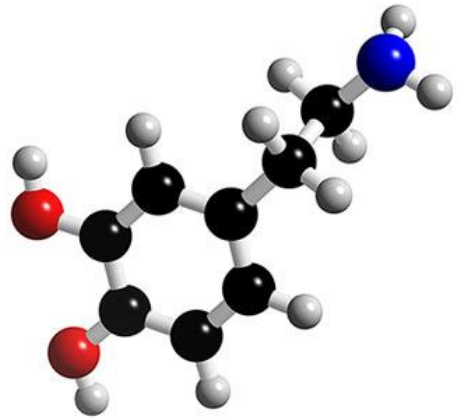
- Major NT in the peripheral nervous system at the neuromuscular junction
- Synthesized from choline and acetyl coenzyme A
- Inhibitor/Excitator
- After it is released and activates receptors on the postsynaptic membrane, degredaded by acetylcholinesterase (located on the presynaptic and postsynaptic membranes) to choline and acetate.

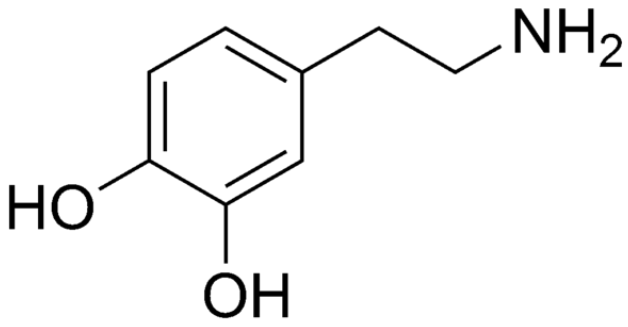
- Choline is transported back into the presynaptic axon terminals where it is reused in the synthesis of new ACh.



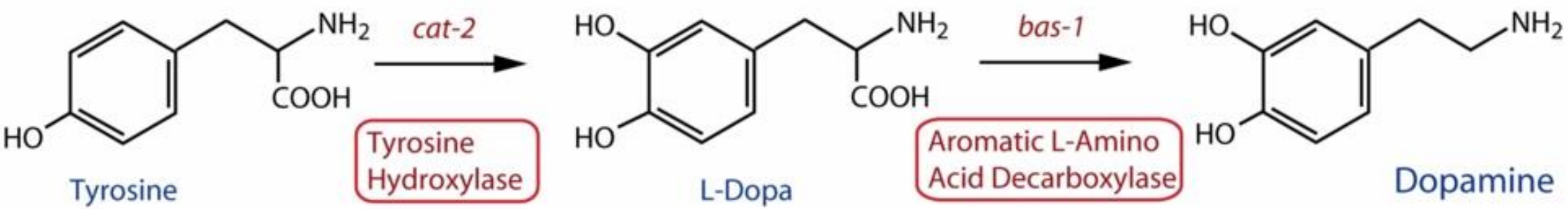
Dopamine (DA)

- Synthesized from tyrosine
- Motor activity, mood, motivation, attention, sleep regulation, memory, processing of rewarding experiences



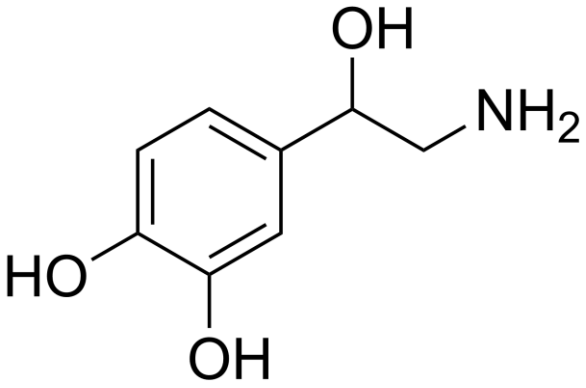


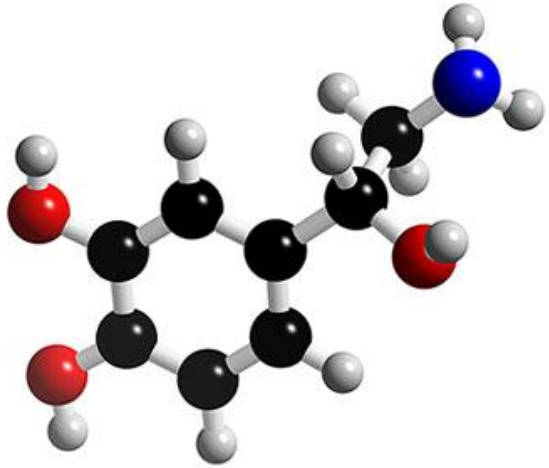
Dopamine (DA)

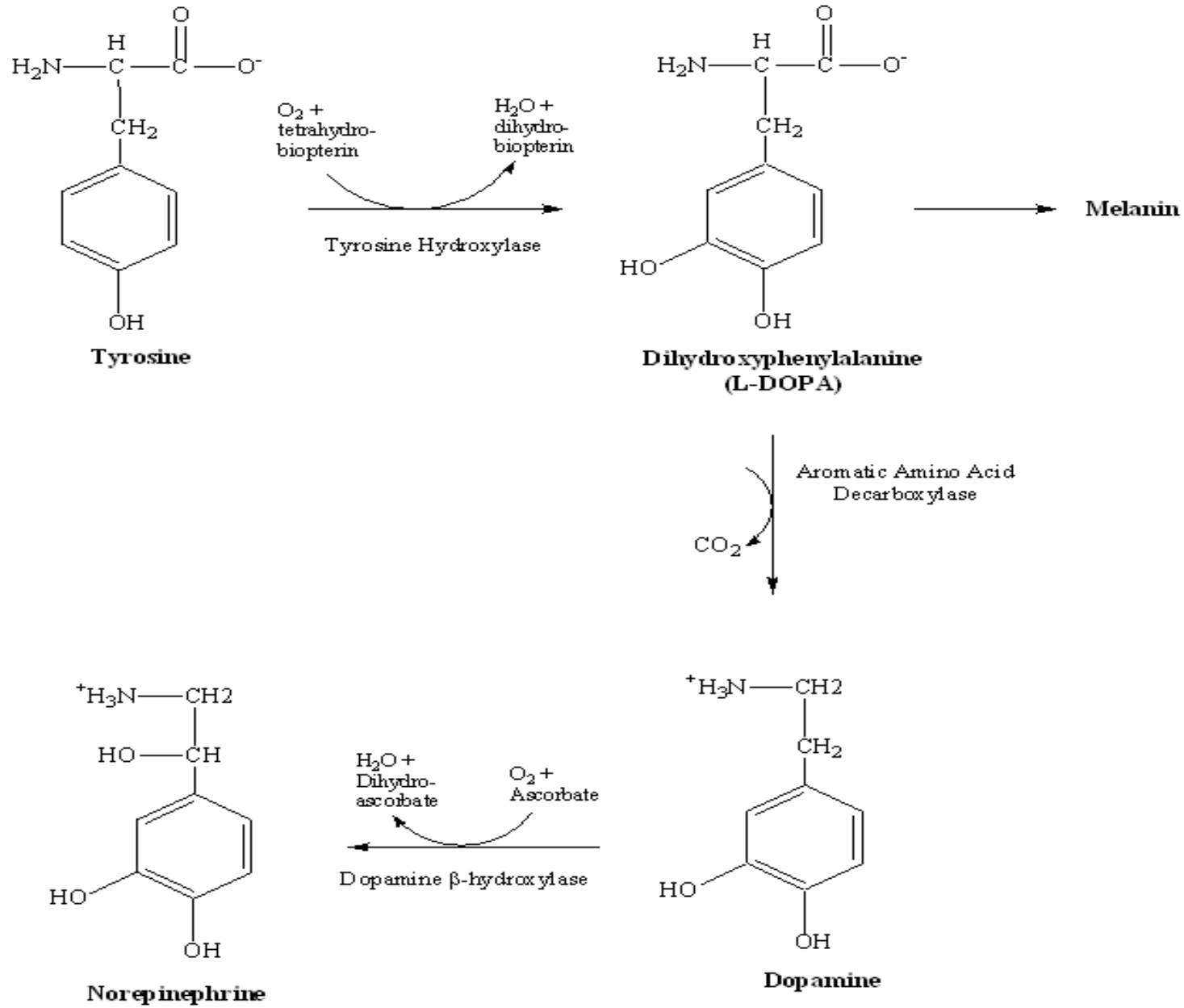

NH2
cat-2
COOH
HO
Tyrosine
Tyrosine Hydroxylase
HO
NH2
COOH
HO
L-Dopa
bas-1
Aromatic L-Amino Acid Decarboxylase
HO
NH2
HO
Dopamine

Norepinephrine = Noradrenaline (NE)

- Synthesized directly from dopamine
- It is the precursor of epinephrine.
- It is synthesized in the synaptic vesicle.
- CNS
  - Sleep-wake cycle
  - Attention
  - Vigilance
- PNS: Causes an increase in heart rate and blood pressure

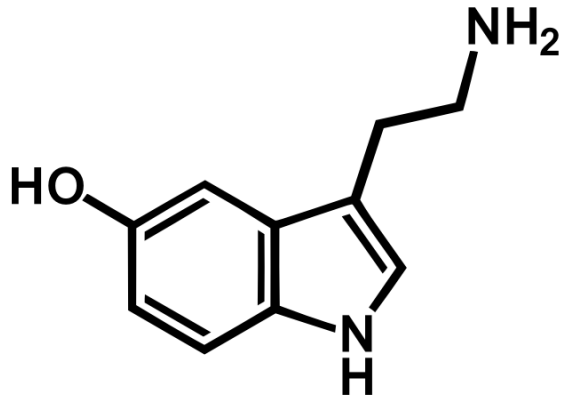


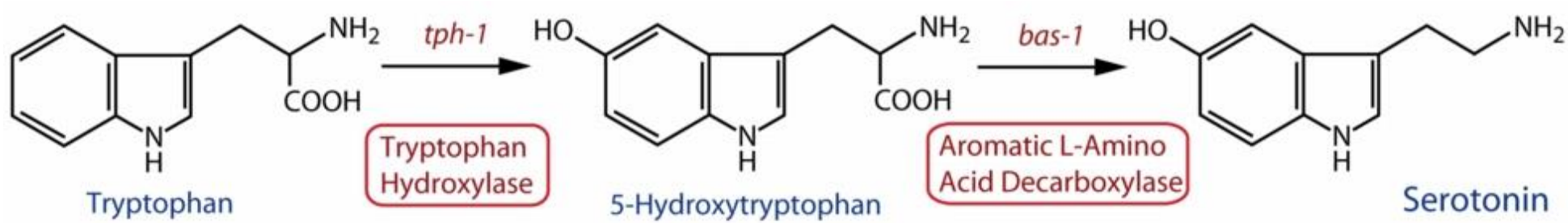



Tyrosine
O2 + tetrahydro-biopterin
H2O + dihydro-biopterin
Tyrosine Hydroxylase
Dihydroxyphenylalanine (L-DOPA)
Melanin
Aromatic Amino Acid Decarboxylase
CO2
Dopamine
H2O + Dihydro-ascorbate
O2 + Ascorbate
Dopamine β-hydroxylase
Norepinephrine

Serotonin (5-HT)

- 5-Hydroxytryptamine
- Plays a role in complex cognitive functions such as attention, mood, pain regulation
- Synthesized from tryptophan in 2 steps




NH2
COOH
N
H
Tryptophan
tph-1
Tryptophan
Hydroxylase
HO
NH2
COOH
N
H
5-Hydroxytryptophan
bas-1
Aromatic L-Amino
Acid Decarboxylase
HO
NH2
N
H
Serotonin

Neurotransmitter Cycle

- Synthesis of NTs
- Packing of NTs in synaptic vesicles
- Relaese by exocytosis
- Re-uptake from the extracellular environment
  - Termination of synaptic transmission
  - Recycling of NT for next secretion

Deposition of all classical NTs in synaptic vesicles depends on the driving force of the electrochemical gradient of H+ generated by vesicular H+/ATPase (V-ATPase).

The vesicular NT transporter (eg VGLUT) transfers the NT molecule into the vesicle against its concentration gradient (active transport).

The energy required for this is provided by the energy released during passive transport of the protons to the outside of the vesicle.

Neurotransmitter Receptors

Neurotransmitter Receptors

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

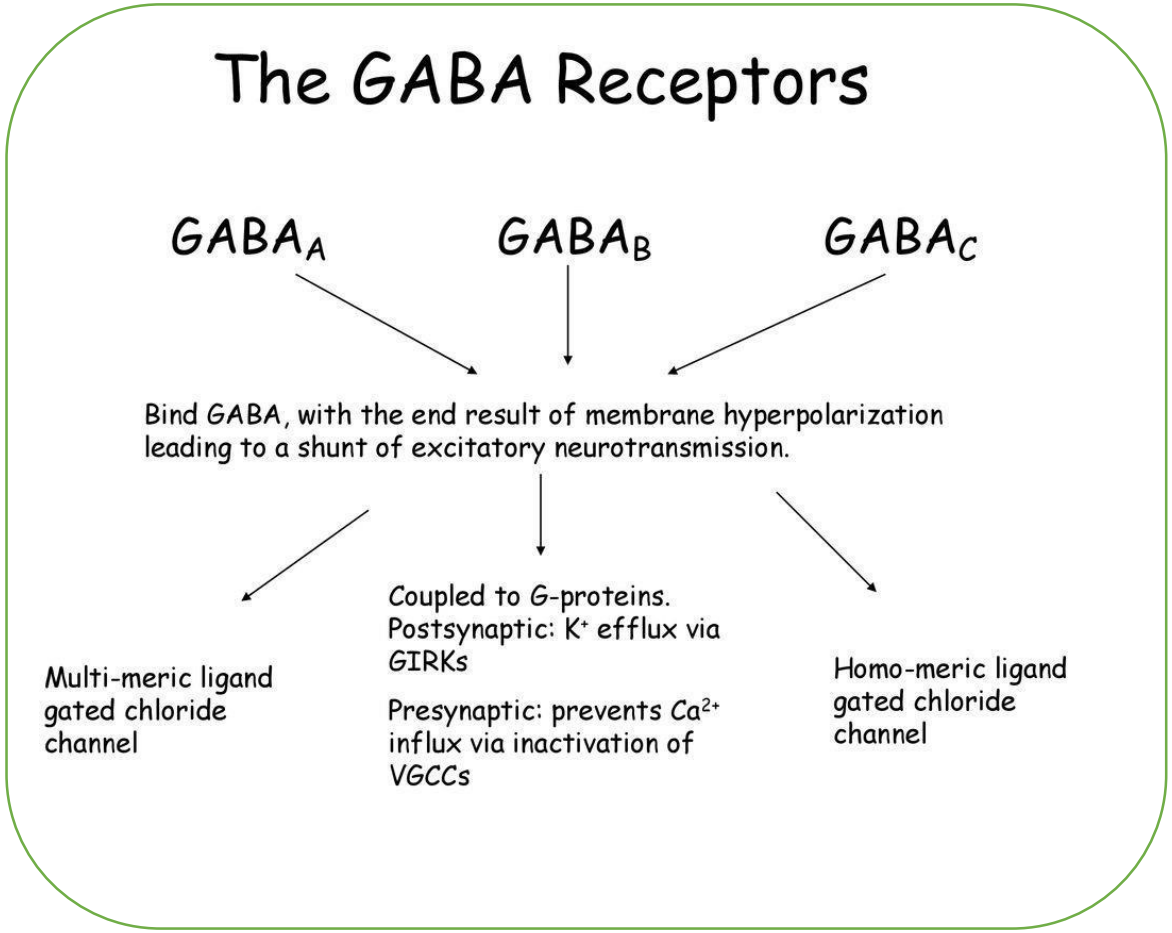
- Metabotropic receptors
  - produce slower synaptic actions lasting seconds to minutes
  - can modulate behavior by altering the excitability of neurons and the strength of the synaptic connections of the neural circuitry mediating behavior, (e.g., learning)

Glutamate Receptors

- AMPA or Kainate
  - Na+, K+
  - Actively recyled (endo, exocytosis)
- NMDA
  - Mg^{2+} block
    - Released with depolarization
  - Ca2+, Na+, K+
- Metabotropic Glu Receptors

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



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

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

References

- Widmaier E.P., Raff H., Strang K.T. (2019) Vander's Human Physiology. Mc Graw Hill Education.
- Bear M.F., Connors B.W., Paradiso M.A. (2016) Neuroscience: Exploring the Brain. Wolters Kluwer