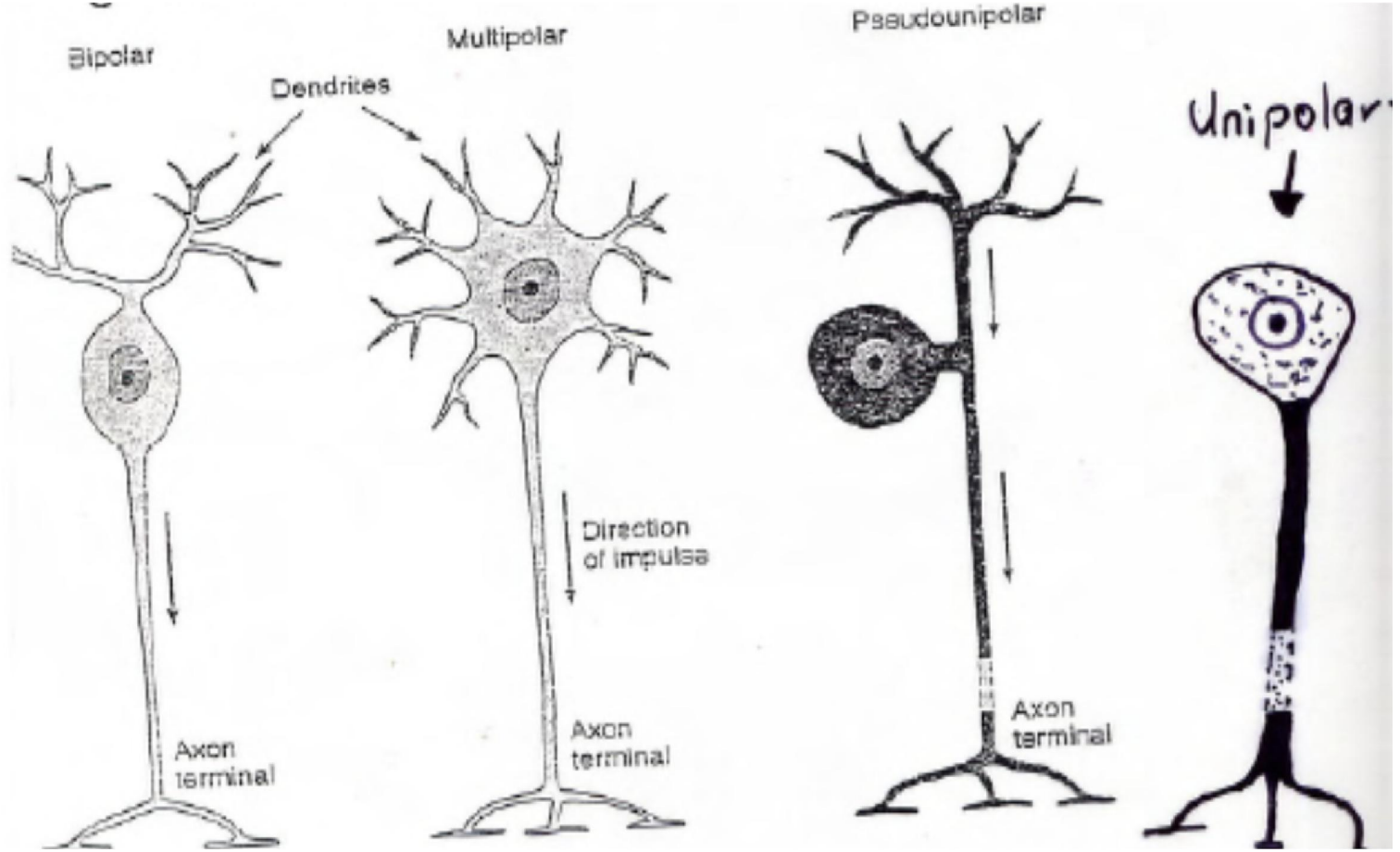
BCM 317
Neurochemistry

- **Nerve tissue:** this is composed of two major types of cells namely,
- Neurons (nerve cells) and neuroglial cells
- Neuroglial cells are the supportive cells of the nervous tissue.
- They provide physical support, nutrients, defense, insulation and re-absorption of neurotransmitters in the nervous system.

- Neuroglial cells are found in the peripheral and central nervous system.
- Fibrous astrocytes (astroglia) in the white matter of the CNS
- Oligodendroglia forms myelin sheaths in the CNS and facilitates rapid conduction of impulses.
- Schwann cells: form myelin sheaths around axons in the peripheral nervous system. Etc.

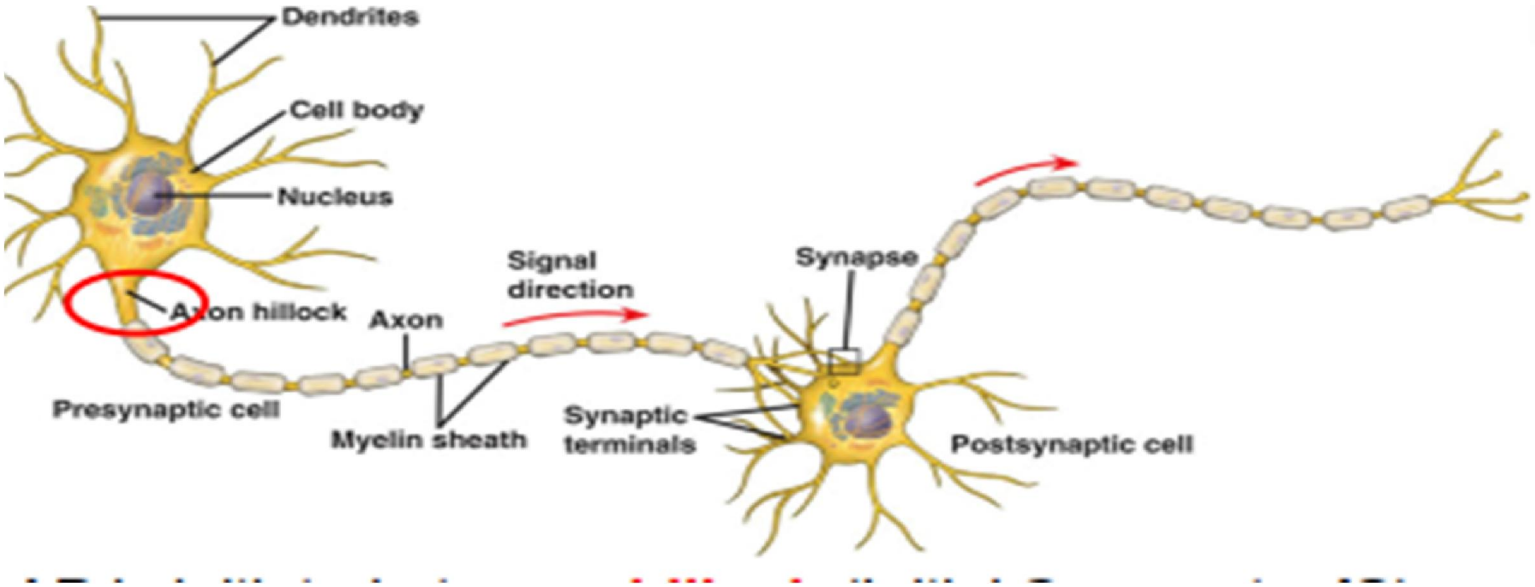
- **NEURONS**
- These are specialized cells in the nervous system capable of detecting and reacting to stimuli, by generating and conducting nerve impulses.

- Types of neurones based on morphology or structure
- Multipolar neurons
- Dipolar neurons
- Unipolar neurons

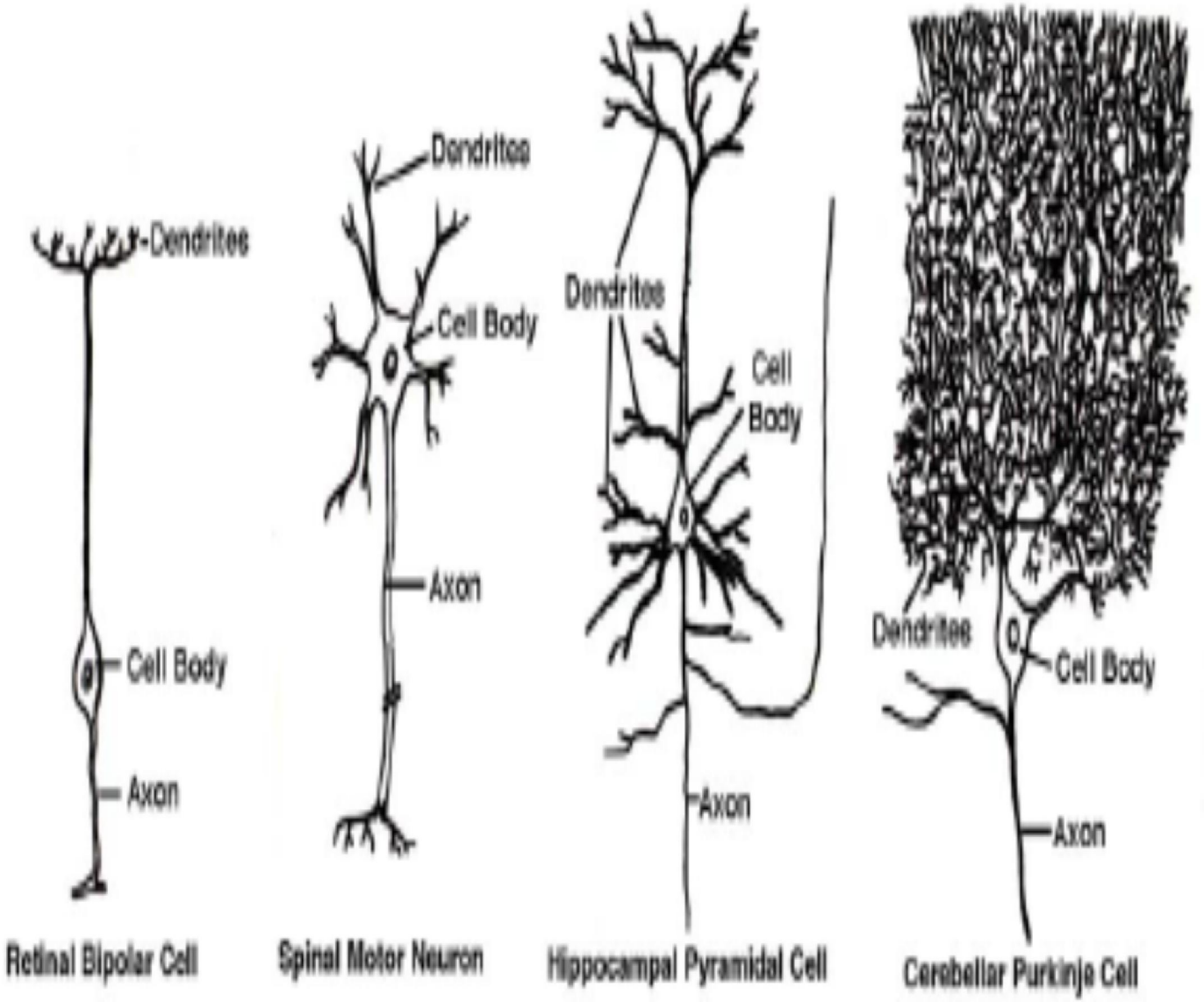

Bipolar
Dendrites
Axon terminal
Multipolar
Direction of impulse
Axon terminal
Pseudounipolar
Axon terminal
Unipolar

- **Types of neurons based on functions**
- **sensory neurons:** these carry messages from extracellular to the spinal cord and brain.
- **motor neurons:** Those that carry the messages to the external in order to control the movement of muscles and activities of glands.
- **Interneurons:** they are the most numerous in the human brain and mediate simple reflexes as well as being responsible for the highest functions of the brain.

- **Structure of neurons**
- A typical neuron possesses morphologically distinct parts such as the soma (cell body), axon (neurite) and dendrites and synaptic terminals (nerve endings).



- STRUCTURE-FUNCTION RELATIONSHIP OF NEURON
- Their chemical composition and morphological structure differ with the function they perform.


Dendrites
Cell Body
Axon
Retinal Bipolar Cell
Dendrites
Cell Body
Axon
Spinal Motor Neuron
Dendrites
Cell Body
Axon
Hippocampal Pyramidal Cell
Dendrites
Cell Body
Axon
Cerebellar Purkinje Cell

- **Synapse**
- A synapse is the junction between two neurons, or between a neuron and an effector organ (muscle or gland).

- **Myelin lipids composition**
- The CNS myelin mainly composed of cerebroside (galactosylceramide).
- Other major lipids of myelin are cholesterol and ethanolamine-containing plasmalogens and lecithin while sphingomyelin is in relatively small amount.

- **Nerve tissue protein**
- These constitute part of the solid portion of the nerve tissue. E.g. globulins etc
- **Nerve tissue lipid**
- Nerve tissue has one of the highest content of lipid. Examples are phospholipids, cerebrosides etc.

- **Biochemistry of nerve transmission**
- Neuron, an example of excitable cell has a resting potential also known as the membrane potential which is the electrical charge across the plasma membrane.
- **The Action Potential**
- Action potential is a temporary change in membrane potential that is transmitted along the axon.
- It uses all-or-nothing mechanism

Neurotransmission at the neuromuscular junction

- When an action potential reaches the axon terminal it causes Ca channels to open, leading to the release of the neurotransmitter acetylcholine from the vesicles.
- ACh diffuses across the neuromuscular junction and binds to the ACh receptor protein in the postsynaptic membrane;
- Binding causes an ion channel to open causing the depolarization of the membrane, producing an EPSP (Excitatory postsynaptic potential;
- In muscle a single impulse usually causes enough depolarization to reach threshold; Action potential is generated in the muscle membrane;
- Muscle action potential causes release of Ca2+ from the Sarcoplasmic Reticulum of the muscle and this triggers muscle contraction;
- At the receptor site in the neuromuscular junction the ACh is broken down to acetate and Choline by the enzyme Acetylcholinesterase; Choline is recycled;
- Choline pump transports it back into the nerve terminal and there it is converted back into Ach;

NEUROTRANSMITTER

- These are the chemicals responsible for the transmission of signals between different neurons.

- **Chemical classification of neurotransmitters**
- Acetyl choline
- Biogenic amines: these are formed by amino acid losing a hydroxyl or carboxyl group e.g. catecholamines- dopamine, norepinephrine and epinephrine; indolamines; serotonin and histamine (5-hydroxytryptamine or 5HT).
- Amino acids: gamma amino butyric acid; glycine; aspartate; glutamate
- Neuropeptides: substance P; endorphins and enkephalins; somatostatin, gastrin, cholecystokinin, oxytocin, vasopressin, leutinizing hormone releasing hormone (LHRH)
- Purines: adenosine and ATP.
- Gases and lipids: nitric oxide; carbonmonoxide; cannabinoids

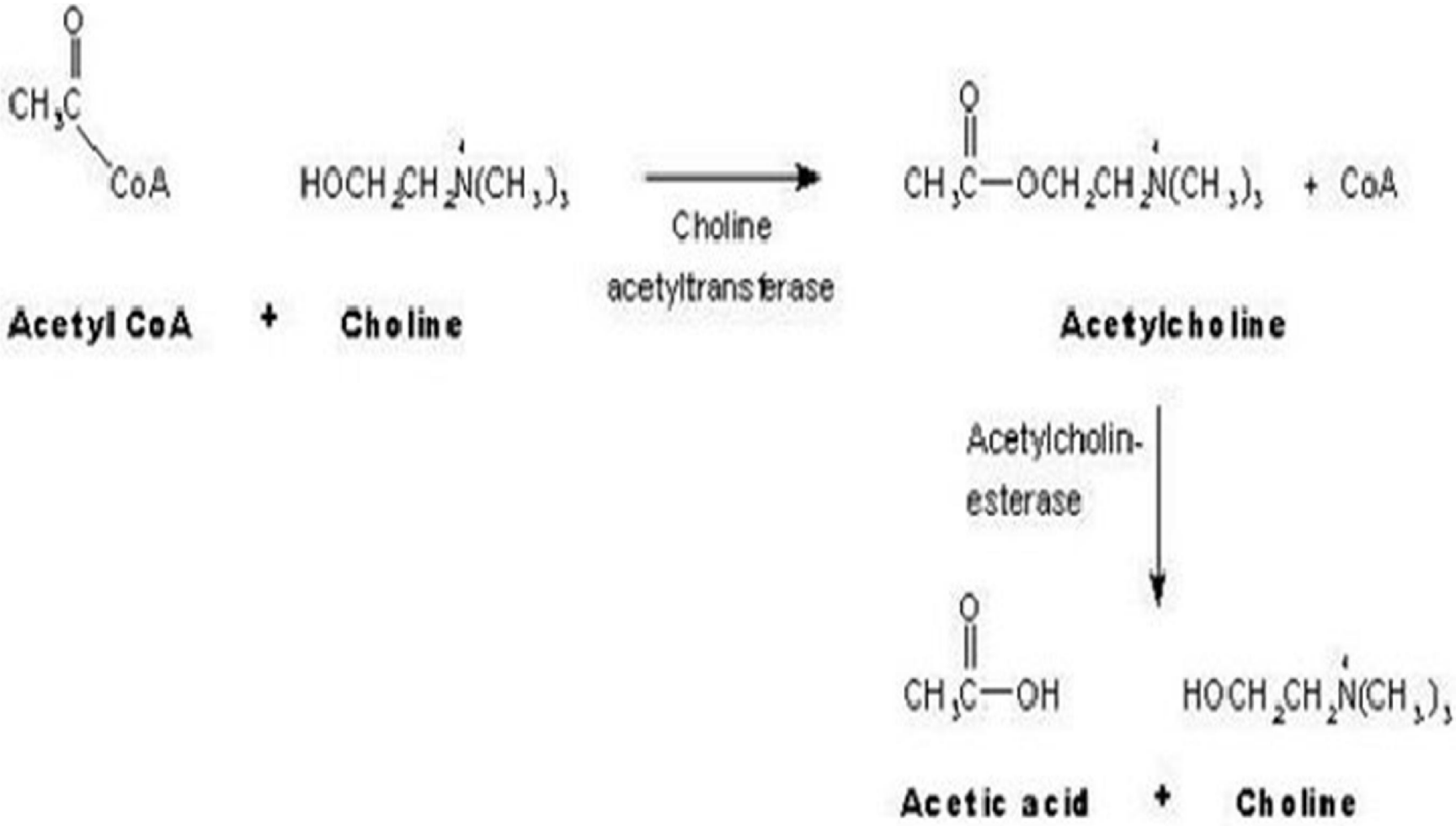
- **Functional classification of neurotransmitters**
- There are two classes
- Excitatory neurotransmitter
- Inhibitory neurotransmitter

- Excitatory neurotransmitters are small molecules that act as natural body stimulants
- Examples include dopamine, histamine, norepinephrine, epinephrine, glutamate and acetylcholine.

- Inhibitory neurotransmitters are chemicals that function to checkmate the activity of the excitatory neurotransmitters in order to balance signal transduction in the neurons.
- Examples are GABA, dopamine, serotonin, acetylcholine and taurine.

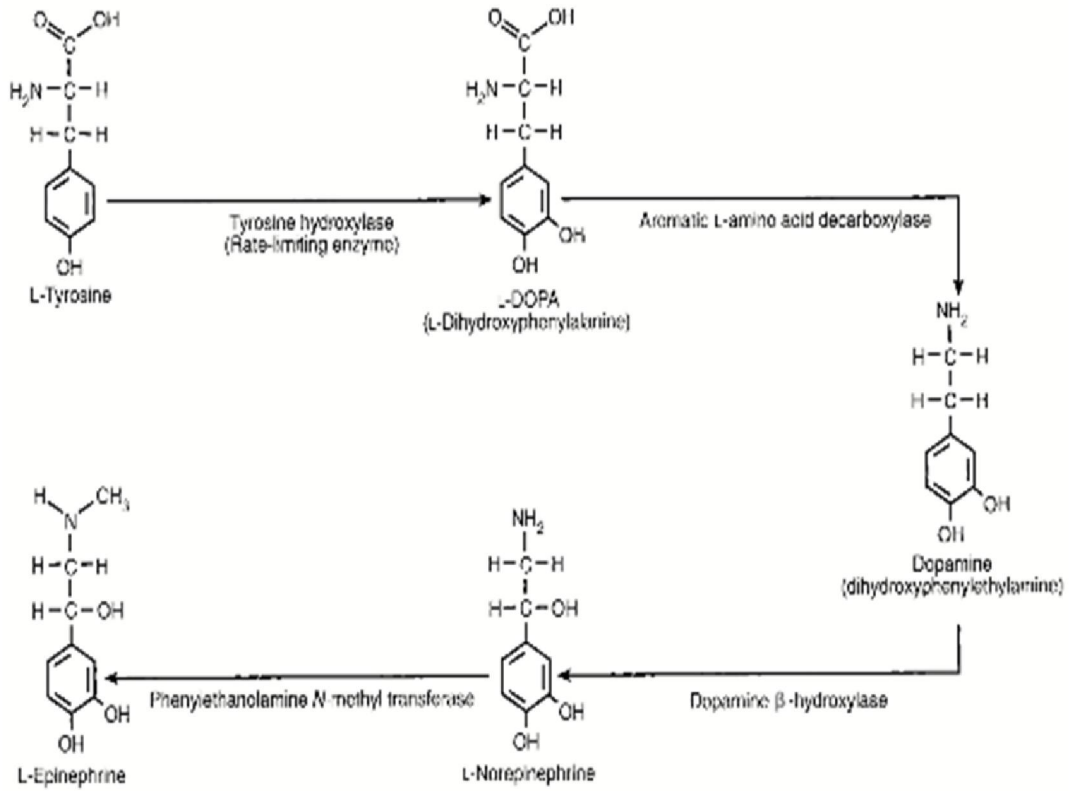
Synthesis and breakdown of neurotransmitters

- **Acetylcholine:** neurons that use acetylcholine as neurotransmitter are known as cholinergic neurone.
- The rate-limiting step of acetylcholine synthesis is the availability and the high-affinity uptake system of choline.


CH3C
CoA
HOCH2CH2N(CH3)3
Choline
acetyltransferase
CH3C—OCH2CH2N(CH3)3 + CoA
Acetyl CoA + Choline
Acetylcholine
Acetylcholin-
esterase
CH3C—OH
HOCH2CH2N(CH3)3
Acetic acid + Choline

- **Biogenic amines**
- The catecholamine transmitters, dopamine, norepinephrine and epinephrine are synthesized from the aromatic amino acid tyrosine.

Biosynthesis of catecholamines



- Two enzymes are involved in degrading the catecholamines after vesicle exocytosis.
- Monoamine oxidase which remove the amine group, and catechol-O-methyltransferase which methylates the 3-OH group on the catechol ring.

- **Serotonin (5-hydroxytryptamine)** is the neurotransmitter in the serotonergic neurons.
- Tryptophan hydroxylase, converts tryptophan, an indole amino acid to 5-hydroxytryptophan, which is then converted to serotonin, 5-hydroxytryptamine.
- Serotonin is also degraded by monoamine oxidase.

- **Glutamate and aspartate**: Both glutamate and aspartate serve as excitatory transmitters of CNS.
- Neurons that use them are referred to as glutamatergic neurons.
- The source of Glu for neurotransmission is the diet and mitochondrial conversion of α-ketoglutarate derived from TCA cycle.

- **GABA and glycine:** They are inhibitory amino acid neurotransmitters
- They bind to their respective receptors, causing hyperpolarization of the postsynaptic membrane.
- GABAergic neurons represent the major inhibitory neurons of the CNS, whereas glycinergic neurons are found in limited numbers, only restricted to the spinal cord and brainstem.

- The synthesis of GABA in neurons is by decarboxylation of Glu by enzyme glutamic acid decarboxylase.
- The GABA enters the Krebs cycle in both neuronal and glial mitochondria and is converted to succinic semialdehyde by the enzyme GABA-transaminase.
- Glutamate produced in the glial cell is converted to glutamine and transported back into the presynaptic terminal, where it is converted into glutamate.

- Glycine is synthesized from serine, by the catalytic action of serine hydroxymethyltransferase in the presence of tetrahydrofolate as the cofactor.
- It can be degraded to carbon (IV) oxide by glycine cleavage enzyme.

- **Neuropeptides**: naturally active peptides are stored in the synapse and the rate of release from the vesicles is at higher stimulation frequency compared to the non-peptide neurotransmitters.
- They are synthesized as large prepropeptides in the endoplasmic reticulum and are packaged into vesicles that reach the axon terminal by axoplasmic transport.

- It then undergoes posttranslational modification by proteases to smaller peptides, followed by other enzymes that alter the peptides by hydroxylation, amidation, sulfation and other reactions.
- Peptides are degraded by proteases in the extracellular space.

- **Nitric oxide and arachidonic acid**: they are membrane-soluble molecules that diffuse through neuronal membranes and activate postsynaptic cell via second messenger pathways.

- Nitric oxide is a labile free-radical gas that is synthesized on demand from its precursor, L-arginine, by nitric oxide synthase (NOS).

- Because NOS activity is exclusively regulated by calcium ion, the release of NO is calcium-dependent even though it is not packaged into synaptic vesicles.
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- It is a relatively common neurotransmitter in peripheral autonomic pathway and found in nitrergic neurons.
- The effects of NO are mediated through its activation of second messengers, guanyly cyclase.

- Arachidonic acid is a fatty acid released from phospholipids in the membrane when phospholipase A2 is activated by ligand-gated receptors. The arachidonic acid then diffuses retrogradely to affect the presynaptic cell by activating second messenger.