Sem – II (PG)
Paper ZOO-202
Group B: Biochemistry

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Protein metabolism

Formation of specialized products from amino acids

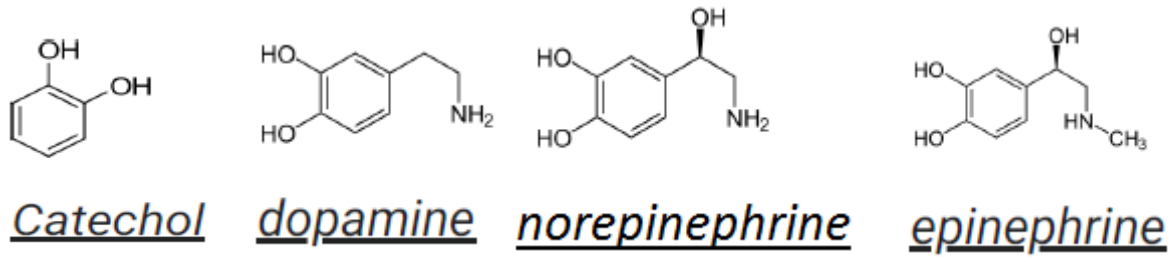
Catecholamine

A catecholamine (CA) is a monoamine neurotransmitter, an organic compound that has a catechol (benzene with two hydroxyl side groups) and a side chain amine.

Catechol can be either a free molecule or a substituent of a larger molecule, where it represents a 1, 2-dihydroxybenzene group.

Catecholamines are derived from the amino acid tyrosine, which is derived from dietary sources as well as synthesis from phenylalanine. Catecholamines are water-soluble and are 50% bound to plasma proteins in circulation.

Included among catecholamines are epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine. Release of the hormones epinephrine and norepinephrine from the adrenal medulla of the adrenal glands is part of the fight-or-flight response.



Tyrosine is created from phenylalanine by hydroxylation by the enzyme phenylalanine hydroxylase. Tyrosine is also ingested directly from dietary protein. Catecholamine-secreting cells use several reactions to convert tyrosine

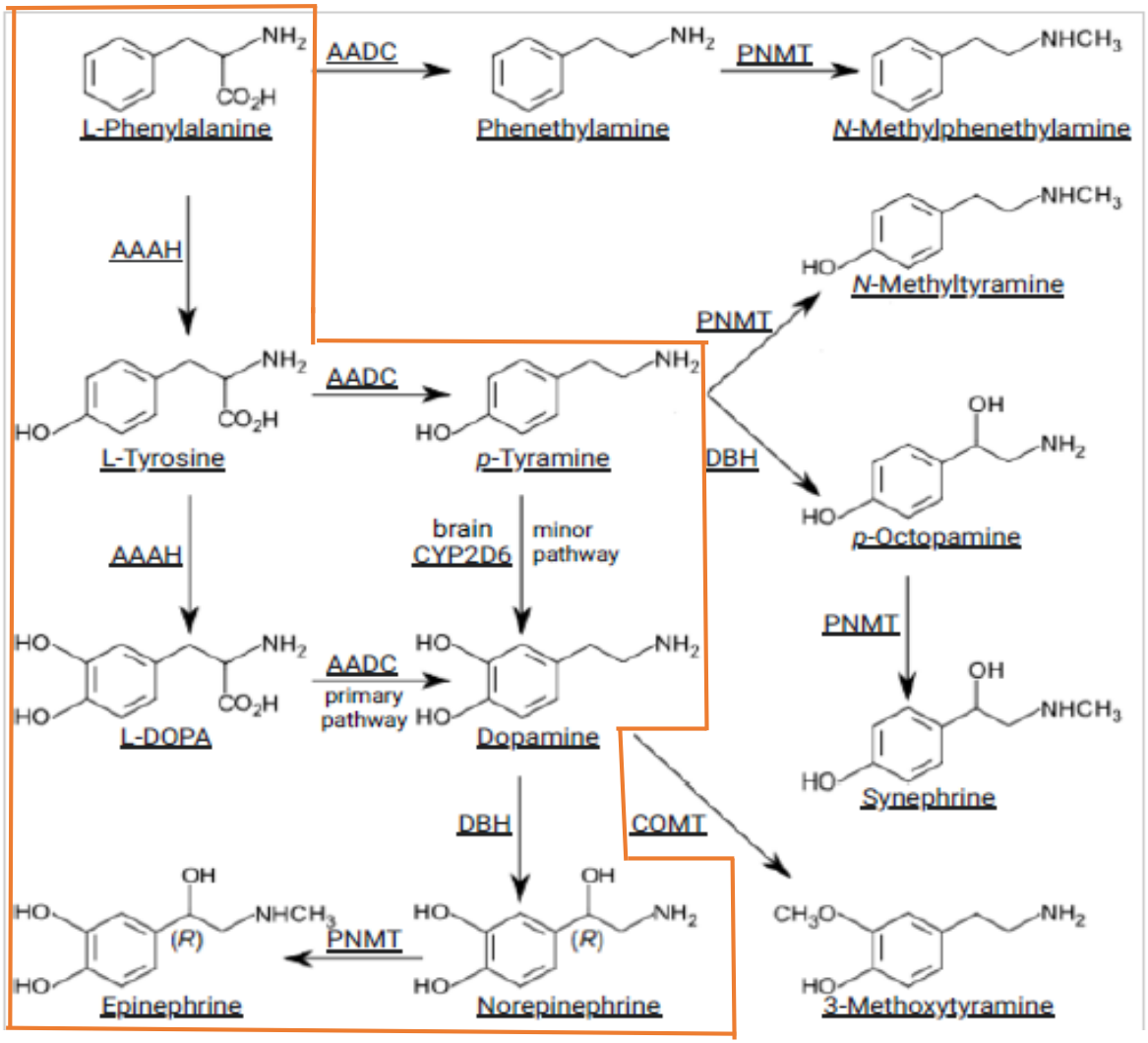
serially to L-DOPA and then to dopamine. Depending on the cell type, dopamine may be further converted to norepinephrine or even further converted to epinephrine.

Structure:

Catecholamines have the distinct structure of a benzene ring with two hydroxyl groups, an intermediate ethyl chain, and a terminal amine group. Phenylethanolamines such as norepinephrine have a hydroxyl group on the ethyl chain. Structures are given above.

Biosynthesis:

Biosynthetic pathways for catecholamines and trace amines in the human brain:



AAAH – Aromatic Amino Acid Hydroxylase, AADC – L-Amino Acid Decarboxylase, PNMT – Phenylethanolamine N- Methyl Transferase, DBH – Dopamine β-Hydroxylase, DOPA – Dihydroxyphenylalanine, COMT – Catechol – O –Methyltransferase. Orange lined region is the pathway for catecholamine synthesis, outside compounds are other trace amines produced in this pathway.

- L-Phenylalanine is converted into L-tyrosine by an AAAH enzyme (phenylalanine 4-hydroxylase), with molecular oxygen (O_2) and tetrahydrobiopterin as cofactors.
- L-Tyrosine is converted into L-DOPA by another AAAH enzyme (tyrosine 3-hydroxylase) with tetrahydrobiopterin, O_2, and ferrous iron (Fe^{2+}) as cofactors.
- L-DOPA is converted into dopamine by the enzyme aromatic L-amino acid decarboxylase (AADC), with pyridoxal phosphate as the cofactor. Dopamine itself is also used as precursor in the synthesis of the neurotransmitters norepinephrine and epinephrine.
- Dopamine is converted into norepinephrine by the enzyme dopamine β-hydroxylase (DBH), with O_2 and L-ascorbic acid as cofactors. Norepinephrine is converted into epinephrine by the enzyme phenylethanolamine N-methyltransferase (PNMT) with S-adenosyl-L-methionine as the cofactor.

Location:

Catecholamines are produced mainly by the chromaffin cells of the adrenal medulla and the postganglionic fibers of the sympathetic nervous system. Dopamine is largely produced in neuronal cell bodies in two areas of the brainstem: the ventral tegmental area and the substantia nigra. The neuromelanin-pigmented cell bodies of the locus coeruleus produce norepinephrine. Epinephrine is produced in small groups of neurons (which project from a nucleus adjacent to area postrema) in the human brain.

Functions:

Modality

Two catecholamines, norepinephrine and dopamine, act as neuromodulators in the CNS and as hormones in the blood circulation. The catecholamine norepinephrine is a neuromodulator of the peripheral sympathetic nervous system but is also present in the blood.

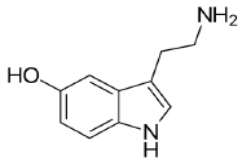
General physiological functions:

Catecholamines cause general physiological changes that prepare the body for physical activity (the fight-or-flight response). Some typical effects are increases in heart rate, blood pressure, blood glucose levels, and a general reaction of the sympathetic nervous system.

Serotonin and Melatonin

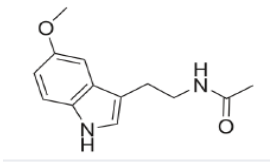
Serotonin (other names: 5-hydroxytryptamine or 5-HT, Enteramine, Thrombocytin, Thrombotonin) is a monoamine neurotransmitter. It has a popular image as a contributor to feelings of well-being and happiness, though its actual biological function is complex and multifaceted, modulating cognition, reward, learning, memory, and numerous physiological processes such as vomiting and vasoconstriction.

Serotonin



Melatonin (N-acetyl-5-methoxy Tryptamine) is a hormone that is primarily released by the pineal gland. In animals (including humans), melatonin is involved in synchronizing the circadian rhythm including sleep–wake timing, blood pressure regulation, and seasonal reproduction. Many of its effects are through activation of the melatonin receptors, while others are due to its role as an antioxidant.

Melatonin



Biosynthesis:

- *Serotonin:* In animals including humans, serotonin is synthesized from the amino acid L- tryptophan by a short metabolic pathway consisting of two enzymes: tryptophan hydroxylase (TPH) and aromatic amino acid decarboxylase (AADC) with coenzyme pyridoxal phosphate (PLP). TPH has been shown to exist in two forms: TPH1, found in several tissues, and TPH2, which is a neuron specific isoform.
- *Melatonin:* In animals, biosynthesis of melatonin occurs through hydroxylation, decarboxylation, acetylation and a methylation starting with L-tryptophan. L-tryptophan is produced in the shikimate pathway from chorismate or is acquired from protein catabolism. First L-tryptophan is hydroxylated on the indole ring by tryptophan hydroxylase to produce 5-hydroxytryptophan. This intermediate (5-HTP) is decarboxylated by pyridoxal phosphate and 5-hydroxytryptophan decarboxylase (an AADC for this pathway) to produce serotonin (as in above). Serotonin is itself an important neurotransmitter, but is also converted into N-acetylserotonin by serotonin N-acetyltransferase (SNAT) with acetyl-CoA. N-acetylserotonin O-methyltransferase [formarly known as Hydroxyindole O-methyltransferase (HIOMT)] and S-adenosyl methionine (SAM) convert N-acetylserotonin into melatonin through methylation of the hydroxyl group.

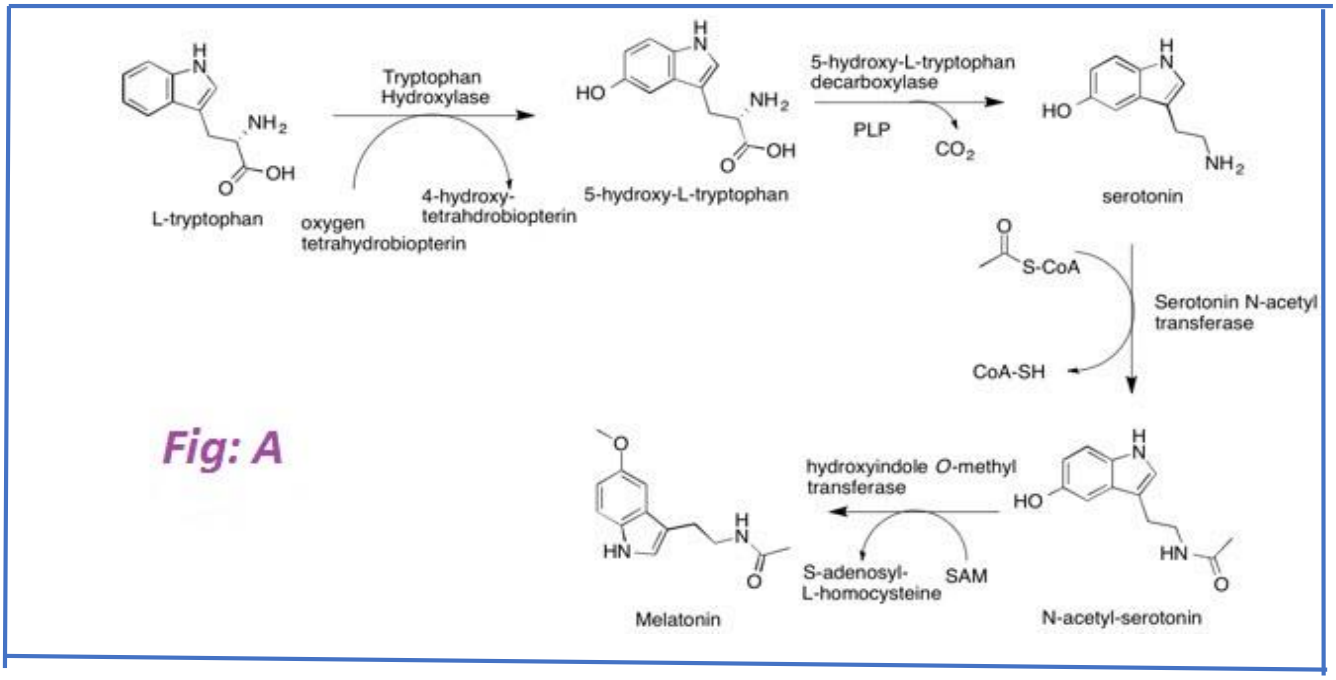


Fig: A

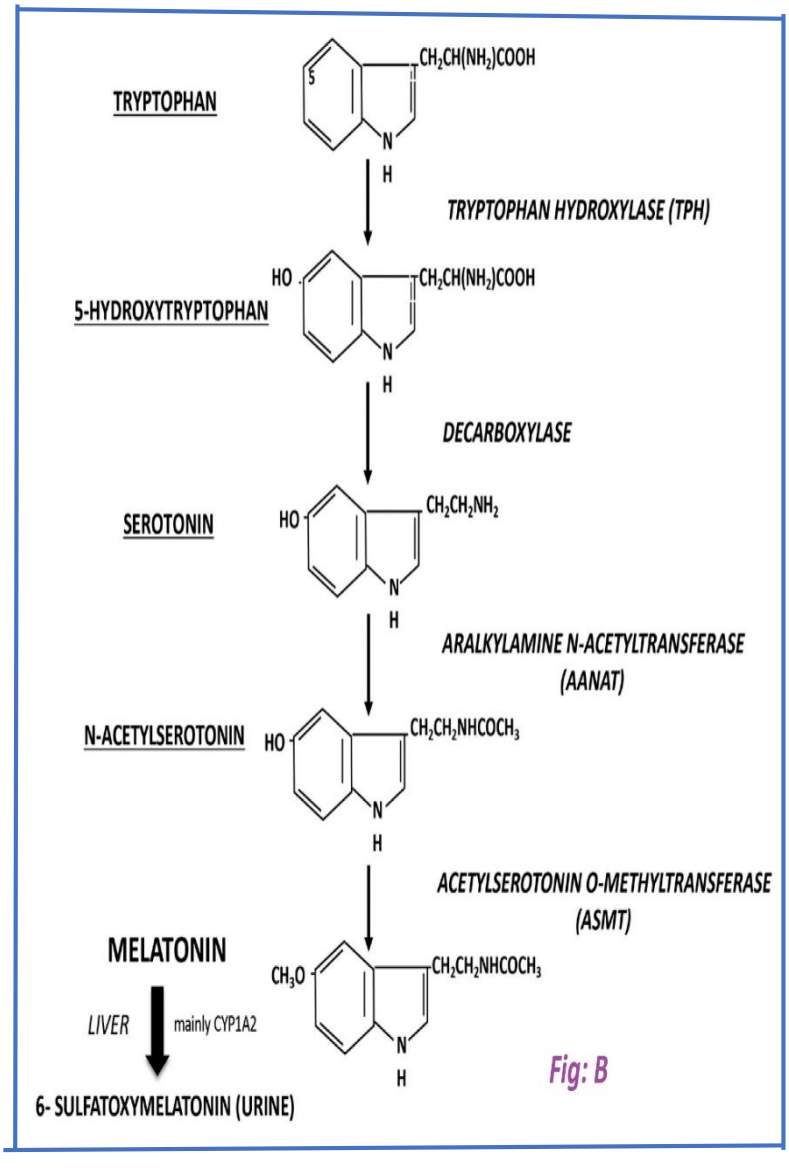


Fig: B

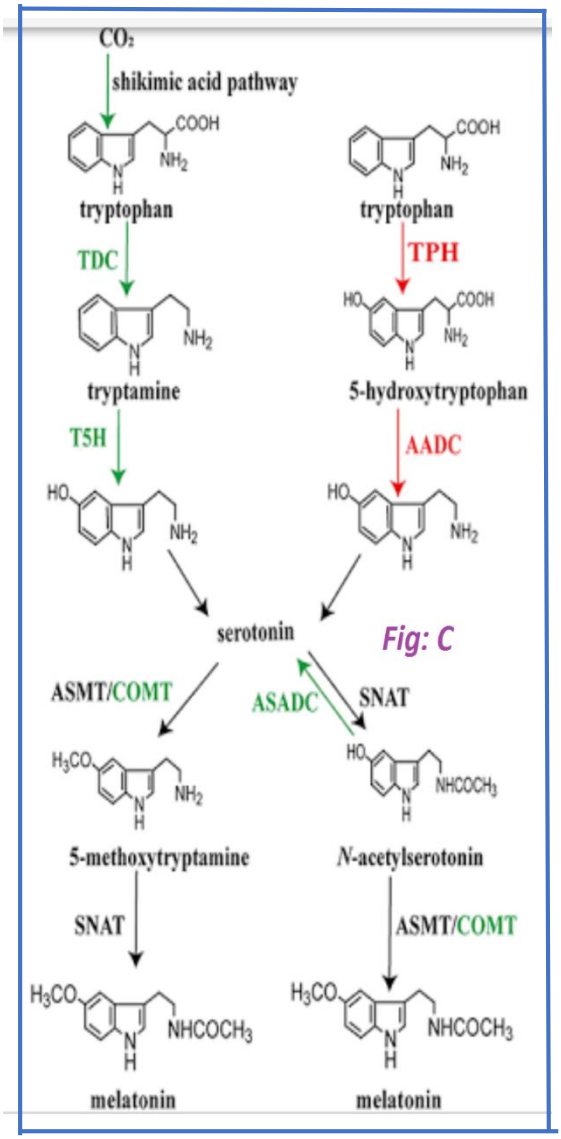


Fig: C

Fig A, B: Pathways of serotonin and melatonin synthesis.

Fig C: Pathways of melatonin synthesis in different plant (left) and animal (right) taxa. Differing from the formation of serotonin, the two alternative pathways for the conversation of serotonin to melatonin, likely occur in both plants and animals as well as in microorganisms.

In bacteria, protists, fungi, and plants, melatonin is synthesized indirectly with tryptophan as an intermediate product of the shikimate pathway. In these cells, synthesis starts with D-erythrose 4- phosphate and phosphoenolpyruvate, and in photosynthetic cells with carbon dioxide. Tryptophan is decarboxylated to tryptamine by tryptophan decarboxylase (TDC), followed by serotonin biosynthesis by tryptamine 5-hydroxylase (T5H) in plants. Plants evolved caffeic acid O-methyltransferase (COMT), which is involved in the synthesis of melatonin by methylating N-acetylserotonin.

Melatonin is made in the mitochondria (animals & plants) and chloroplasts (plants). Depending on the organism, not all of the events necessarily take place in the chloroplasts or mitochondria of every species.

Location:

- Serotonin is primarily found in the enteric nervous system and the enterochromaffin cells located in the GI tract. It is also produced in the serotonergic neurons of the CNS, specifically in the Raphe nuclei located in the brainstem. Additionally, serotonin is stored in blood platelets and is released during agitation and vasoconstriction.
- In vertebrates, melatonin is produced in darkness, thus usually at night, by the pineal gland, a small endocrine gland located in the center of the brain but outside the blood–brain barrier. Light/dark information reaches the suprachiasmatic nuclei from retinal photosensitive ganglion.
  Melatonin is metabolised in the liver by cytochrome P450 enzyme CYP1A2 to 6-hydroxymelatonin. Metabolites are conjugated with sulfuric acid or glucuronic acid for excretion in the urine (Fig B).

Functions:

- Serotonin regulates gastrointestinal motility, mood, appetite, sleep and some cognitive functions (memory, learning). It is one of the important neurotransmitter in body, acting through serotonergic neurons.
- In animals, melatonin plays an important role in the regulation of sleep–wake cycles (circadian rhythm). It plays role as antioxidant and free radicle scavenger.