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PHYSIOLOGY

Dopamine Synthesis.

Dopamine is synthesized from the amino acid tyrosine, which is taken up into the brain via an active transport mechanism.
Tyrosine is produced in the liver from phenylalanine through the action of phenylalanine hydroxylase.
Tyrosine is then transported to dopamine containing neurons where a series of reactions convert it to dopamine
Within catecholaminergic neurons, tyrosine hydroxylase catalyzes the addition of a hydroxyl group to the meta position of tyrosine, yielding L-dopa. This rate-limiting step in catecholamine
synthesis is subject to inhibition by high levels of catecholamines (end product inhibition). Because tyrosine hydroxylase is normally saturated with substrate, manipulation of tyrosine levels does not readily impact the rate of catecholamine synthesis.
Once formed, L-dopa is rapidly converted to dopamine by dopa decarboxylase, which is located in the

cytoplasm. It is now recognized that this enzyme acts not only on L-dopa but also on all naturally occurring aromatic L-amino acids, including tryptophan, and thus it is more properly termed aromatic amino acid decarboxylase

Serotonin Synthesis.

Serotonin (5-hydroxytryptamine) is principally found stored in three main cell types - i) serotonergic neurons in the CNS and in the intestinal myenteric plexus, ii) enterochromaffin cells in the mucosa of the gastrointestinal tract, and iii) in blood platelets. Serotonergic neurons and enterochromaffin cells can synthesize serotonin from its precursor amino acid L-tryptophan, whereas platelets rely upon uptake of serotonin for their stores. Likewise, serotonergic neurons also have the capacity for amine uptake via serotonin transporters. Serotonin is also synthesized in the pineal gland as a precursor for the subsequent enzymatic formation of the pineal hormone melatonin (N-acetyl-5-methoxytryptamine).

The biochemical pathway for serotonin synthesis initially involves the conversion of L-tryptophan to 5-hydroxytryptophan by the enzyme L-tryptophan hydroxylase (TPH), which has been found both in cytosolic and particulate brain cell fractions. This enzyme provides the rate-limiting step for serotonin

synthesis, in the same manner that norepinephrine and dopamine synthesis in adrenergic and dopaminergic neurons is controlled by the ability of the related enzyme, L-tyrosine hydroxylase, to convert L-tyrosine to L-dihydroxyphenylalanine (L-DOPA). Some inhibitors of TPH (e.g. α-propyldopacetamide) are also active against tyrosine hydroxylase, whereas others such as p-chlorophenylalanine are more selective for TPH. Although p-chloroamphetamine and fenfluramine can also inhibit TPH, they have important actions (including neurotoxic effects) upon various other regulatory processes of serotonergic neuronal function. The identification of two enzyme isoforms, called TPH1 and TPH2, which are apparently associated selectively with peripheral tissues and the brain, respectively, suggests the possibility that drug inhibitors with specificity for targeting individual isoforms may be found in the future.

The subsequent metabolic step in the synthesis of serotonin (and also norepinephrine or dopamine) involves the decarboxylation of 5-hydroxytryptophan (and L-DOPA) by the action of the cytosolic enzyme L-aromatic amino acid decarboxylase. Inhibitors of this enzyme include the drugs benserazide and carbidopa, which do not cross the blood brain barrier, and are used clinically to prevent peripheral decarboxylation of the L-DOPA administered as a precursor for central dopamine formation in Parkinsonian patients.

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