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## DOPAMINE SYNTHESIS

Dopamine is synthesized from the amino acid tyrosine; the majority of circulating tyrosine originates from dietary sources, but small amounts are derived from hydroxylation of phenylalanine by the liver enzyme phenylalanine hydroxylase .

Blood-borne tyrosine is taken up into the brain by a low-affinity amino acid transport system and subsequently from brain extracellular fluid into dopaminergic neurons by high- and low-affinity amino acid transporters.

Tyrosine is converted to dopamine by the enzymes tyrosine hydroxylase (TH) and L-amino acid decarboxylase (AADC) also called dihydroxyphenylalanine (DOPA) decarboxylase (DDC). The aromatic amino acid hydroxylases 2000

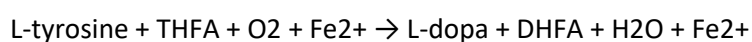
TH is the rate-limiting step in their biosynthetic pathway; the TH gene is localized to chromosome 11p in humans and encodes a single form of TH that can be alternatively spliced. The mRNA expression of the TH is abundant throughout the human mesencephalon.

The mature enzyme is a soluble cytosolic protein composed of four subunits of approximately 60 kDa each.

TH activity is the most critical factor that controls dopamine synthesis, and considerable efforts have been devoted to understanding activation/inactivation of this enzyme. Assignment of the human tyrosine hydroxylase gene to chromosome 1984

As previously say, AADC is the second and terminal enzyme in dopamine biosynthesis. The enzyme uses pyridoxal phosphate as a cofactor and can convert both DOPA to dopamine and 5-hydroxytryptophan to serotonin [5-hydroxytryptamine (5-HT)]. Aromatic L-amino acid decarboxylase modulation and Parkinson's disease 1995

The following is the complete reaction:

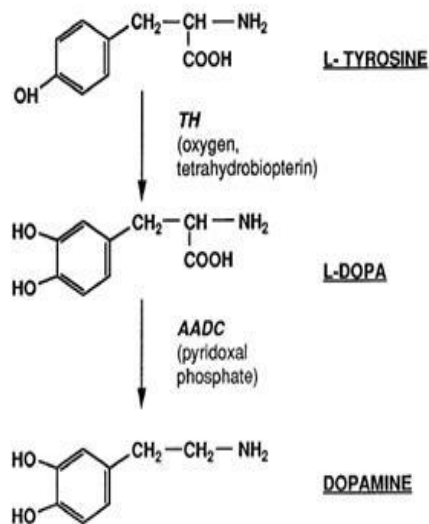


So for L-dopa formation, L-tyrosine, THFA (tetrahydrofolic acid), and ferrous iron are essential and for dopamine biosynthesis from L-dopa, pyridoxal phosphate is essential.

The activity of the enzyme rises and falls according to how much pyridoxal phosphate there is.

Besides two enzymes being required for the formation of dopamine from L-tyrosine (L-tyrosine >>> L-dopa >>> dopamine), three coenzymes are also required. They are : THFA (for L-tyrosine to L-dopa), pyridoxal phosphate (for L-dopa to dopamine), and NADH (for the formation of THFA and Pyridoxal phosphate). The cofactor tetrahydrobiopterin (BH4) donates the hydrogen atom needed for hydroxylation of tyrosine to DOPA.

Because pterin also serves as a cofactor for other monooxygenases as well as nitric oxide synthase, its availability is a determinino factor in the control of TH activity. Regulation of pteridine-requiring enzymes by the cofactor tetrahydrobiopterin 1999



### Norepinephrine Synthesis

Norepinephrine (NE) is the primary neurotransmitter for postganglionic sympathetic adrenergic nerves. It is synthesized inside the nerve axon, stored within vesicles, then released by the nerve when an action potential travels down the nerve. Below are the details for release and synthesis of NE:

1. The amino acid tyrosine is transported into the sympathetic nerve axon.
2. Tyrosine (Tyr) is converted to DOPA by tyrosine hydroxylase (rate-limiting step for NE synthesis).
3. DOPA is converted to dopamine (DA) by DOPA decarboxylase.
4. Dopamine is transported into vesicles then converted to norepinephrine (NE) by dopamine  $\beta$ -hydroxylase (DBH); transport into the vesicle can be blocked by the drug reserpine.
5. An action potential traveling down the axon depolarizes the membrane and causes calcium to enter the axon.
6. Increased intracellular calcium causes the vesicles to migrate to the axonal membrane and fuse with the membrane, which permits the NE to diffuse out of the vesicle into the extracellular (junctional) space. DBH, and depending on the nerve other secondary neurotransmitters (e.g., ATP), is released along with the NE.
7. The NE binds to the postjunctional receptor and stimulates the effector organ response.