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**Synthesis of Acetylcholine**

Acetylcholine (Ach) is synthesized by a single step reaction catalysed by the biosynthetic enzyme choline acetyltransferase. As is the case for all nerve terminal proteins, choline acetyltransferase CAT is produced in the cholinergic cell body and transported down the axon to the nerve endings. Both CAT and ACh may be found throughout the neuron, but their highest concentration is in axon terminals. The presence of CAT is the "marker" that a neuron is cholinergic, only cholinergic neurons contain CAT.

The rate-limiting steps in ACh synthesis are the availability of choline and **acetyl-CoA**. During increased neuronal activity the availability of acetyl-CoA from the mitochondria is upregulated as is the uptake of choline into the nerve ending from the synaptic cleft. Ca2+ appears to be involved in both of these regulatory mechanisms. As will be described later, the inactivation of ACh is converted by metabolism to choline and acetic acid. Consequently much of the **choline** used for ACh synthesis comes from the recycling of choline from metabolized ACh. Another source is the breakdown of the phospholipid, **phosphatidylcholine**. One of the strategies to increase ACh neurotransmission is the administration of choline in the diet. However, this has not been effective, probably because the administration of choline does not increase the availability of choline in the CNS. In the nervous system, this enzyme is thought to exist primarily in the nerve terminal cytoplasm. Coenzyme A is synthesized in mitochondria and accesses choline acetyltransferase following transport across the mitochondrial membrane into the cytoplasm. In addition to its synthesis in the liver, choline employed in acetylcholine production is derived from dietary sources. There is a carrier system in capillary endothelial cells that is responsible for transport of choline, in its free and phospholipid forms, into the brain. Hydrolysis of choline-containing phospholipids may also liberate choline that is used in acetylcholine synthesis. As choline acetyltransferase is not saturated by concentrations of acetyl coenzyme A and choline that are estimated to be present in the nerve terminal, it appears that the rate of acetylcholine synthesis is dependent on precursor availability. Enzyme activity is also regulated by product inhibition; by binding at an allosteric site on choline acetyltransferase, acetylcholine inhibits its activity. In addition, mass action and neuronal activity influence the rate of acetylcholine formation. Short-term regulation of enzyme activity is partly achieved by phosphorylation induced by protein kinases. There are no very specific and potent inhibitors of the enzyme and it should be noted that pharmacological blockade of this step (e.g. with naphthylvinylpyridine) in the life-cycle of acetylcholine produces a less profound effect on the transmitter than does inhibition of choline transport.

### **Synthesis of Dopamine**

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).
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.
TH activity is the most critical factor that controls dopamine synthesis
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)].
The following is the complete reaction:

L-tyrosine + THFA + O2 + Fe2+ → L-dopa + DHFA + H2O + Fe2+

L-dopa + pyridoxal phosphate → dopamine + pyridoxal phosphate + CO2

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 monoxygenases as well as nitric oxide synthase, its availability is a determinino factor in the control of TH activity.