

Dopamine, Norepinephrine and Epinephrine Synthesis

Key References

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Overview

Phenylalanine is an essential amino acid that is converted to tyrosine primarily in the liver by phenylalanine hydroxylase. Blood borne tyrosine, derived from dietary proteins and from phenylalanine metabolism, enters the brain by a low affinity amino acid transport system. Tyrosine in brain extracellular fluid is taken up into catecholamine neurons by high and low affinity amino acid transporters. The relative circulating levels of tyrosine and phenylalanine can affect central catecholamine metabolism, as these amino acids compete for transport into the brain, and for transport into the neuron. In phenylketonuria, there is an impaired ability to convert phenylalanine to tyrosine, so that in this condition there is an elevated level of phenylalanine in the blood and in brain extracellular fluid. As phenylalanine is a relatively weak substrate for tyrosine hydroxylase, its presence in high concentrations inhibits hydroxylation of tyrosine by tyrosine hydroxylase.

The conversion of tyrosine to dihydroxyphenylalanine (L-DOPA) is catalyzed by tyrosine hydroxylase in the cytosol. This is normally the rate-limiting step in catecholamine biosynthesis, so that pharmacological blockade of this enzyme has profound effects on catecholamine formation. However, it is possible for any of the reactions to be rate-limiting in certain pharmacological or pathological situations. Tyrosine hydroxylase has a relatively high degree of substrate specificity. Tyrosine availability does not normally influence the rate of tyrosine hydroxylation *in vivo*, but when the neuronal system is activated, or has a high basal firing rate (e.g. mesoprefrontal dopamine neurons), tyrosine levels can alter the rate of conversion to L-DOPA.

Increased impulse flow can lead to short term activation of tyrosine hydroxylase, which appears to involve phosphorylation of the regulatory domain by protein kinases to produce an activated form of tyrosine hydroxylase with a lower K_m for its pterin cofactor and a higher K_i for catecholamine (product inhibition). In addition, activation or blockade of autoreceptors can alter the rate of tyrosine hydroxylation. In primates, but not rodents, multiple tyrosine hydroxylase mRNAs are produced through alternative mRNA splicing from a single primary transcript. The rate of decline of catecholamine levels following inhibition of tyrosine hydroxylase provides an index of turnover.

Aromatic amino acid decarboxylase catalyzes the cytosolic conversion of L-DOPA to dopamine, although all naturally occurring aromatic L-amino acids are substrates for the enzyme. The enzyme so rapidly decarboxylates L-DOPA that the levels of the amino acid are relatively low, and supplying the enzyme with additional substrate can lead to increased product formation, which is the basis of L-DOPA treatment for Parkinson's disease. The accumulation of DOPA following inhibition of aromatic amino acid decarboxylase provides an index of synthesis rate.

Dopamine- β -hydroxylase is located inside amine storage vesicles of norepinephrine neurons. Dopamine is actively transported from the cytoplasm into the vesicles. As the enzyme is a copper containing protein, its activity can be inhibited by copper chelating agents, such as diethyldithiocarbamate and FLA-63. Inhibition of the enzyme effectively reduces tissue norepinephrine levels. The enzyme does not have a high degree of substrate specificity.

The occurrence of phenylethanol-amine-N-methyltransferase is largely restricted to the adrenal medulla, but with detectable levels in association with epinephrine neurons in brain. Inhibition of enzyme activity decreases epinephrine biosynthesis. There is, however, a less specific N-methyltransferase present in many tissues. While there may be soluble phenylethanolamine-N-methyl-transferase in the cytoplasm, there is good evidence for a particulate location of the enzyme, probably associated with the granule or vesicle membrane.

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COMPOUND	ENZYME	Co-FACTORS	INHIBITORS
L-Phenylalanine (P 2126) ↓	→ Phenylalanine-4-hydroxylase	Oxygen Tetrahydrobiopterin (T 4425)	α -Methylphenylalanine (M 3635) 7-Tetrahydropterin p -Chlorophenylalanine (C 6506 , C 8655)
L-Tyrosine (T 2006) ↓	→ Tyrosine-3-hydroxylase	Oxygen Tetrahydrobiopterin (T 4425)	3-Chlorotyrosine (C 5897) 3-Iodotyrosine (I 8250) α -Methyl- p -tyrosine (M 8131)
L-Dihydroxyphenylalanine (D 9628) ↓	→ L-Aromatic amino acid decarboxylase	Pyridoxal phosphate (P 9255)	Benserazide (Ro 4-4602) (B 7283) Brocresine Carbidopa (MK-486) (C-126 , C 1335) Difluoromethyl dopa NSD 1015 (H 9382) α -Methyl dopa (M-129) Monofluoromethyl dopa
Dopamine (H 8502) ↓	→ Dopamine- β -hydroxylase	Ascorbate (A 7631) Oxygen	Diethyldithiocarbamate (D 3506) FLA-63 FLA-57 Fusaric acid (F 6513) Nepicastat Phenylpropargylamine (P-106) SKF 102698
L-Norepinephrine (A 9512) ↓	→ Phenylethanolamine-N-methyltransferase (PNMT) (P 8924)	S-Adenosyl-L-methionine (A 7007)	CGS19281A Cyclooctyl-2-hydroxyethylamine (C-108) Dichloromethylbenzylamine (D-103) 3-Fluoromethyl-1,2,3,4-tetrahydroisoquinolines LY-134046 SKF 29661 SKF 64139
L-Epinephrine (E 4375)			

ABBREVIATIONS

CGS19281A: 4,9-Dihydro-7-methoxy-3H-pyrido[3,4b]indole
FLA-63: *bis*-(4-Methyl-1-homopiperazinylthiocarbonyl)-disulphide
FLA-57: 4-Methyl-homopiperazine-1-dithiocarboxylic acid
LY-134046: 8,9-Dichloro-2,3,4,5-tetrahydro-1H-2benzazepine
NSD 1015: *m*-Hydroxybenzylhydrazine
SKF 29661: 7-(Aminosulfonyl)-1,2,3,4-tetrahydroisoquinoline
SKF 64139: 7,8-Dichloro-1,2,3,4-tetrahydroisoquinoline