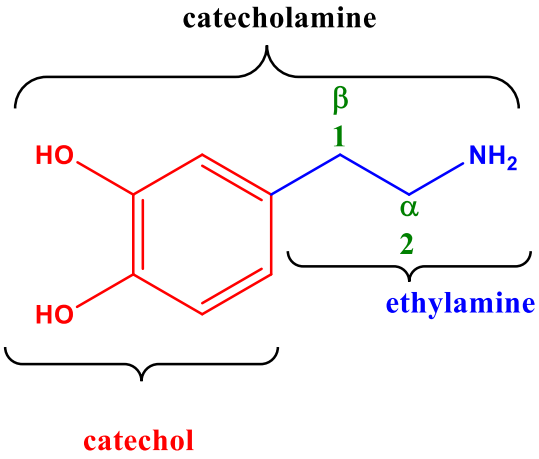
Adrenergic neurotransmitter

Structure and physicochemical properties

Norepinephrine (NE, noradrenaline), Epinephrine (E, adrenaline), and Dopamine (DA) are chemically catecholamines (CAs), which refer generally to all organic compounds that contain a catechol nucleus (ortho-dihydroxybenzene) and an ethylamine group. In a physiological context, the term usually means DA and its metabolites NE and E. E contains one secondary amino group and three hydroxyl groups. Using the polyfunctional solubilizing potential and calculated log P (-0.63) of E, one would expect the molecule is polar and soluble in water, and, indeed, this turns out to be the case.



Biosynthesis

The first step in CA biosynthesis is the 3-hydroxylation of the amino acid L-tyrosine to form L-dihydroxyphenylalanine (L-DOPA). L-Tyrosine is normally present in the circulation and transported actively into the adrenergic neuron, where it is 3-hydroxylated by tyrosine hydroxylase (TH, tyrosine-3-monooxygenase). TH is stereospecific and requires molecular O_2, Fe^{2+}, and a tetrahydropteridine cofactor. As usual for the first enzyme in a biosynthetic pathway, TH hydroxylation is the rate-limiting step in the biosynthesis of NE. Further proof that this step is rate limiting in CA biosynthesis is that inhibitors of TH markedly reduce endogenous NE and DA in the brain and NE in the heart, spleen, and other sympathetically innervated tissues. This enzyme plays a key role in the regulation of CA biosynthesis and is, therefore, the logical biological target of some drugs. Some effective TH inhibitors include **-methyl-p-tyrosine, -methyl-3-iodotyrosine, and -methyl-5-hydroxytryptophan**. In general, -methyl analogs are more potent than the unmethylated analogs. Most of the agents in this category act as **competitive inhibitors of TH**.

The second step in CA biosynthesis is the decarboxylation of L-DOPA to give DA, which is an important NT. The enzyme involved is DOPA decarboxylase, the enzyme is **not**

specific and act on **all natural occur amino acid**. Therefore, this enzyme is more appropriately referred to as L-aromatic amino acid decarboxylase (AADC).

In simplest term, parkinsonism can be characterized as a **DA deficiency** in the brain. Thus, increasing brain levels of DA should ameliorate the symptoms. Unfortunately, direct parenteral DA administration is useless because the compound does not penetrate the blood-brain barrier (BBB). However, oral dosing with L-DOPA (levodopa, Dopar) could act as a prodrug because it entered the brain (on a specific carrier) and then was decarboxylated to DA there. Unfortunately, many adverse systemic effects were the result of the high doses needed to achieve the desired results. The main reason is the relatively higher concentration of AADC in peripheral system than in the brain. Inhibition of peripheral AADC activity by co-administration of at peripheral decarboxylase inhibitor such as carbidopa.

The third step in CA biosynthesis is side-chain β- hydroxylation of DA to give NE. DA formed in the cytoplasm of the neuron is actively transported into storage vesicles by a 12-helix membrane–spanning proton antiporter called the **vesicular monoamine transporter (VMAT)** and is then hydroxylated stereo specifically at the β-carbon to NE inside the vesicle by dopamine β-hydroxylase (DBH, dopamine β-monooxygenase)

The last step in CA biosynthesis is the N-methylation of NE to give E in the adrenal medulla. The reaction is catalyzed by the enzyme phenylethanolamine-N-methyltransferase (PENMT). PENMT is a cytosolic enzyme and the methyl donor S-adenosyl methionine (SAM) is required for the N-methylation of NE.

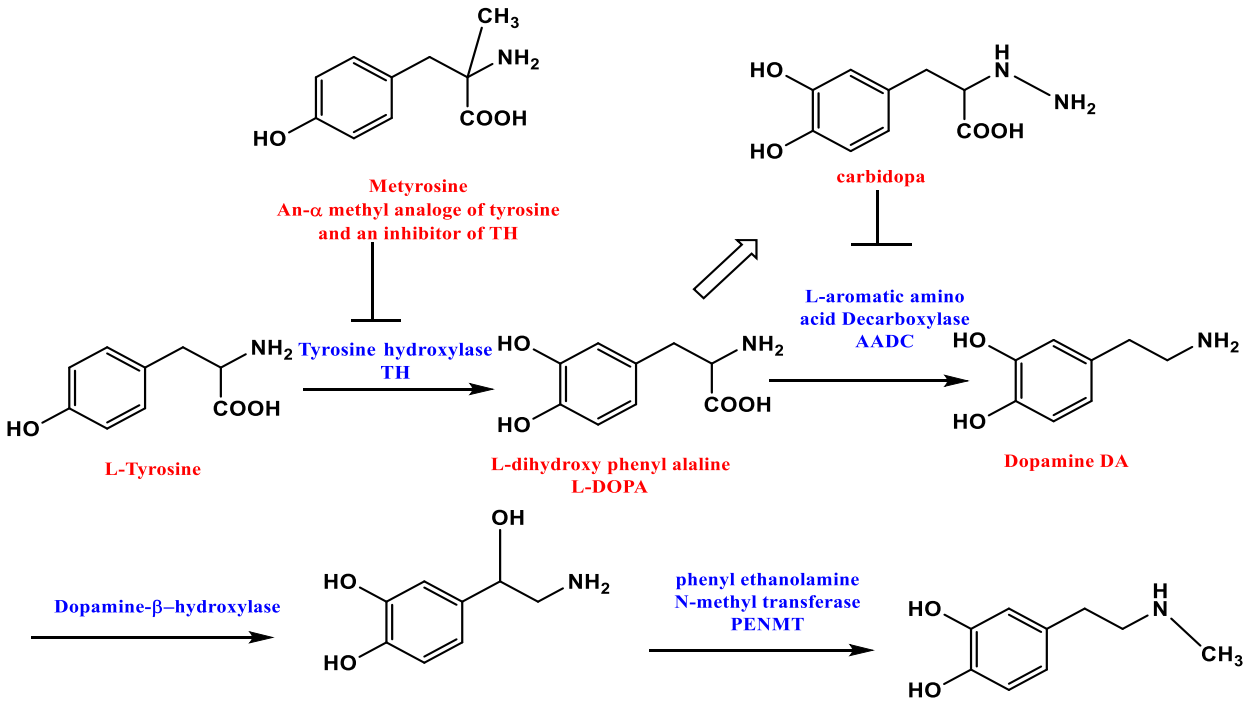


Figure: Biosynthesis of the catecholamine dopamine, norepinephrine, and epinephrine.

Storage, Release, Uptake, and Metabolism

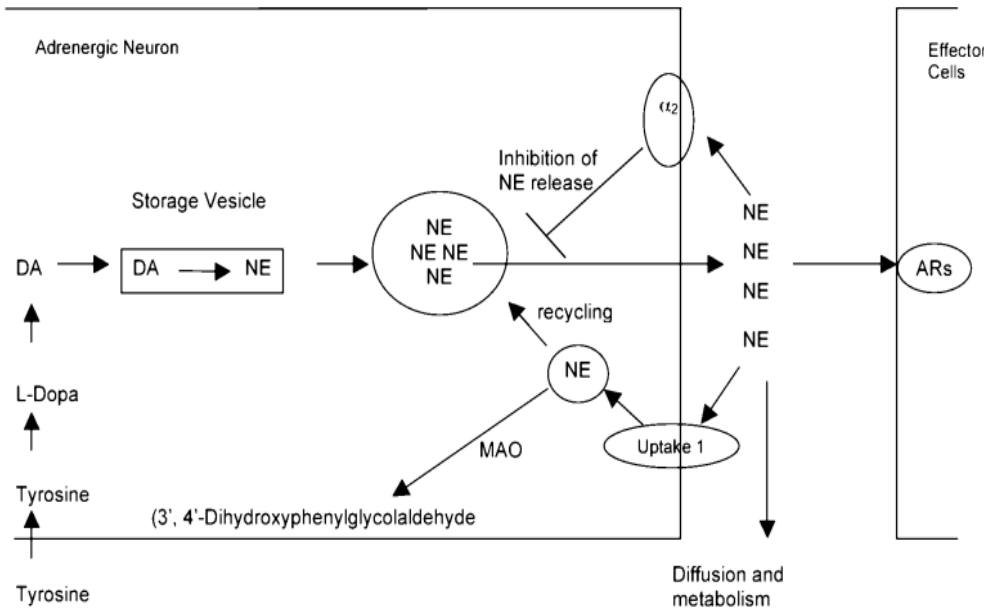


Figure: model of life cycle of NE

Metabolism

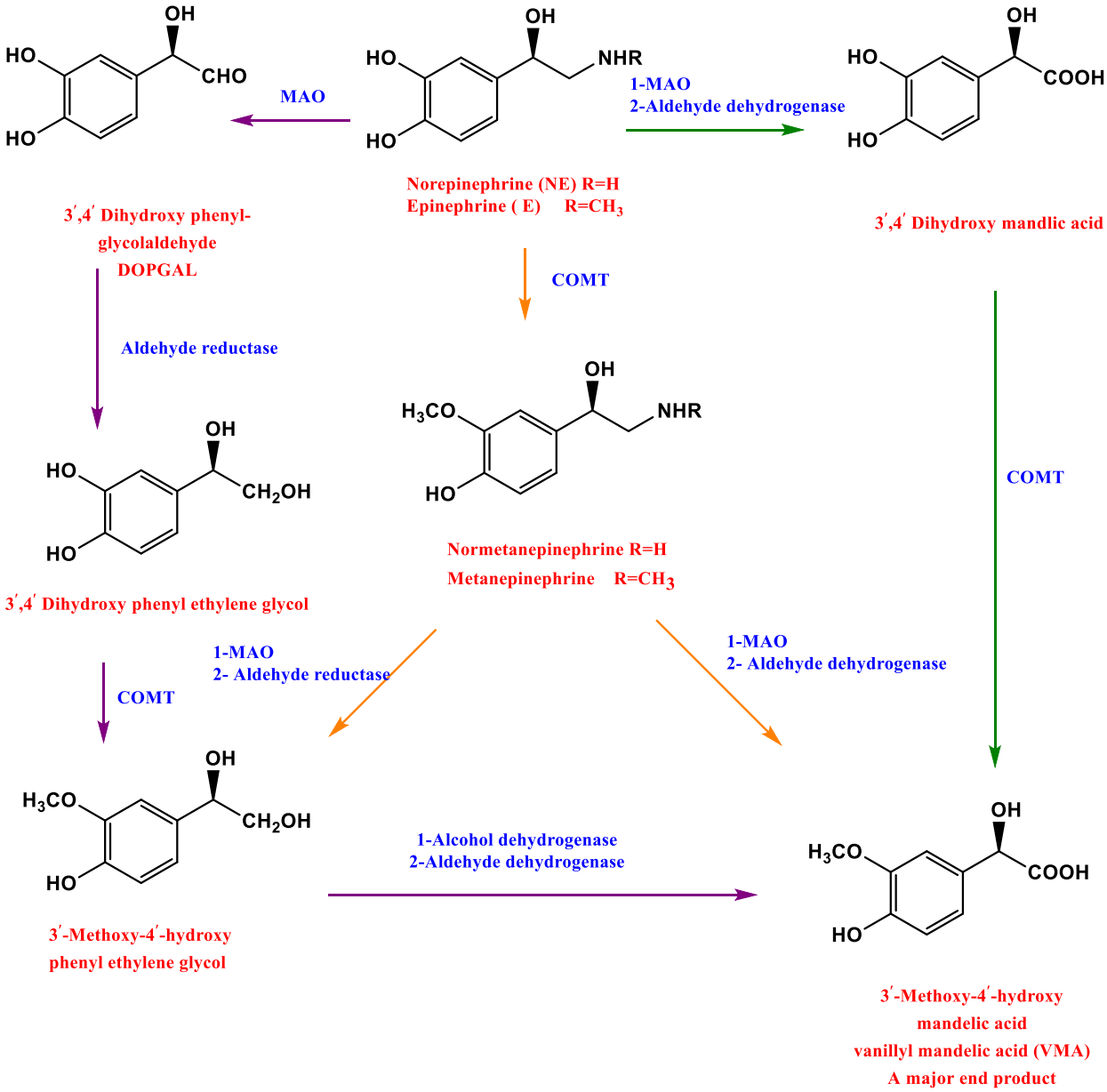


Figure: metabolism pf norepinephrine and epinephrine by MAO and COMT

Reference: Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry , twelfth edition, chapter 16 (adrenergic agents.