The Catecholamines

The *catecholamines* (dopamine, norepinephrine, and epinephrine) are derivatives of tyrosine. Dopamine (D) and norepinephrine (NE) are used in the brain as excitatory neurotransmitters. Outside the central nervous system, NE and epinephrine (E) are released primarily from the adrenal medulla, as well as the peripheral nervous system. Because both NE and E regulate aspects of metabolism, they are often considered hormones.

The first, and rate-limiting, step in catecholamine synthesis is the hydroxylation of tyrosine to form 3,4-dihydroxyphenylalanine (l-DOPA) (**Figure 1**). Tyrosine hydroxylase, the mitochondrial enzyme that catalyzes the reaction, requires a cofactor known as *tetrahydrobiopterin* (BH_4). A folic acid–like molecule, BH_4 is an essential cofactor in the hydroxylation of aromatic amino acids; it is regenerated from its oxidized metabolite, BH_2, by reduction with NADPH.

Tyrosine hydroxylase uses BH_4 to activate O_2. One oxygen atom is attached to tyrosine's aromatic ring, while the other atom oxidizes the coenzyme. DOPA, the product of the reaction, is used in the synthesis of the other catecholamines.

DOPA decarboxylase, a pyridoxal phosphate–requiring enzyme, catalyzes the synthesis of dopamine from l-DOPA. Dopamine is produced in neurons found in certain structures in the brain. It is believed to exert an inhibitory action in the central nervous system. Deficiency in dopamine production has been found to be associated with Parkinson's disease, a serious degenerative neurological disorder. The precursor l-DOPA is used to alleviate the symptoms of Parkinson's disease because dopamine cannot penetrate the blood-brain barrier. (Although most lipid-soluble substances readily pass across the blood-brain barrier, many polar molecules and ions cannot move from blood capillaries.) Once l-DOPA has been transported into appropriate nerve cells, it is converted to dopamine.

Norepinephrine is synthesized from tyrosine in the chromaffin cells of the adrenal medulla in response to fright, cold, and exercise, as well as low levels of blood glucose. NE acts to stimulate the degradation of triacylglycerol and glycogen. It also increases cardiac output and blood pressure. The hydroxyl ation of dopamine to produce NE is catalyzed by the copper-containing enzyme dopamine-*β*-hydroxylase, an oxidase that requires ascorbic acid, acting as a reducing agent, for full activity.

As described, the secretion of epinephrine in response to stress, trauma, extreme exercise, or hypoglycemia causes a rapid mobilization of energy stores, that is, glucose from the liver and fatty acids from adipose tissue. The reaction in which NE is methylated to form E is catalyzed by the enzyme phenylethanolamine–*N*-methyltransferase (PNMT). Although the enzyme occurs predominantly in the chromaffin cells of the adrenal medulla, it is also found in certain portions of the brain, where E functions as a neurotransmitter. Recent evidence indicates that both

E and NE are present in several other organs (e.g., liver, heart, and lung). Bovine PNMT is a monomeric protein (30 kDa) that uses SAM as a source of methyl groups.

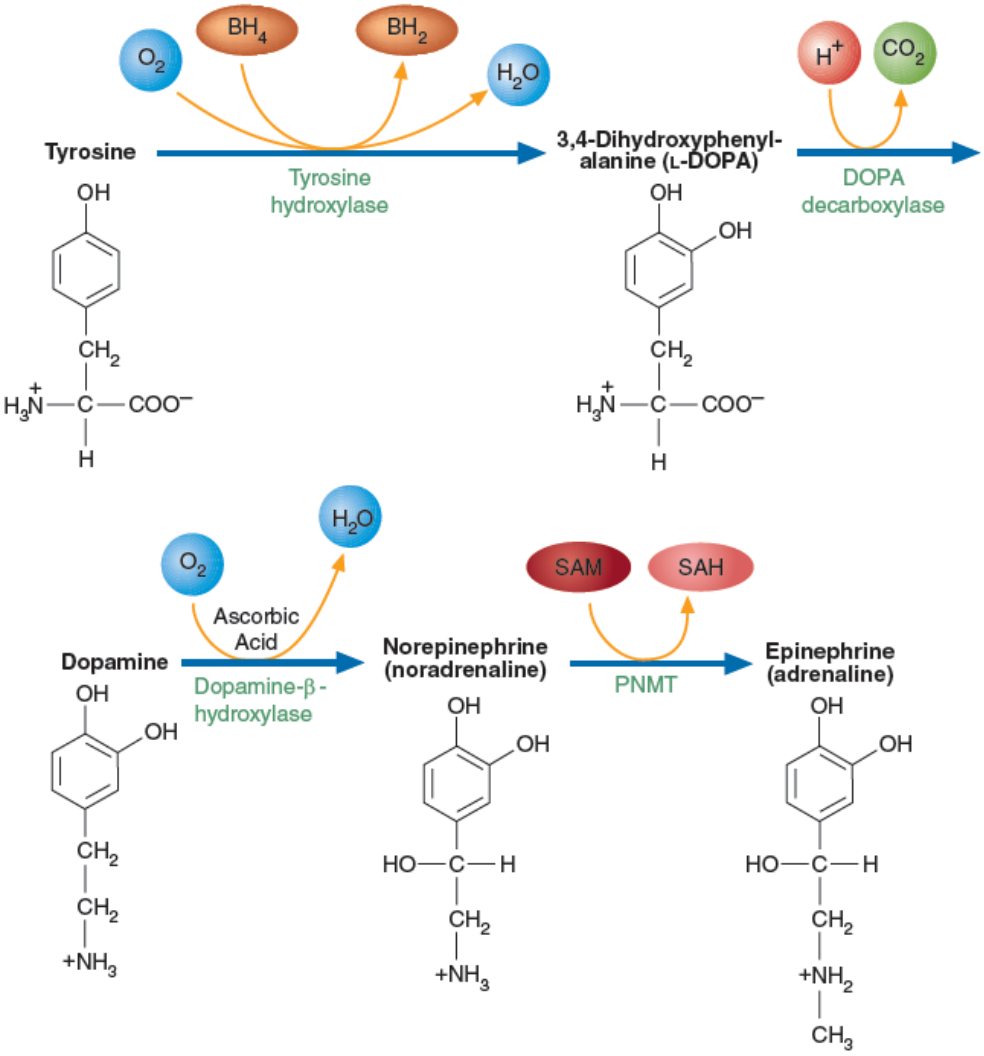

FIGURE 1

Biosynthesis of the Catecholamines

Dopamine, norepinephrine, and epinephrine act as neurotransmitters and/or hormones. (PNMT = phenylethanolamine–*N*-methyltransferase).