Neurochemistry and defects of biogenic amine neurotransmitter metabolism

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Summary: The purpose of the current review is to present a brief background examining the mechanisms controlling synthesis, storage, release and action of the biogenic amine neurotransmitters and to provide examples of newly defined conditions that expand our awareness of the diversity and complexity of the inherited diseases that affect these important regulators of central and peripheral homeostasis.

BIOSYNTHESIS AND CATABOLISM OF THE BIOGENIC AMINES

The term biogenic amine originally encompassed all amines with an origin in biological processes. This definition is rather broad, and it is now generally accepted that a biogenic amine refers to the catecholamines (dopamine, epinephrine (adrenaline) and norepinephrine (noradrenaline)) and serotonin. The amines are formed from tryptophan and tyrosine in reactions catalysed by tryptophan hydroxylase (EC 1.14.16.4) and tyrosine hydroxylase (EC 1.14.16.2) (Figure 1). Both enzymes are rate limiting and both require tetrahydrobiopterin and molecular oxygen for their activity (Kaufman 1981). 3,4-Dihydroxy-L-phenylalanine and 5-hydroxytryptophan, the products of the hydroxylation reactions, are then decarboxylated by pyridoxine-dependent aromatic L-amino acid decarboxylase (EC 4.1.1.28) to form the active neurotransmitters. In noradrenergic neurons, dopamine is further hydroxylated by dopamine β-hydroxylase (EC 1.14.17.1) to form norepinephrine. Within the pineal gland, serotonin is converted to melatonin via acetylation and methylation reactions catalysed by serotonin N-acetylase (EC 2.3.1.87) and 5-hydroxyindole O-methyltransferase (EC 2.1.1.4). Dopamine, serotonin and norepinephrine are catabolized using monoamine oxidase (EC 1.4.3.4) and catechol O-methyltransferase (EC 2.1.1.6) to form homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG), respectively. These are the major metabolites detected in human CSF and their levels are thought to accurately reflect the turnover of the neurotransmitters within the brain.

REGULATION OF BIOGENIC AMINE NEUROTRANSMISSION

The catecholamines and serotonin are defined as chemical neurotransmitters. They are synthesized and then stored in the presynaptic nerve terminal. Following arrival
of a nerve impulse, they are released into the synaptic cleft where they act on postsynaptic membrane receptor sites to produce either excitation or inhibition of the target cell. The mechanisms controlling the different stages of this process are diverse and complex and are designed to ensure that there is neither overactivity nor underactivity of the neurotransmission process. Figure 2 illustrates many of the mechanisms that interact to provide overall control of dopaminergic neurotransmission. Although the control mechanisms in serotonergic and noradrenergic neurons differ in several respects, many of the mechanisms are similar; therefore, the dopamine system is provided as a model.

Dopamine is synthesized in the cytoplasm and the initial regulation of the dopaminergic pathway acts at the level of tyrosine hydroxylase. Eight mechanisms that regulate this enzyme have been described, but in vivo the most important are probably reversible feedback inhibition by catecholamines, and phosphorylation via a Ca\(^{2+}\), cAMP-dependent mechanism (Kumer and Vrana 1996). Once formed, dopa-