

Dopamine and Norepinephrine Metabolism

Key References

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Overview

While reuptake of catecholamines plays an important role in regulating their synaptic levels, metabolism also contributes significantly to the termination of catecholamine neurotransmission. The relative abundance and activity of the catecholamine metabolizing enzymes varies in different species and in different cell groups, so these factors dictate the relative concentration of a particular metabolite present in a particular tissue or fluid. Either monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT) can catalyze the first step in catecholamine catabolism.

MAO is located on the outer membranes of mitochondria and thus, in brain, is present primarily in nerve terminals and glia. In the periphery, MAO is found in particularly high concentrations in liver and kidney. Separate genes encode two isoforms of MAO (types A and B), which were distinguished by substrate specificity and sensitivity to the irreversible selective inhibitors clorgyline and deprenyl (selegiline). In brain, MAO-A is preferentially located in dopaminergic and noradrenergic neurons, while MAO-B appears to be the major form present in serotonergic neurons and glia. Inhibitors of MAO are used in the treatment of depression and Parkinson's disease, and reversible inhibitors of both MAO-A (e.g., moclobemide) and MAO-B (lazabemide) are now available.

Membrane-bound COMT appears to be located principally in postsynaptic neurons, although a soluble form with lower affinity for catecholamines is present in glia, and is also widely distributed outside the brain. In clinical trials, inhibitors of COMT have been shown to extend the duration of action of L-dopa in the treatment of Parkinson's disease.

The potentially toxic aldehyde intermediate generated in the MAO reaction (3,4-dihydroxyphenylacetaldehyde for dopamine, 3,4-dihydroxyphenylglycolaldehyde for norepinephrine) is either rapidly reduced to an alcohol (by cytosolic aldehyde reductase and/or aldose reductase) or oxidized to an acid (by mitochondrial aldehyde dehydrogenase). In brain, the formation of acid metabolites from dopamine is favored, whereas for central norepinephrine catabolism the alcohol metabolites predominate. Alcohol dehydrogenase is capable of catalyzing the interconversion of the alcohol and aldehyde. The substrate and inhibitor specificity of these latter three enzymes is limited.

Because of the cellular distribution of MAO, 3,4-dihydroxyphenylacetic acid (DOPAC) and 3,4-dihydroxyphenyl-glycol (DHPG) can be formed either intraneuronally or extraneuronally, whereas, because of the extraneuronal location of COMT, homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenyl-glycol (MHPG) are principally formed extraneuronally. Under resting conditions, a considerable portion of metabolism derives from amine that has passively leaked from vesicular storage. The major end products of catecholamine metabolism in primate brain are HVA (for dopamine) and MHPG (for norepinephrine) respectively, whereas in rat brain they are DOPAC and DOPAC-sulfate (for dopamine) and MHPG-sulfate (for norepinephrine), respectively. In the periphery, the major metabolite of norepinephrine metabolism is VMA (formed from circulating MHPG in the liver), and for dopamine the principle end metabolite is HVA (formed to a large extent outside the liver).

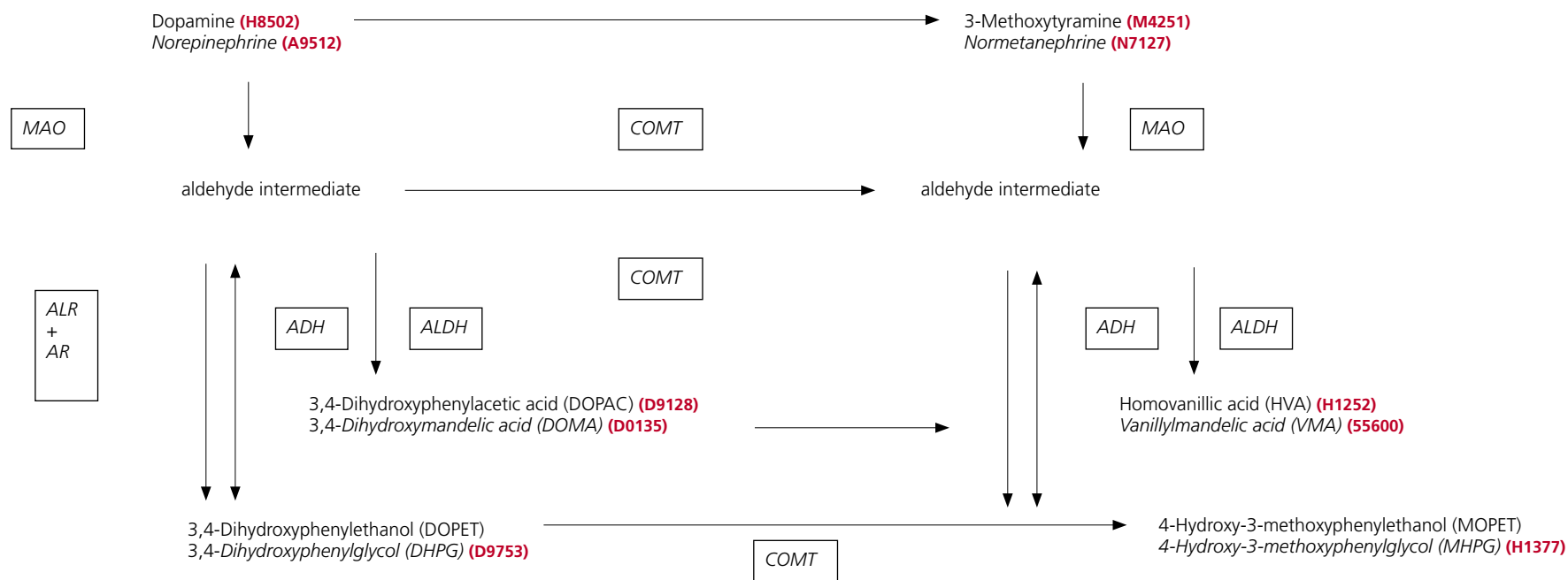
Catecholamines and their metabolites in brain and periphery are, in addition, sub-

strates for phenolsulfotransferase, forming sulfate conjugates. Quercetin, mefenamic acid and tolfenamic acid are inhibitors of phenolsulfotransferase, but show more selectivity for the P-form, whereas the catechols are preferential substrates for the M-form. In the periphery, glucuronide conjugates of catecholamines and metabolites are formed by the action of UDP-glucuronosyltransferases. Once conjugated, the compound is no longer an effective substrate for MAO or COMT.

Measurement of the tissue concentration of catecholamine metabolites (or the ratio of the concentrations of metabolite to parent amine) can be a useful biochemical index of metabolic activity or transmitter utilization in a neuronal system. Although present in very low concentration, and subject to rapid postmortem change, the careful measurement of tissue concentration of 3-methoxytyramine appears to provide a post-mortem index of dopamine release.

Dopamine and Norepinephrine Metabolism

| ENZYME | Co-FACTORS | INHIBITORS |
|---|--|---|
| Monoamine oxidase (MAO) (M7316 , M7441) | Oxygen | MAO-A Selective: Brofaromine, Clorgyline (M3778), Moclobemide, Ro 41-1049 (R107), Befloxadone MAO-B Selective: Deprenyl (M003 , M005), Lazabemide (Ro 19-6327), Pargyline (P8013), Ro 16-6491 (R106) MAO-A/B Non-selective: Hydralazine (H1753), Iproniazid (I7627), Isocarboxazid, Nialamide (N1392), Phenelzine (P6777), 6-Methoxy-tetrahydro-9H-pyrido-indole (M008), Tranylcypromine (P8511), Entacapone, Nitecapone, OR-486 (D131), Ro 41-0960 (R108), Tolcapone, Tropolone (T7387), Cyanamide (C1920), Daidzin (D7802), Genistin (G0897), Barbiturates (P5178 , P3761), Sodium valproate (P4543), AL 1576, Tolrestat, Ponalrestat, 4-Methylpyrazole (M1387), 1,10-phenanthroline (P9375) |
| Catechol-O-methyltransferase (COMT) (C1897) | S-Adenosyl-L-methionine (A7007) | |
| Aldehyde dehydrogenase (ALD-DH) (A9770) | NAD ⁺ (N7004) | |
| Aldehyde reductase (ALR) | NADP ⁺ (N0505) | |
| Aldose reductase (AR) | NADP ⁺ (N0505) | |
| Alcohol dehydrogenase (ADH) (A7011) | NAD ⁺ (N7004) | |



FOOTNOTES