Metabolism

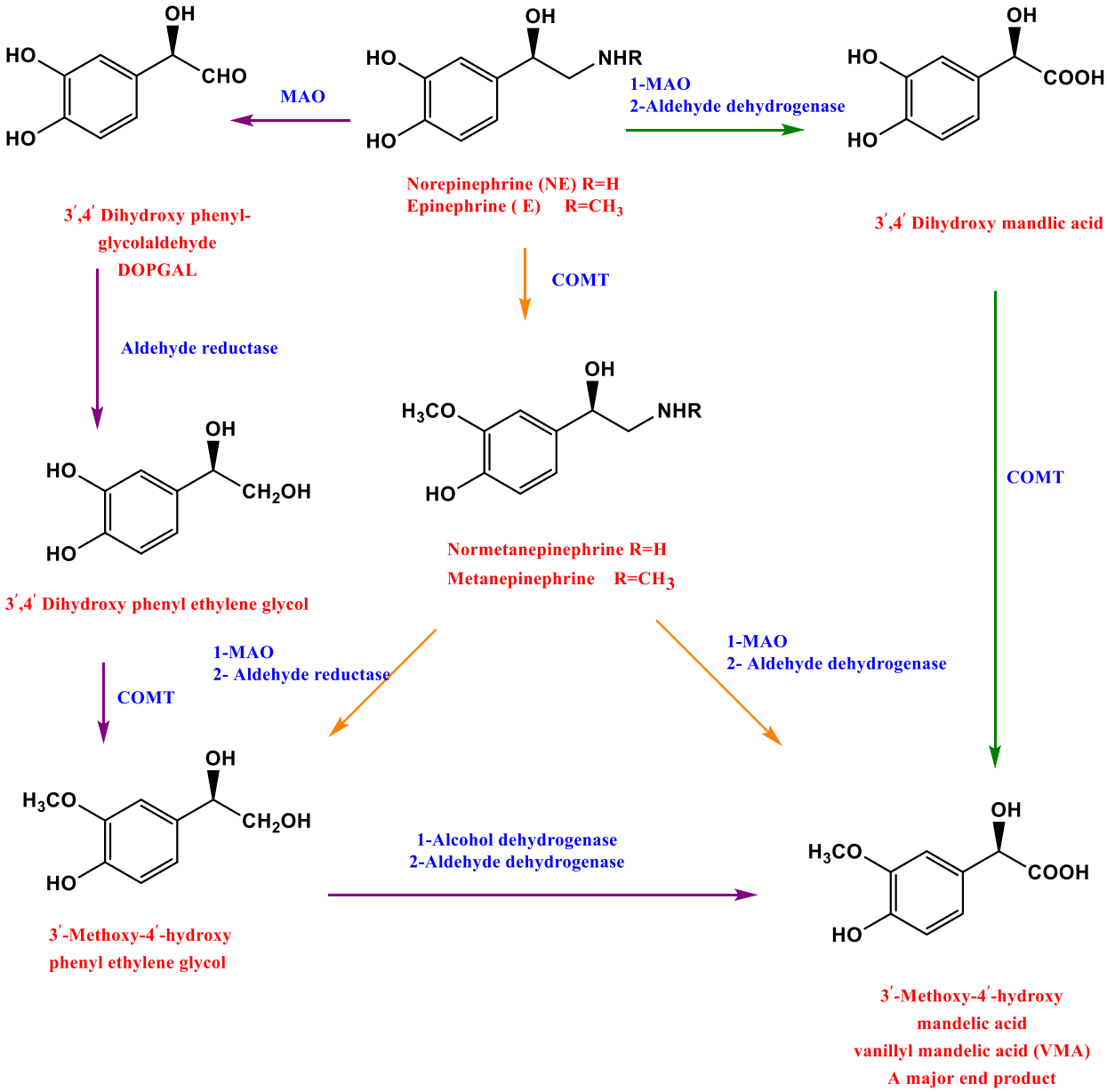
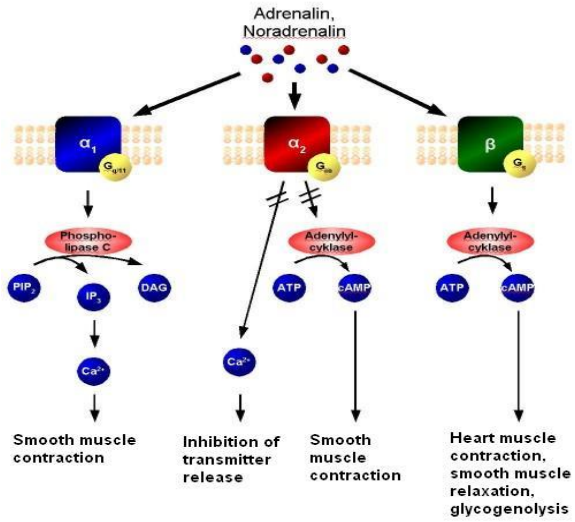


Figure: metabolism pf norepinephrine and epinephrine by MAO and COMT

Adrenergic Receptor Subtypes

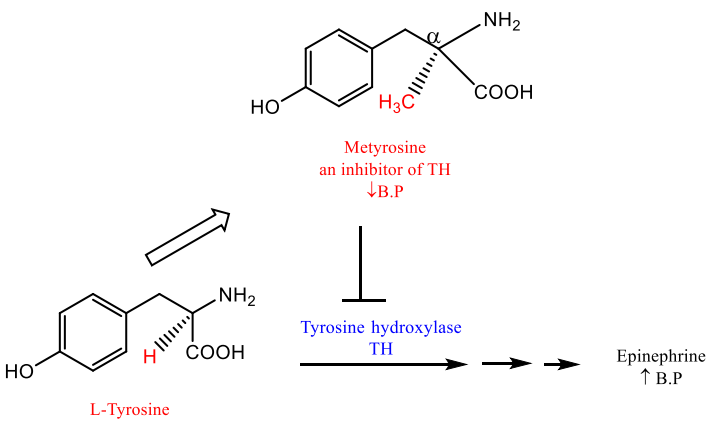


Drug affecting aderinergic neurotransmitter

1. Drugs Affecting Catecholamine Biosynthesis

Metyrosine (α-Methyl-L-tyrosine, Demser).

Metyrosine differs structurally from tyrosine only in the presence of an **α-methyl group**. It is one example of a CA-biosynthesis inhibitor in clinical use. Although metyrosine is used as a racemic mixture, it is the (-) isomer that possesses the inhibitory activity. Metyrosine reduces the frequency and severity of these episodes by significantly lowering CA production (35%–80%). The drug is polar (log P =0.73) and excreted mainly unchanged in the urine. Because of its limited solubility in water caused by intramolecular bonding of the zwitterions, crystalluria is a potential serious side effect. It can be minimized by maintaining a daily urine volume of more than 2 L. Inhibitors of CA synthesis have limited clinical utility because such agents nonspecifically inhibit the formation of all CAs and result in many side effects. Sedation is the most common side effect of this drug.



A similar example is the use of α-methyl-m-tyrosine in the treatment of shock. It differs structurally from metyrosine only in the presence of m-OH instead of p-OH in metyrosine. This unnatural amino acid is accepted by the enzymes of the biosynthetic pathway and converted to metaraminol (an α -agonist).

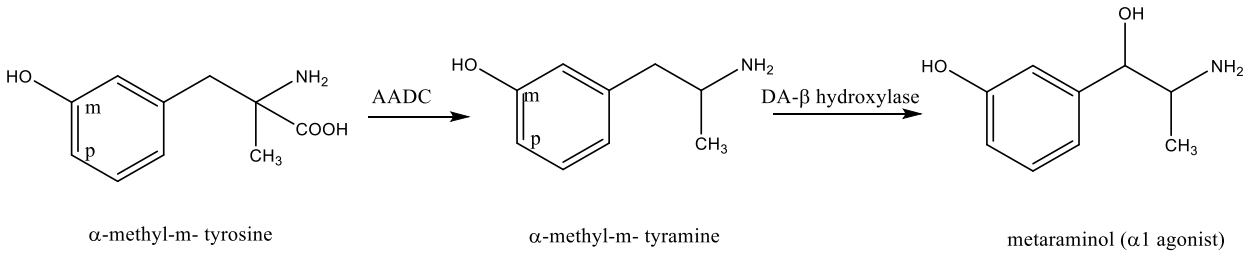


Figure: metabolic activation of α-methyl-m-tyrosine to metaraminol

Inhibitors of AADC (e.g., carbidopa) have proven to be clinically useful, but not as modulators of peripheral adrenergic transmission. Rather these agents are used to inhibit the metabolism of drug L-DOPA administered in the treatment of Parkinson disease

2. Drugs Affecting Catecholamine Storage and Release

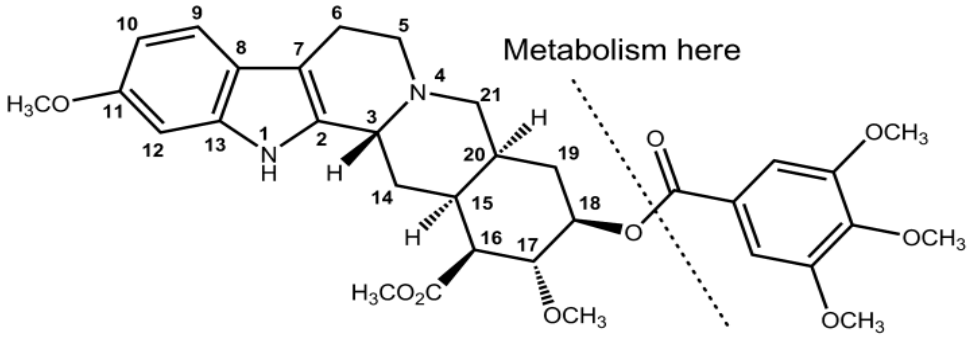
Reserpine (an NT Depleter). Reserpine, a prototypical and historically important drug, is an indole alkaloid obtained from the root of *Rauwolfia serpentina* found in India. reserpine is susceptible to decomposition by light and oxidation. Reserpine is extensively metabolized through hydrolysis of the ester function at position 18 and yields methyl reserpate and 3,4,5-trimethoxybenzoic acid. It not only depletes the vesicle storage of NE in sympathetic neurons in PNS, neurons of the CNS, and E in the adrenal medulla, but also depletes the storage of serotonin and DA in their respective neurons in the brain.

Mechanism

Reserpine binds extremely tightly with and blocks **vesicular monoamine transporter (VMAT)** that transports NE and other biogenic amines from the cytoplasm into the storage

vesicles. Thus in sympathetic neurons, NE, which normally is transported into the storage vesicles, is instead metabolized by mitochondrial MAO in the cytoplasm.

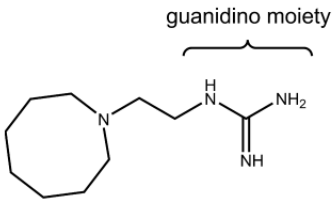
When reserpine is given orally, its maximum effect is seen after a couple of weeks. A sustained effect up to several weeks is seen after the last dose has been given



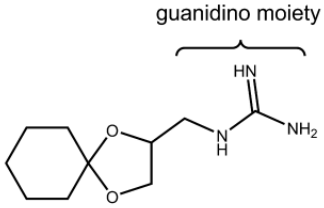
Reserpine (Log P = 4.37, Log D = 3.93)

Guanethidine (Ismelin) and guanadrel (Hylorel)

Both drugs possess a guanidino moiety [CNHC(=NH)NH_2], The presence of the more basic guanidino group (pKa >12) than the ordinary amino group in these drugs means that at physiological pH, they are essentially completely protonated. Thus, these agents do not get into the CNS. As a result, this drug has none of the central effects seen with many of the other antihypertensive agents.



Guanethidine
pKa = 13.43
No CNS activity



Guanadrel
pKa = 12.76
No CNS activity

Subject	Guanethidine	Guanadrel
Use	treat moderate-to-severe hypertension, either alone or in combination with another antihypertensive agent.	Same
Administration	Oral	Same
Mechanism	Enter the adrenergic neuron by way of the **uptake-1 process**	Same

	and accumulate within the neuronal storage vesicles. There they bind to the storage vesicles and stabilize the neuronal storage vesicle membranes, making them less responsive to nerve impulses.	
Absorption	absorbed incompletely after oral administration (3%–50%)	well absorbed, with a bioavailability of 85%
Half- life	5 days	12 hours