Conversion of amino acids to specialized products

α-nitrogen atom of amino acids is a primary source for many nitrogenous compounds:

Heme

Purines and pyrimidines

Hormones

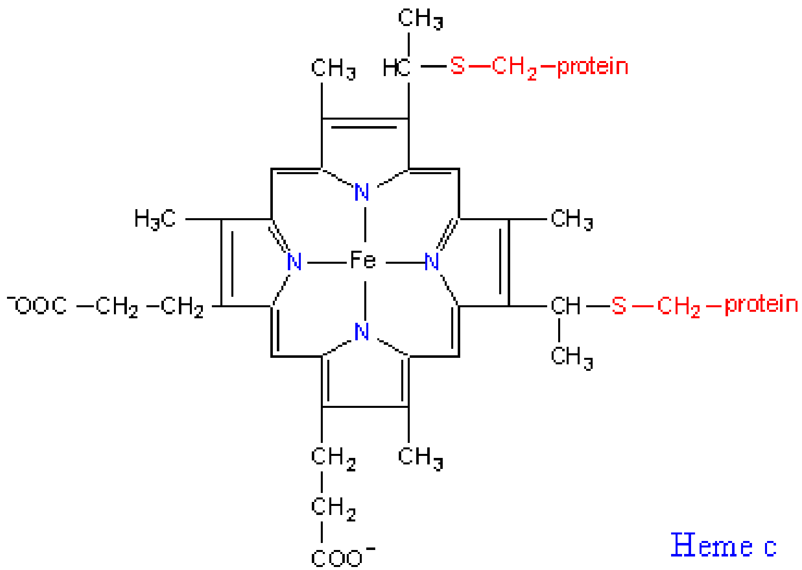
Neurotransmitters

Biologically active peptides

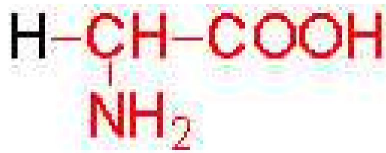
Glycine

Glycine is used for heme, purine and creatin synthesis

α-carbon and α-nitrogen atoms of glycine are used for synthesis of porphyrine, prosthetic group of heme.

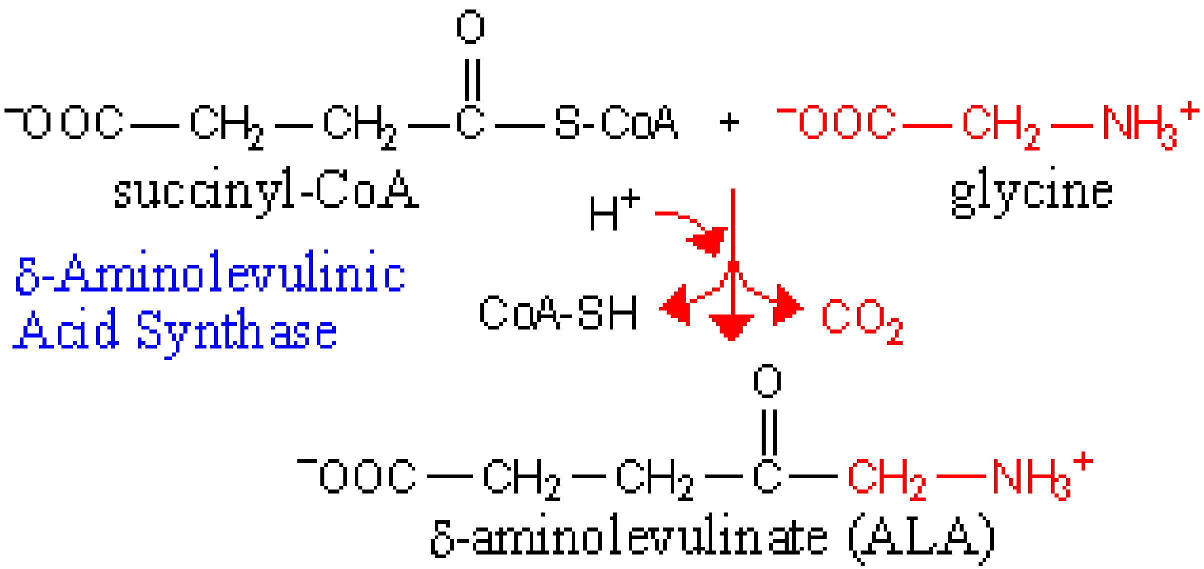


Heme c



Take over: http://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb2/part1/heme.htm

Synthesis of heme

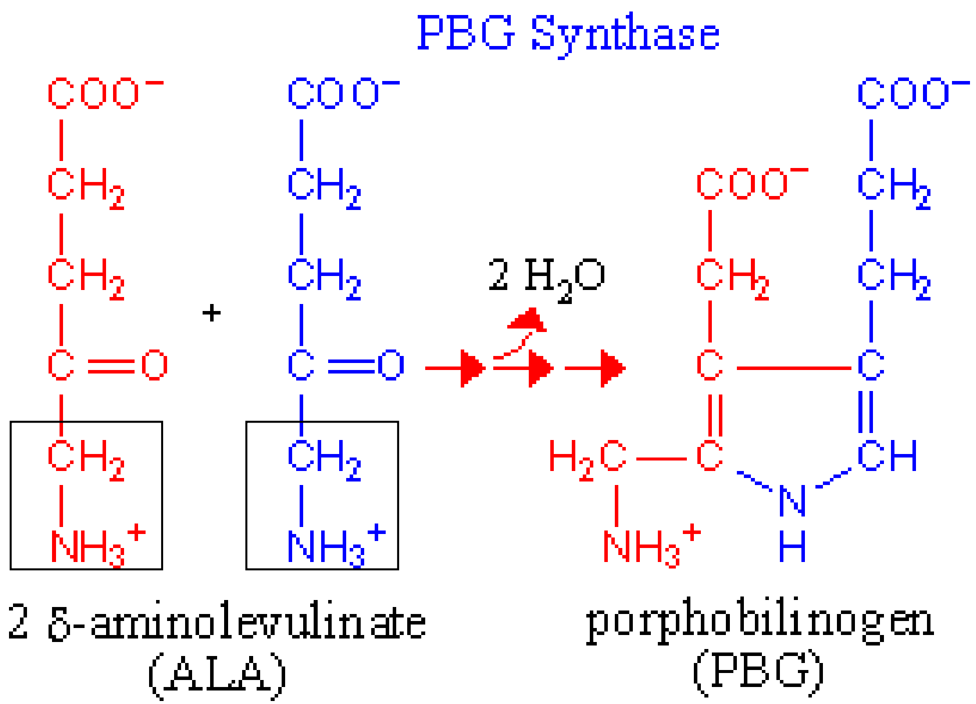


1. Condensation of 1 glycine and 1 succinylCoA by the pyridoxal phosphate-containing enzyme, ***δ-aminolevulinic acid synthase*** **(ALA synthase)** in mitochondria.

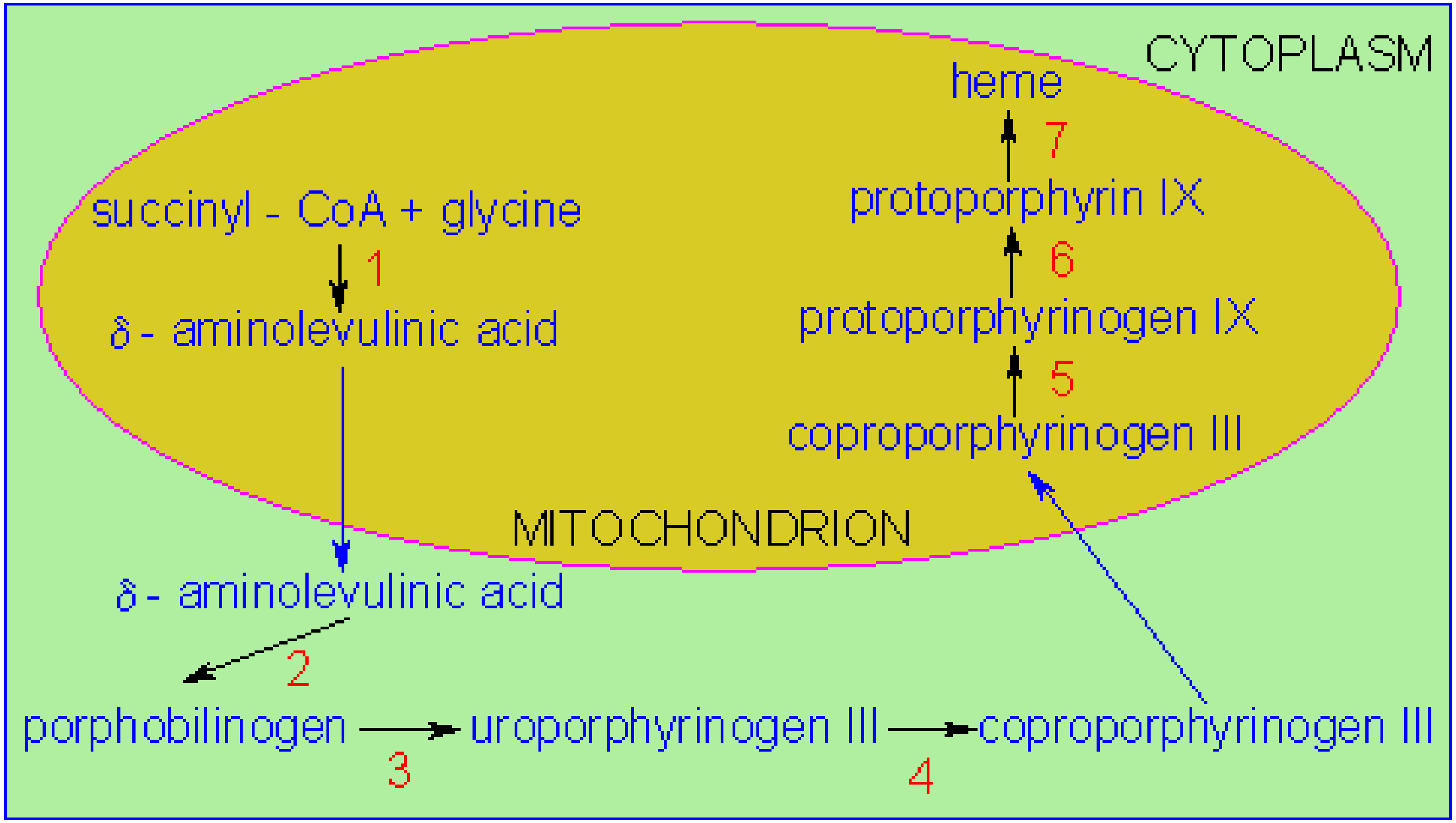
Take over: *http://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb2/part1/heme.htm*

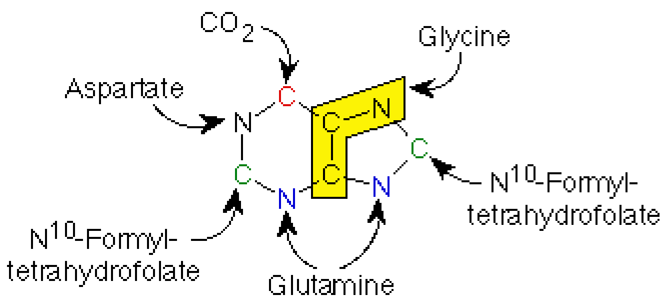
2. δ-aminolevulinic acid (ALA) ⇨ cytosol.

3. Dimerization of 2 molecules of ALA to produce the pyrrole ring - compound **porphobilinogen** – precursor for **porphyrine** synthesis (*porfobilinogen synthase* or *ALA dehydratase*)



Take over: *http://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb2/part1/heme.htm*





Origin of atoms in a purine ring

Glycine is incorporated intact as constituent of purines.

Synthesis of creatine and creatinine

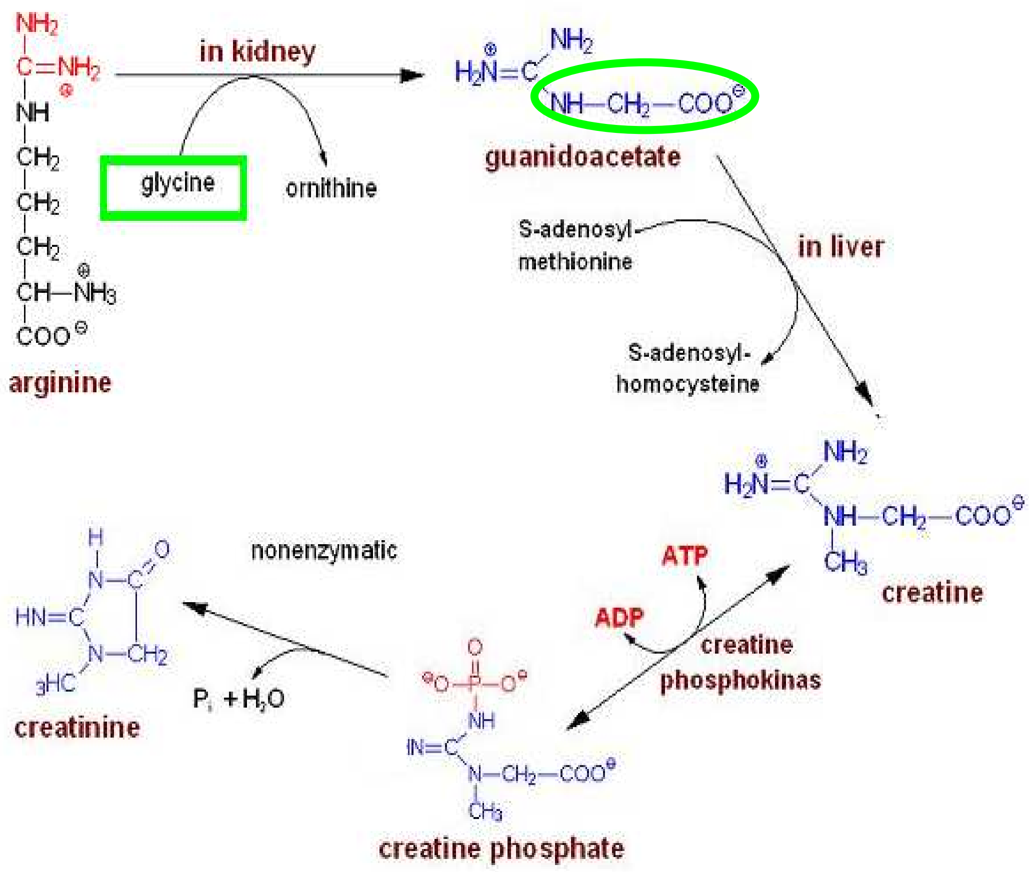
- Creatine – nitrogenous organic acid - helps to supply energy to muscle.

- Creatine ⇨ conversion to phosphocreatine - functions as energy buffer system in vertebrate muscles.

- Keeps the ATP/ADP ratio high at subcellular places where ATP is needed.

- The amount of creatinine produced is related to muscle mass.

- The level of creatinine excretion (clearance rate) is a measure of renal function.



Take over http://www.indstate.edu/thcme/mwking/aminoacidderivatives.html

Synthesis of glutathione (GSH)

The role of GSH as a reductant is extremely important - *erythrocytes*.

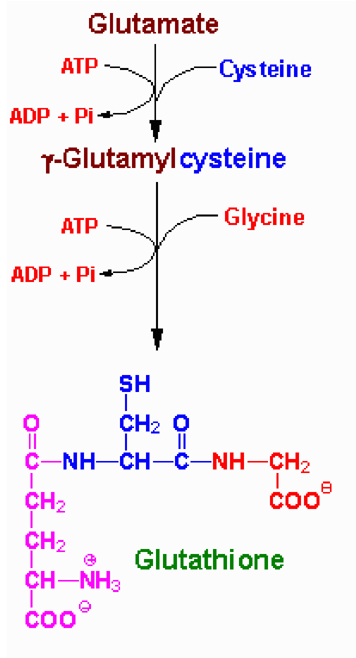
Reduction of peroxides formed during oxygen transport.

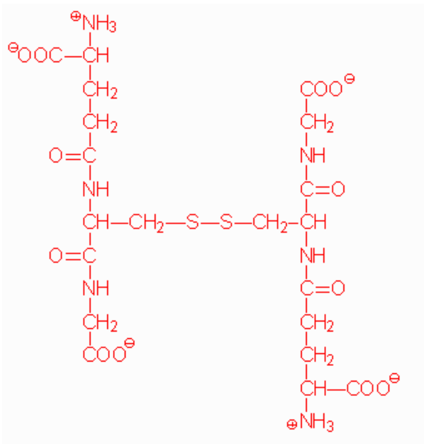
The resulting oxidized form of GSH consists of two molecules disulfide bonded together.

Endogenously produced H_2O_2 is reduced by GSH in the presence of *selenium-dependent GSH peroxidase*.

The enzyme *glutathione reductase* utilizes NADPH as a cofactor.

The role of GSH in detoxification of xenobiotics ⇨ formation of conjugates with GSH (spontaneously or enzymatically) ⇨ excretion from the cell, in the case of liver – to the bile.





Glutathione disulfide (GSSG)

Take over: *http://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/MB1index.html*

The biologically active amines formed by decarboxylation of amino acids

Catecholamines
(dopamine norepinephrine, epnephrine)

γ-aminobutyric acid (GABA)

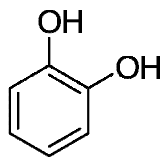
Serotonine, melatonine

Polyamines

NO

Tyrosine-Derived Neurotransmitters

- A ***catecholamine*** (**CA**) is a monoamine compound, that has a catechol (benzene with two -OH side groups) and a side-chain amine.



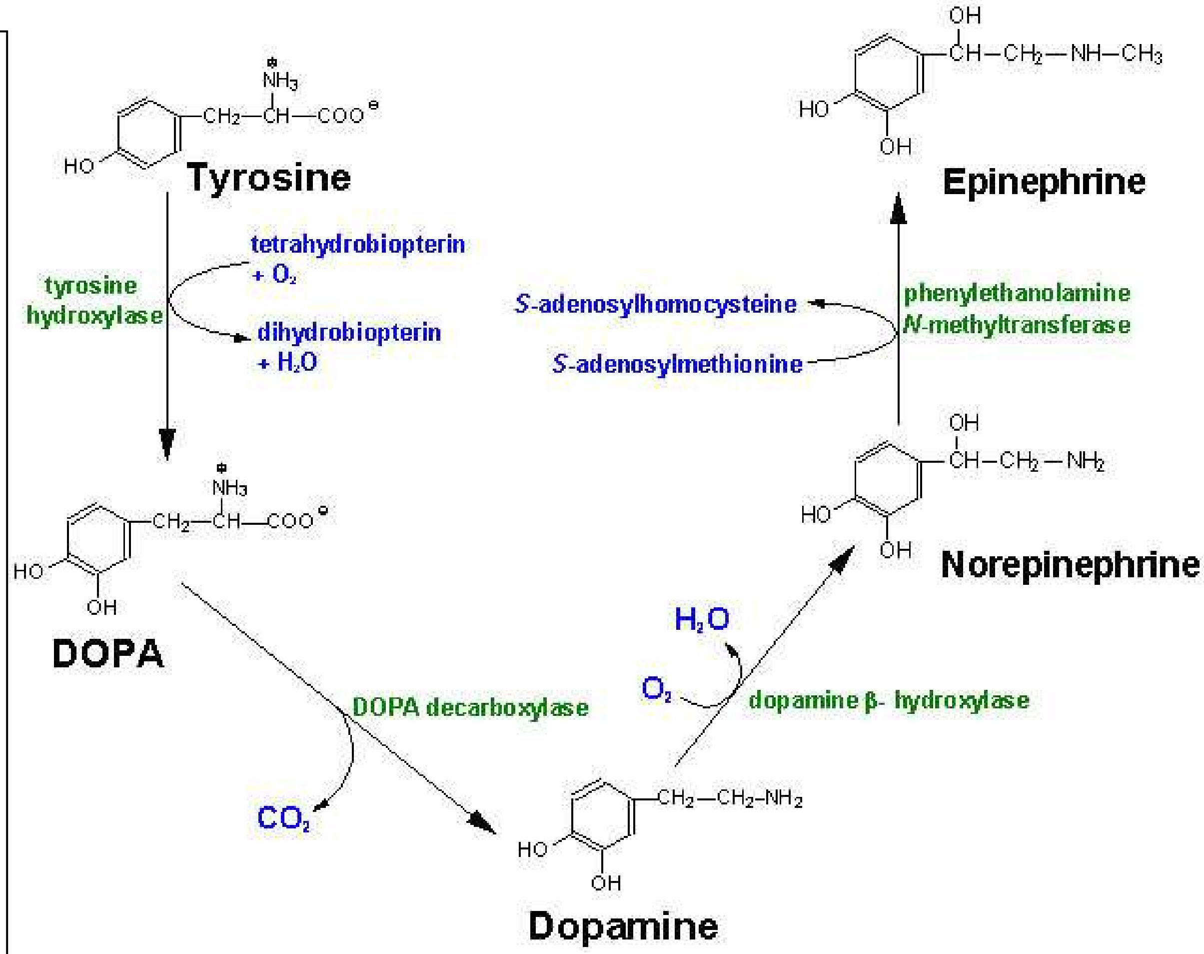
- CA are derivatives of Tyr - *dopamine*, *norepinephrine*, and *epinephrine*.
- CA are require for the body to adapt to a great variety of acute and chronic stress.
- Tyrosine is obtained from dietary proteins and transported from the blood to the brain (catecholamine-secreting neurons) and the adrenal medulla.

Tyrosine-Derived Neurotransmitters

- CA are stored in and released from synaptic vesicles knobs of neurons.
- Norepinephrine (NE) and epinephrine (E) acts via specific adrenergic receptors – $\alpha 1$, $\alpha 2$ and β coupled with G proteins, dopamine binds to dopamineric receptors.
- The action of E and NE in the liver, the adipocyte, the skeletal miscle directly influence fuel metabolism.
- E (80% - 85% of stored CA) – synthesized primarily in adrenal medula, NE (15% -20% of stored CA) – synthesized and in adrenal medula and in CNS.

Synthesis of the catecholamines from tyrosine

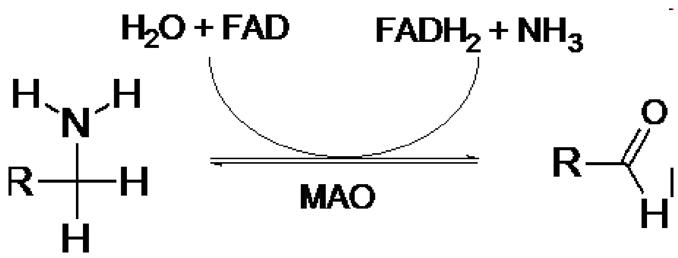
1. *Tyrosine hydroxylase* requires tetrahydrobiopterin as cofactor.
2. The hydroxylation reaction generates DOPA. (3,4-dihydrophenylalanine)
3. *DOPA decarboxylase* converts DOPA to dopamine.
4. *Dopamine β-hydroxylase* converts dopamine to *norepinephrine*.
5. *Phenylethanolamine N-methyltransferase* converts norepinephrine to epinephrine.



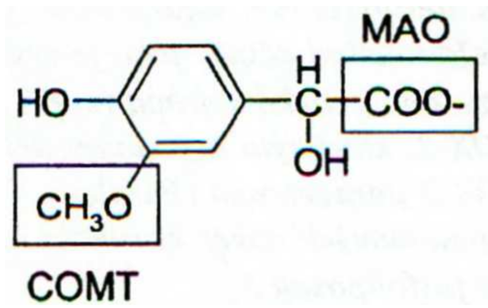
Take over: *http://themedicalbiochemistrypage.org/amino-acid-metabolism.html*

Degradation of catecholamines

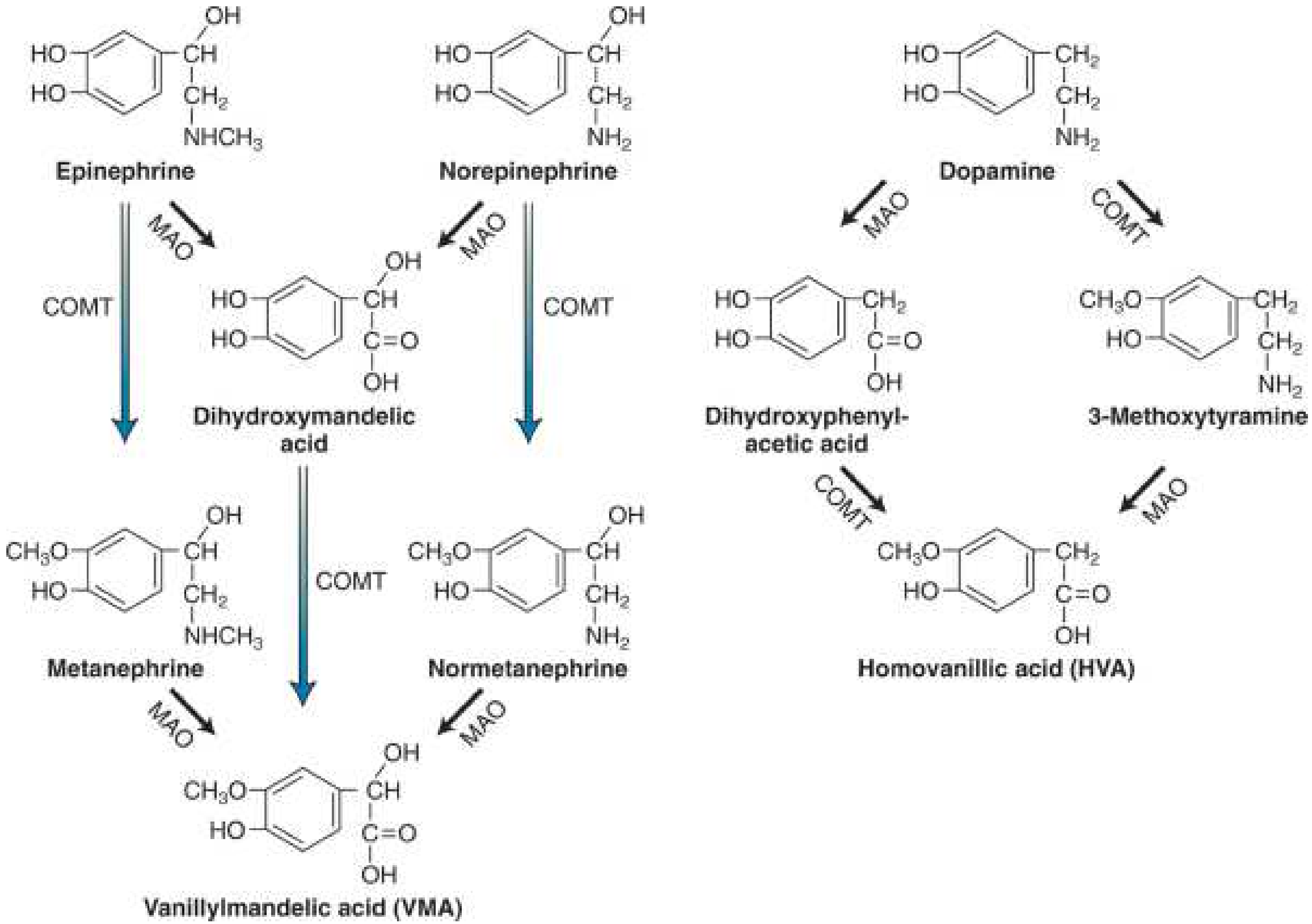
Oxidative deamination by monoamine oxidase (MAO)



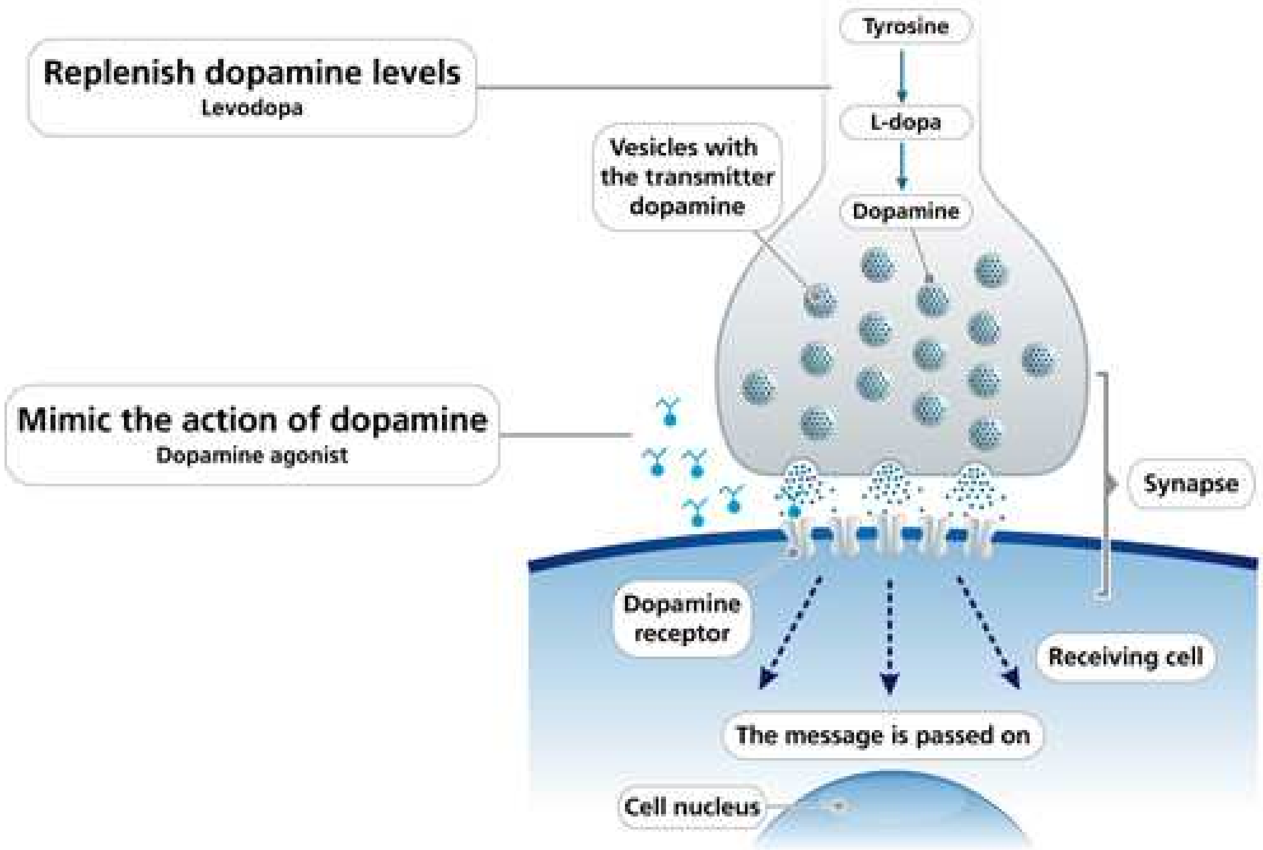
Oxidation and methylation by catecholamine-O-methyl transferase (COMT) convert the products to metanephrines and vanillmandelic acid (4-hydroxy-3-methoxymandelic acid).



Degradation of catecholamines



Treatment of Parkinson's disease



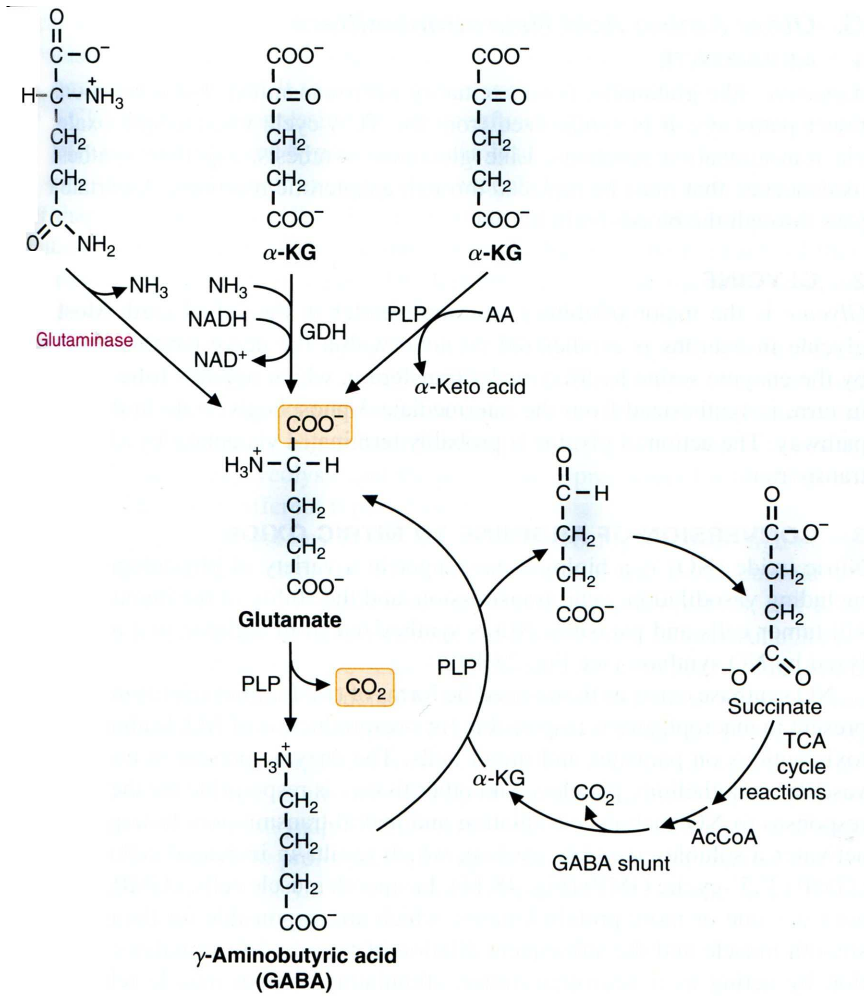
γ-amino butyric acid (GABA)

- Major inhibitory neurotrans-mitter in the CNS.

•GABAergic function plays a role in many neurological and psychiatric disorders (its lack leads to convulsions, epilepsia).

- Directly regulates muscle tone.

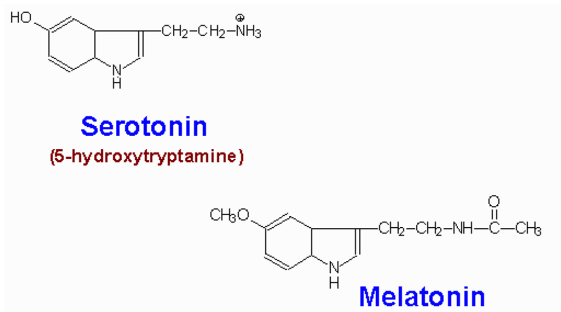
- Involved in mechanism of memory.

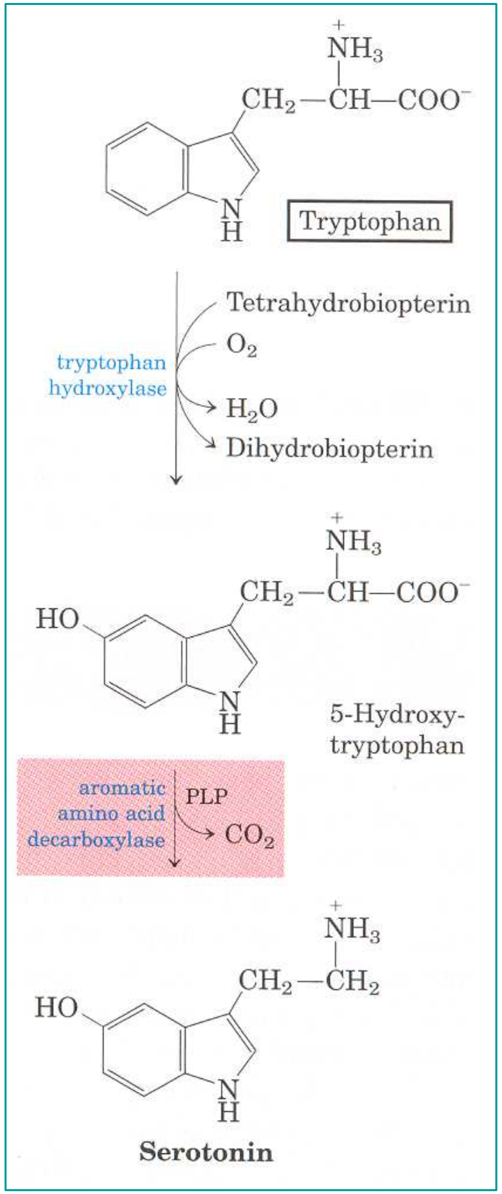


Tryptophan

Tryptopan serves as the precursor for the synthesis of *serotonin* and *melatonin*

1. Hydroxylation reaction (*tryptophan-5-monooxygenase*)
2. Decarboxylation (*aromatic L-amino acid decarboxylase)*
3. Acetylation (*serotonin N-acetylase)*
4. Conversion to melatonin *(hydroxyindole-O-methyltransferase)*.





Take of textbook: D. L. Nelson, M. M. Cox: *Lehninger Principle of Biochemistry*. Fourt Deition.

Serotonin and melatonin

- **Serotonin** - 90% of our serotonin supply is found in the digestive tract and in blood platelets. (powerfull vasoconstrictor) and in the gastrointestinal tract (mediates gut movements).
- Lesser amounts are found in the brain and the retina.
- Serotonin cannot cross the blood-brain barrier. Therefore serotonin that is used inside the brain must be produced within it.
- Imbalance in serotonin levels may influence mood in a way that leads to depression Antidepressant, **Prozac** is to inhibit this reuptake process.
- Synthesis and secretion of **melatonin** increases during the dark period of the day regulates circadian rhythms.
- Concentration maintained at a low level during daylight hours.
- Besides its function as synchronizer of the biological clock, melatonin is a powerful free-radical scavenger - direct scavenger of radical oxygen and nitrogen species including -OH, O_2-, and NO .

Histidine

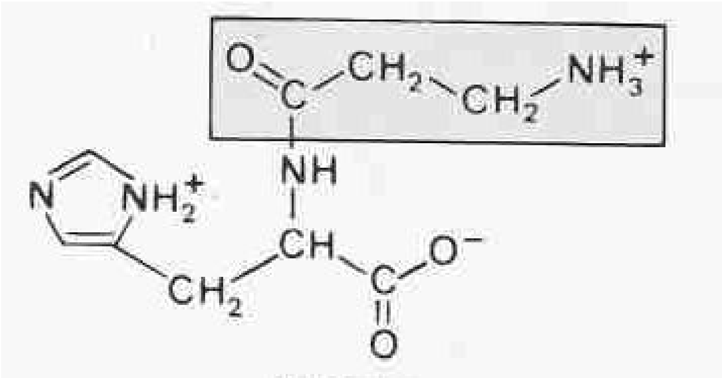
- **Carnosine** is the dipeptide of the amino acids β-alanine and histidine.
- Carnosine is highly concentrated in muscle and brain tissues.

- Scavenger of ROS (radical oxygen species).

- Protects cells against lipoperoxidation

- Membrane fatty acids during oxidative stress.

- Possibly improving Alzheimer´s disease through inhibition of growing an aggregates of β-amiloid proteins in the brain.



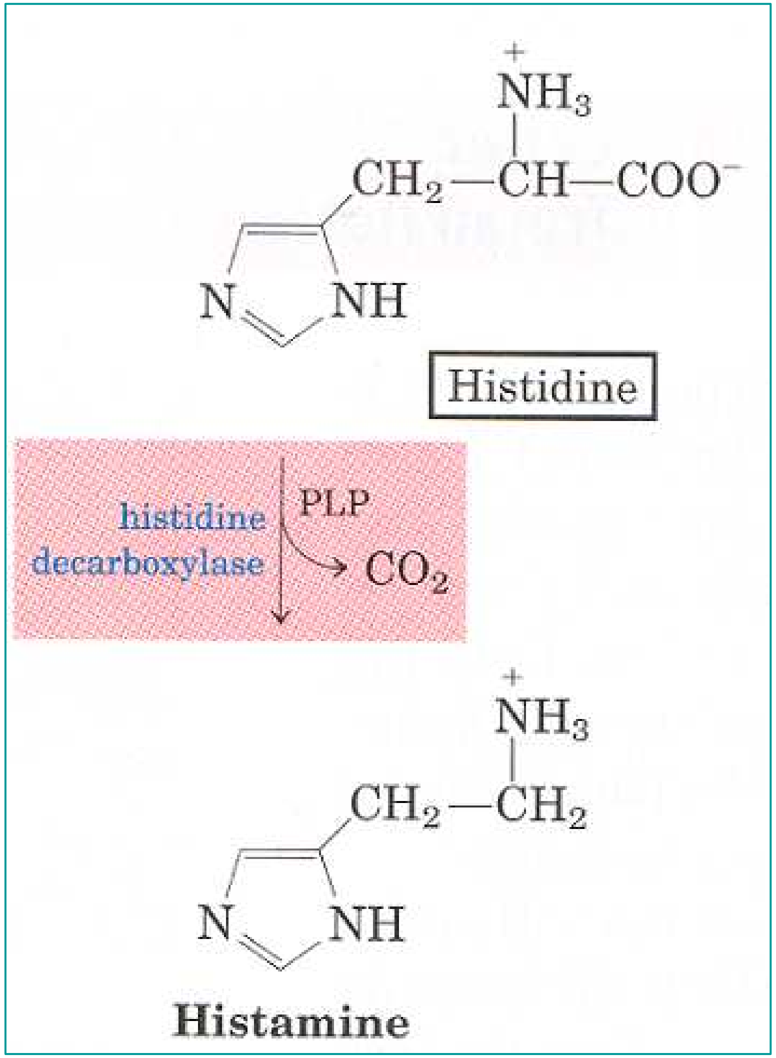
Carnosine

Histamine

- Histamine is derived from the decarboxylation of the amino acid **histidine.**
- Biogenic amine regulating physiological function in the gut and acting as a neurotransmitter - regulates physiological function in the gut and acts as a neurotransmitter Histamine triggers the inflammatory response.

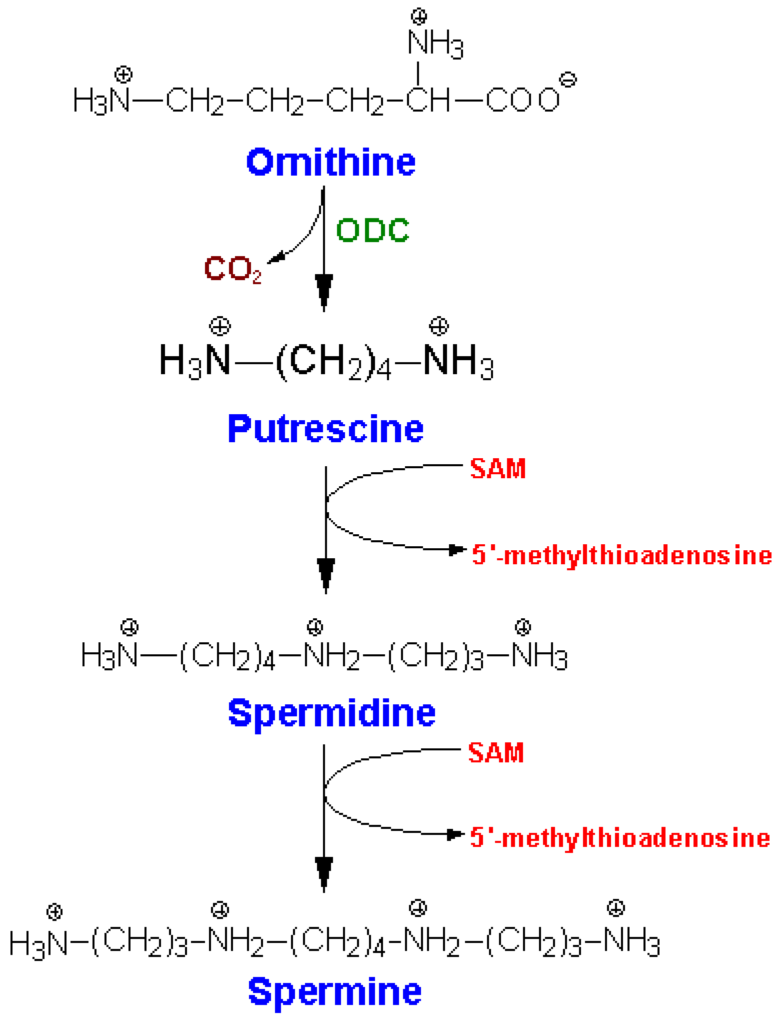
Causes several allergic symptoms.

1. It contributes to an inflammatory response.
2. It causes constriction of smooth muscle.
3. Is cause second type of allergic response (one of the major causes for asthma)



Polyamines

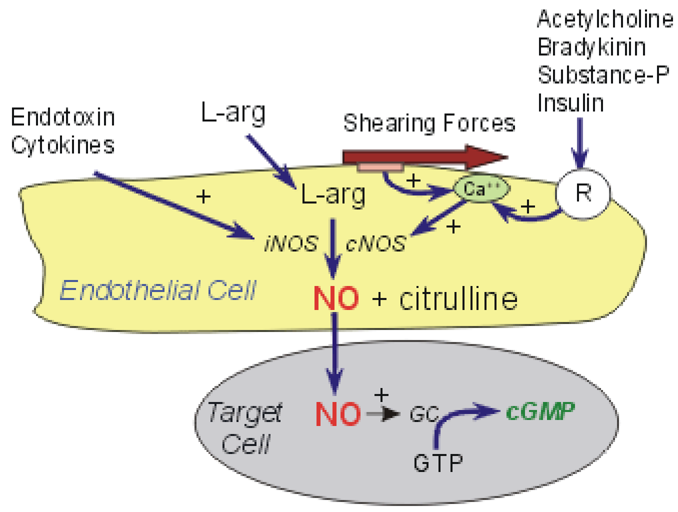
- Polyamines are highly cationic and tend to bind nucleic acids with high affinity.
- Important participants in DNA synthesis, or in the regulation of that process.
- Important modulators of a variety of ion channels (potassium channel).
- Growth factors in both eucaryotic and procaryotic cells.



Take over*: http://themedicalbiochemistrypage.org/amino-acid-metabolism.html*

Nitric Oxide NO

- Nitric oxide (NO) is produced by vascular endothelium and smooth muscle, cardiac muscle, and many other cell types.
- The substrate for NO is L-arginine that is transported into the cell.



•Nitric oxide serves many important functions:

•Vasodilation (ligand mediated and flow dependent)

•Inhibition of vasoconstrictor influences (e.g., inhibits angiotensin II and sympathetic vasoconstriction)

•Inhibition of platelet adhesion to the vascular endothelium (anti-thrombotic)

•Inhibition of leukocyte adhesion to vascular endothelium (anti-inflammatory)

•Antiproliferative action (e.g., inhibits smooth muscle hyperplasia following vascular injury)

•Scavenging superoxide anion (anti-inflammatory)