Conversion of Amino Acids to Specialized Products

Certain proteins contain amino acids that have been posttranslationally modified to permit them to perform specific functions. One example is the hydroxylation of lysine to 5- hydroxylysine, whose subsequent modification and cross-linking stabilizes maturing collagen fibers.

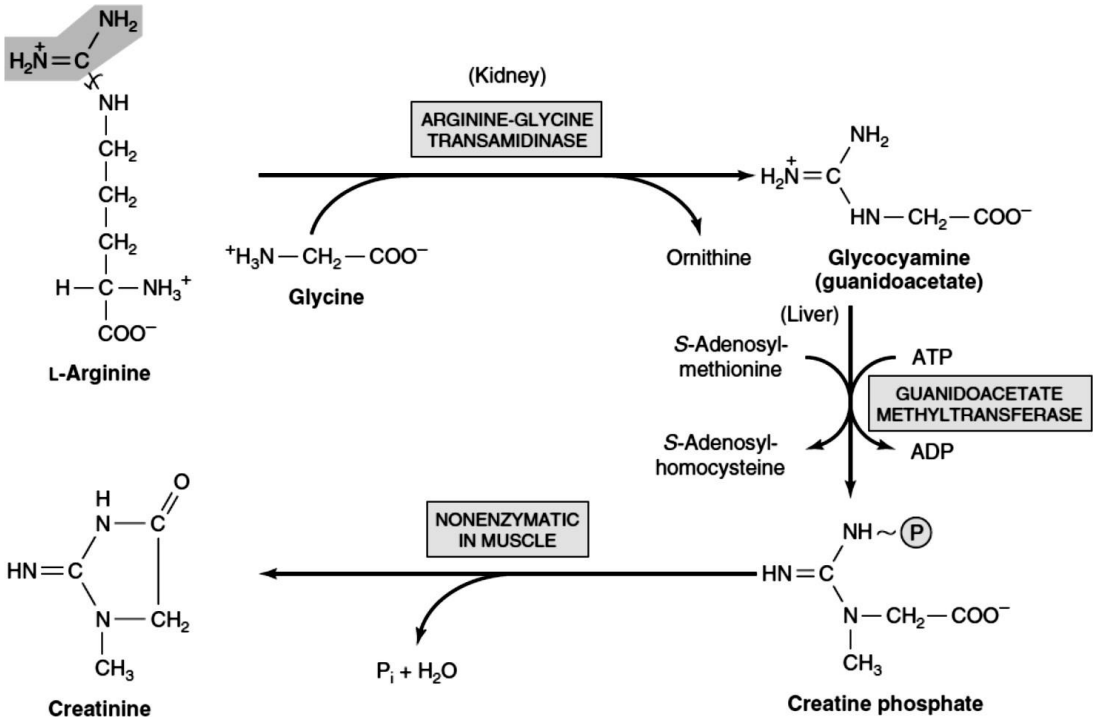
In addition to serving as the **building blocks** for protein synthesis, amino acids serve as **precursors** of diverse biologic materials such as heme, purines, pyrimidines, hormones, neurotransmitters, and biologically active peptides. Histamine plays a central role in many allergic reactions. Neurotransmitters derived from amino acids include γ-aminobutyrate, 5-hydroxytryptamine (serotonin), dopamine, norepinephrine, and epinephrine. Many drugs used to treat neurologic and psychiatric conditions act by altering the metabolism of these neurotransmitters.

Some important biological molecules derived from amino acids

Creatine and Creatinine:

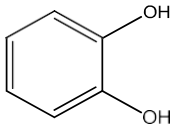
Glycine, **arginine**, and **methionine** all participate in creatine biosynthesis. The first step occurs in kidney which involve transfer of amidine group from arginine to glycine to form quanidinoacetic acid; this step is catalyzed by **arginine-glycine transamidinase**. The second step occur in the liver, which involve the transfer of a methyl group from S-adenosylmethionine to form creatine phosphate (or phosphocreatine); catalyzed by **guanidinoacetate methyltransferase**. Creatine is stored in the muscle in the form of creatine phosphate, which acts as energy store.

Creatinine is formed in muscle from creatine phosphate by **irreversible, nonenzymatic dehydration**, and loss of phosphate (used for muscle contraction). The amount of creatinine produced is constant from day to day and depend on muscle mass. Creatinine is excreted in urine.



Catecholamines:

The name catechol refers to the **dihydroxylated phenyl ring**. The amine derivatives of catechol are called catecholamines.



Catechol

Tyrosine is the precursor for the synthesis of catecholamines, namely **dopamine**, **norepinephrine** (noradrenaline) and **epinephrine** (adrenaline).

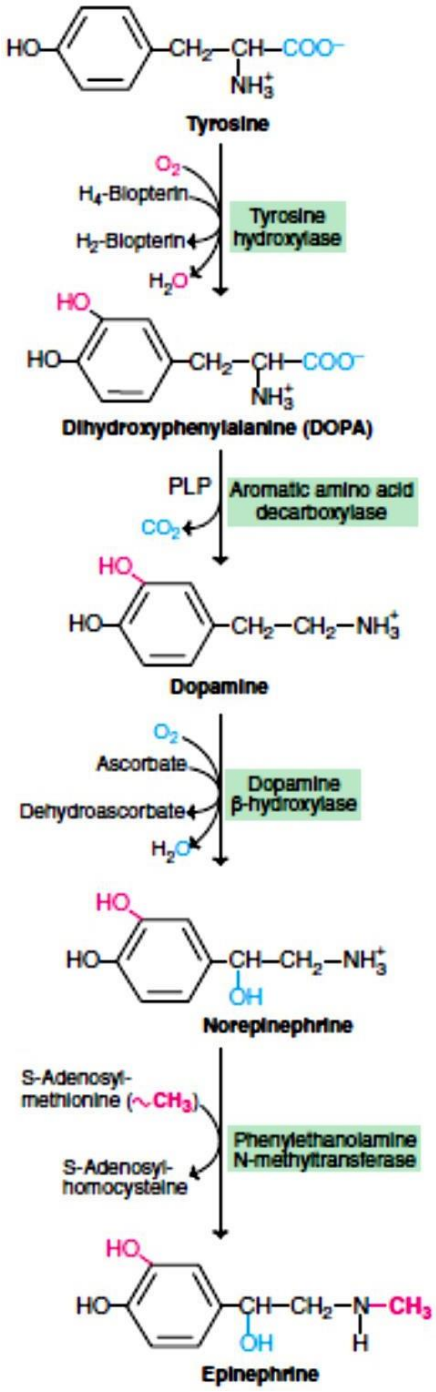
The conversion of tyrosine to catecholamines occurs in adrenal medulla and central nervous system involving the following reactions:

Tyrosine is hydroxylated to 3,4-dihydroxyphenylalanine (DOPA) by **tyrosine hydroxylase**. This enzyme catalyses the **rate limiting** reaction and requires tetrahydrobiopterin as coenzyme.

DOPA undergoes PLP-dependent decarboxylation, catalyzed by **aromatic amino acid decarboxylase (DOPA decarboxylase)**, to give dopamine. In turn, dopamine is hydroxylated by **dopamine β-hydroxylase (dopamine β-oxidase)** to produce norepinephrine, this reaction requires O_2 , vitamin C and Cu^{2+}. Methylation of norepinephrine by S- adenosylmethionine, catalyzed by **phenylethanolamine N-methytransferase** gives epinephrine.

Norepinephrine and epinephrine regulate carbohydrate and lipid metabolisms. They stimulate the degradation of triacylglycerol and glycogen. They cause an increase in the blood pressure. Dopamine and norepinephrine serve as neurotransmitters in the brain and autonomous nervous system.

Tyrosine forms norepinephrine and epinephrine. The thyroid hormones triiodothyronine (T_3) and thyroxine (T_4) are formed following iodination of tyrosine.



NOTE:

In contrast to tyrosine hydroxylase, **tyrosinase** present in **melanocytes** converts tyrosine to DOPA. ***Hence, two different enzyme systems exist to convert tyrosine to DOPA.***

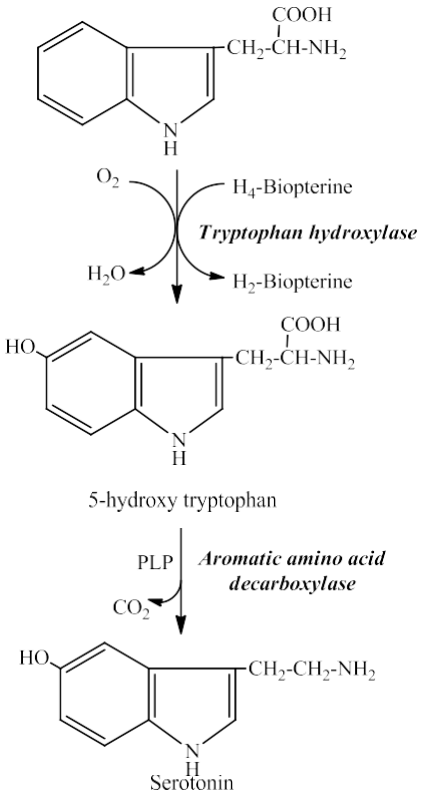
In melanocytes, **tyrosinase** hydroxylates tyrosine to form DOPA. DOPA in turn is oxidized to dopaquinone, followed by couple of spontaneous reactions occur, forming leucodopachrome then 5,6-dihydroxyindole. Oxidation of 5,6-dihydroxyindole yeilds indole 5,6-quinone.

Melanochromes are formed from indole quinone, which on **polymerization** are converted to **black melanin**.

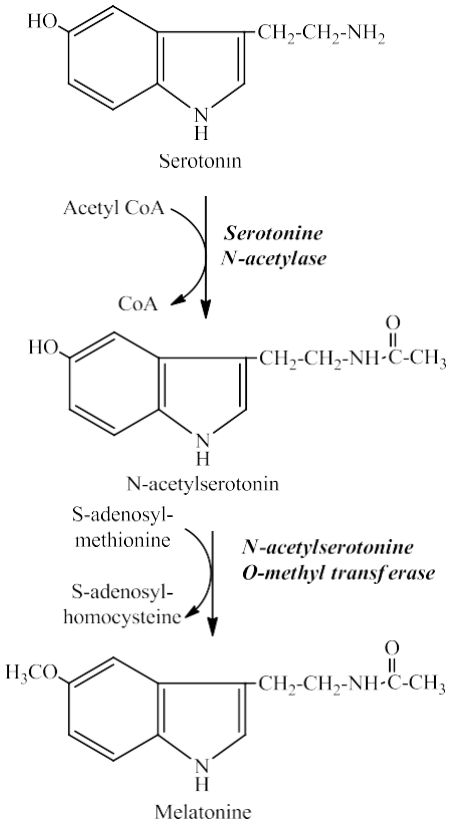
Deficiency of tyrosinase results in **albinism**.

Serotonin and Melatonin:

Serotonin or **5-hydroxytryptamine** (5HT) is a neurotransmitter, synthesized from **tryptophan**. Tryptophan is first hydroxylated at 5th carbon by **tryptophan hydroxylase**. This enzyme requires tetrahydrobiopterin as a coenzyme. 5-Hydroxytryptophan is decarboxylated by **aromatic amino acid decarboxylase** (PLP dependent) to give serotonin.



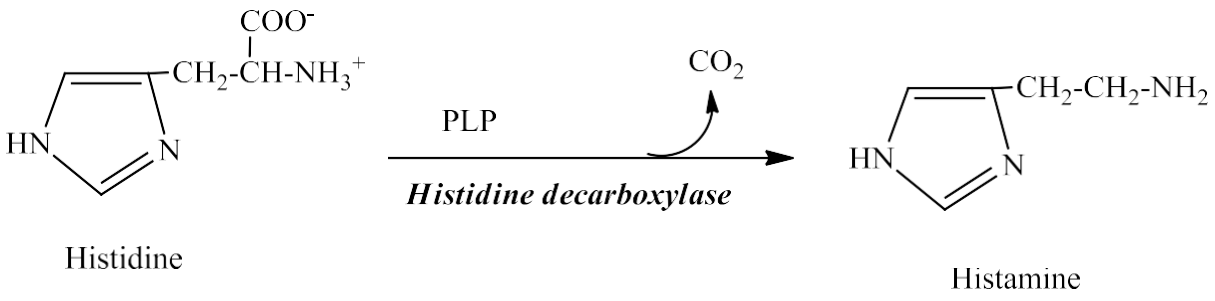
Melatonin or **N-acetyl 5-methoxyserotonin** is a hormone, mostly synthesized by the **pineal gland.** Serotonin (produced from tryptophan) is acted upon by **serotonin N-acetylase** (the rate limiting enzyme), to give N-acetylserotonin. The latter undergoes O-methylation, **S-adenosylmethionine** being the **methyl group donor** to produce N-acetyl, 5-methoxyserotonin (melatonin). The synthesis and secretion of melatonin from pineal gland is controlled by light.



Histamine:

A biogenic amine that functions in allergic reactions and gastric acid secretion, histamine is present in all tissues.

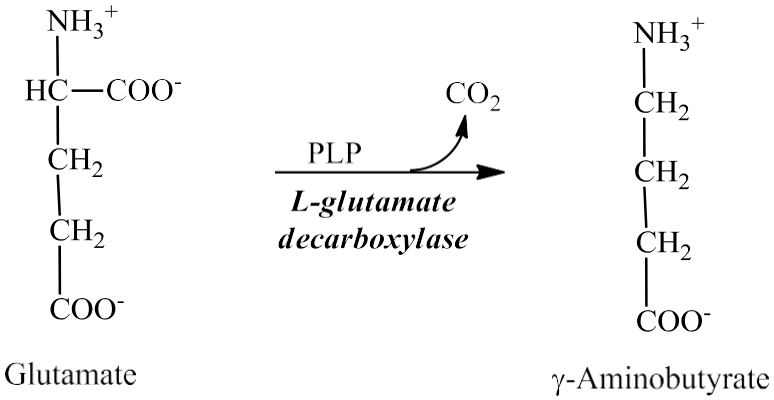
Histamine is formed by **decarboxylation of histidine**; the reaction is catalyzed by the pyridoxal phosphate-dependent enzyme **histidine decarboxylase**.



Histidine compounds present in the human body include **carnosine**, and dietarily derived **ergothioneine** and **anserine**. While their precise physiological functions are unknown, **carnosine (β-alanyl-histidine)** and **homocarnosine (γ-aminobutyrylhistidine)** are major constituents of excitable tissues, brain, and skeletal muscle. Urinary levels of 3-methylhistidine are unusually low in patients with Wilson disease.

γ-aminobutyric acid (GABA):

γ-aminobutyrate (GABA) functions in brain tissue as an **inhibitory** neurotransmitter. GABA isformed by **decarboxylation** of glutamate by **L-glutamate decarboxylase** (PLP dependent).



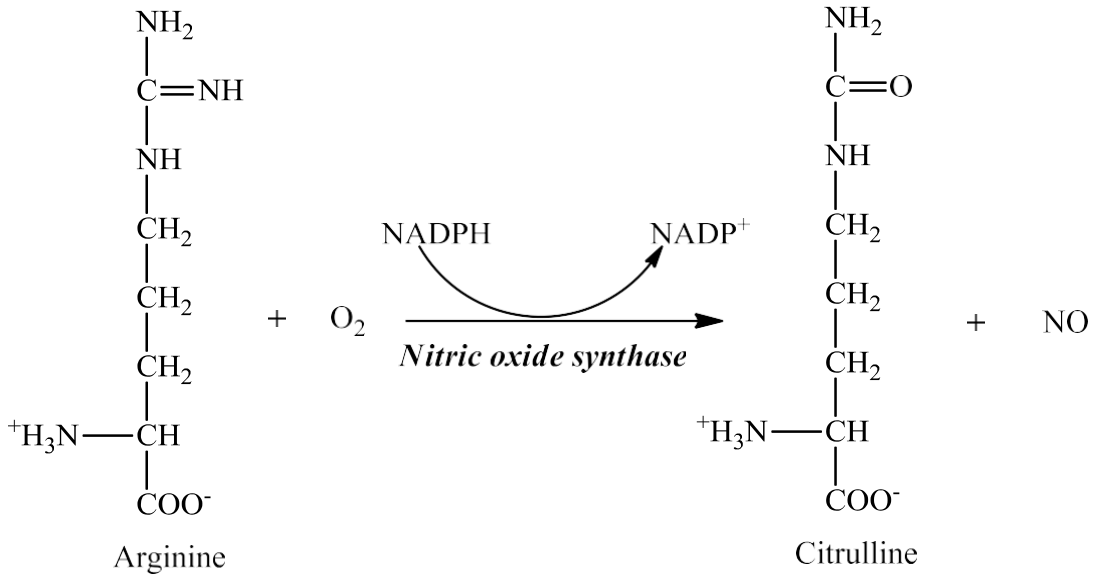
Glutamate γ-Aminobutyrate

A rare genetic disorder of GABA metabolism involves a defective **GABA aminotransferase**, an enzyme that participates in the catabolism of GABA subsequent to its postsynaptic release in brain tissue. Defects in **succinic semialdehyde dehydrogenase**, are responsible for 4-hydroxybutyric aciduria a rare metabolic disorder of γ-aminobutyrate catabolism characterized by the presence of 4-hydroxybutyrate in urine, plasma and cerebrospinal fluid. No present treatment is available for the accompanying mild to severe neurologic symptoms.

Nitric oxide (NO):

In addition to serving as a carrier of nitrogen atoms in urea and creatine biosynthesis, arginine is also the source of nitric oxide (NO). NO is an intercellular signaling molecule that participates in neurotransmission, smooth muscle relaxation, vasodilation, and prevention of platelet aggregation.

The biosynthetic reaction of NO is catalyzed by **NO synthase** (NOS), which converts one nitrogen of the guanidine group of arginine to NO.

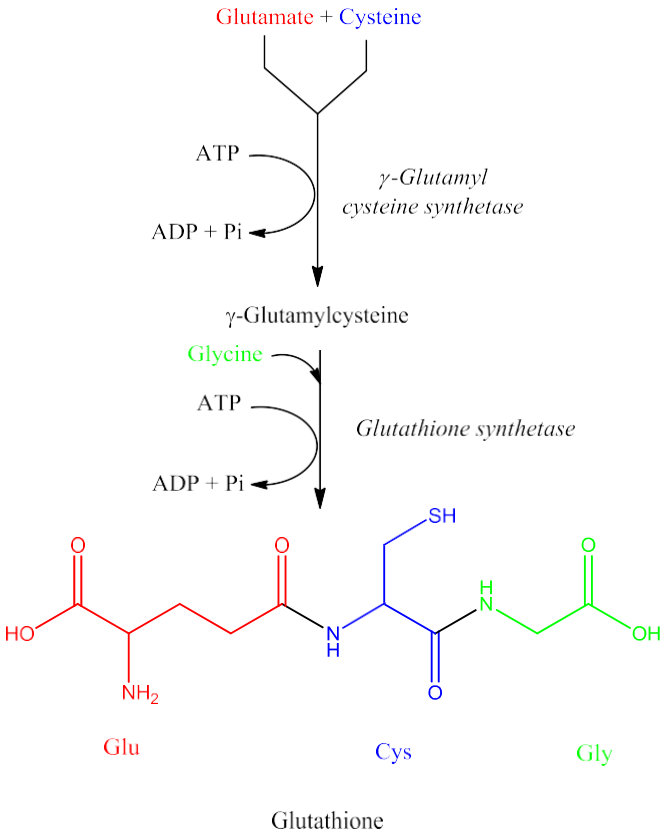


Arginine Citrulline

Glutathione (GSH):

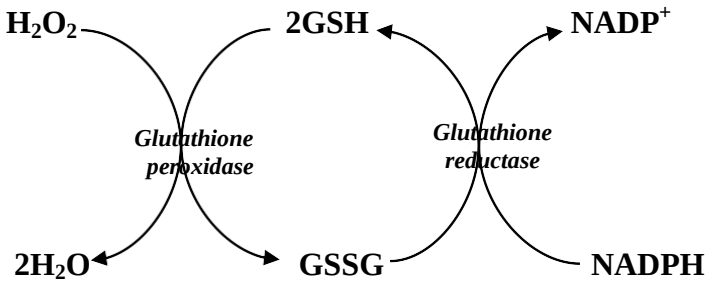
Glutathione is γ-Glutamylcysteinylglycine. γ-glutamate is attached via the γ-carbon instead ofthe α-carbon. The active part is the -SH group of cysteine (sulfhydryl group).

Biosynthetic reactions of GSH are catalyzed by **γ-glutamyl cysteine synthetase** and **GSH synthetase**.



Glutathione

GSH in the reduced form has free -SH group. Two molecules can be bridged by a disulfide bond; which produces the oxidized form (GS-SG). Conversion reactions between the reduced and the oxidized forms are catalyzed by **glutathione peroxidase** and **glutathione reductase.**
By this mechanism GSH peroxidase and GSH reductase **scavenge peroxide free radicals.**



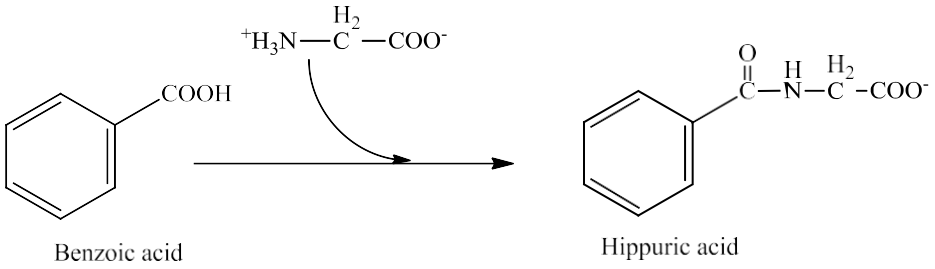
Other functions of GSH include; **conjugation** of lipophilic drugs which converts them to hydrophilic molecules for excretion, and **transport of amino acids** especially in the renal epithelium.

NOTE:

In addition to the role of glutathione in conjugation reactions, glycine also performs two important functions in this regard:

(a) The bile acids, cholic acid and chenodeoxycholic acid are conjugated with glycine, forming glycocholic acid and glycochenodeoxycholic acid respectively

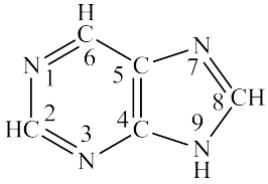
(b) Glycine is important for **detoxification** of benzoic acid (commonly used as a food preservative) to hippuric acid.



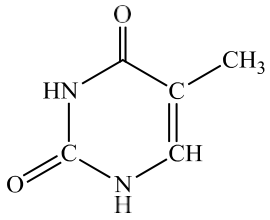
Benzoic acid Hippuric acid

Formation of purine and pyrimidine rings:

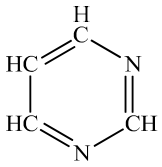
Glycine and serine are involved in purine and pyrimidine rings biosynthesis. The entire molecule of **glycine is utilized for the formation of carbons 4 and 5 and nitrogen at position 7 of purines**. **Serine provides carbons 2 and 8 of purines and the methyl group of thymine**.



Purine rings



Thymine



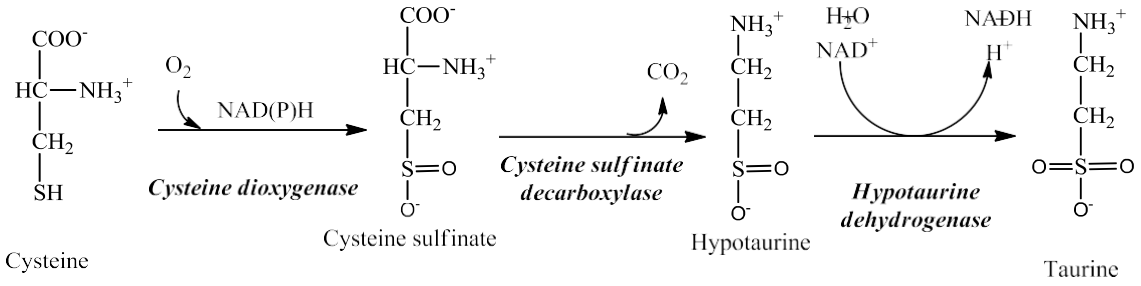
Pyrimidine ring

Heme:

The nitrogen and α-carbon of **glycine** are incorporated into the pyrrole rings and the methylene bridge carbons of heme.

Taurine:

Three enzyme catalyze reactions that convert cysteine to taurine, which can displace the coenzyme A moiety of cholyl-CoA to form the bile acid taurocholic acid. The conversion of cysteine to taurine is initiated by its *oxidation* to cysteine sulfinate, catalyzed by the enzyme **cysteine dioxygenase**. *Decarboxylation* of cysteine sulfinate by **cysteine sulfinate decarboxylase**, forms hypotaurine, whose *oxidation* by **hypotaurine dehydrogenase** forms taurine.



Spermine and spermidine:

These polyamines function in cell proliferation and growth.

Decarboxylated ornithine (by **ornithine decarboxylase**) which is called *putrescine*, react with three carbons and the α-amino group of decarboxylated SAM (formed by **SAM decarboxylase**) to form spermidine. This reaction is catalyzed by **spermidine synthase.**
Another molecule of decarboxylated SAM react with spermidine to form spermine, this reaction is catalyzed by **spermine synthase**.