

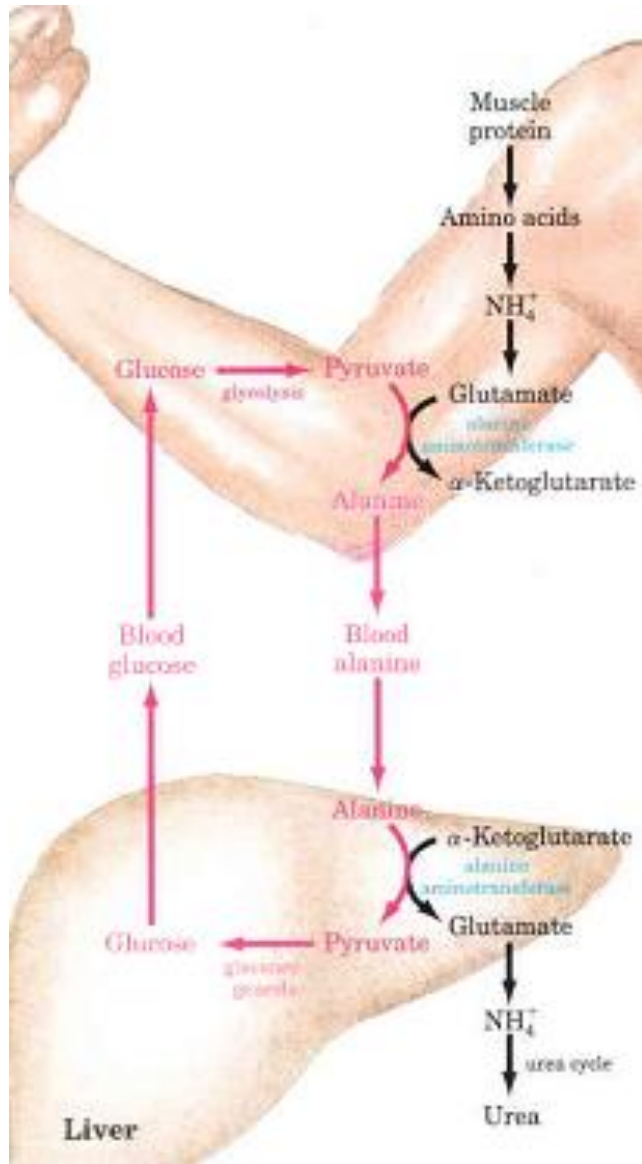
BIOCHEMISTRY: AMINO ACID METABOLISM

Lecture 2

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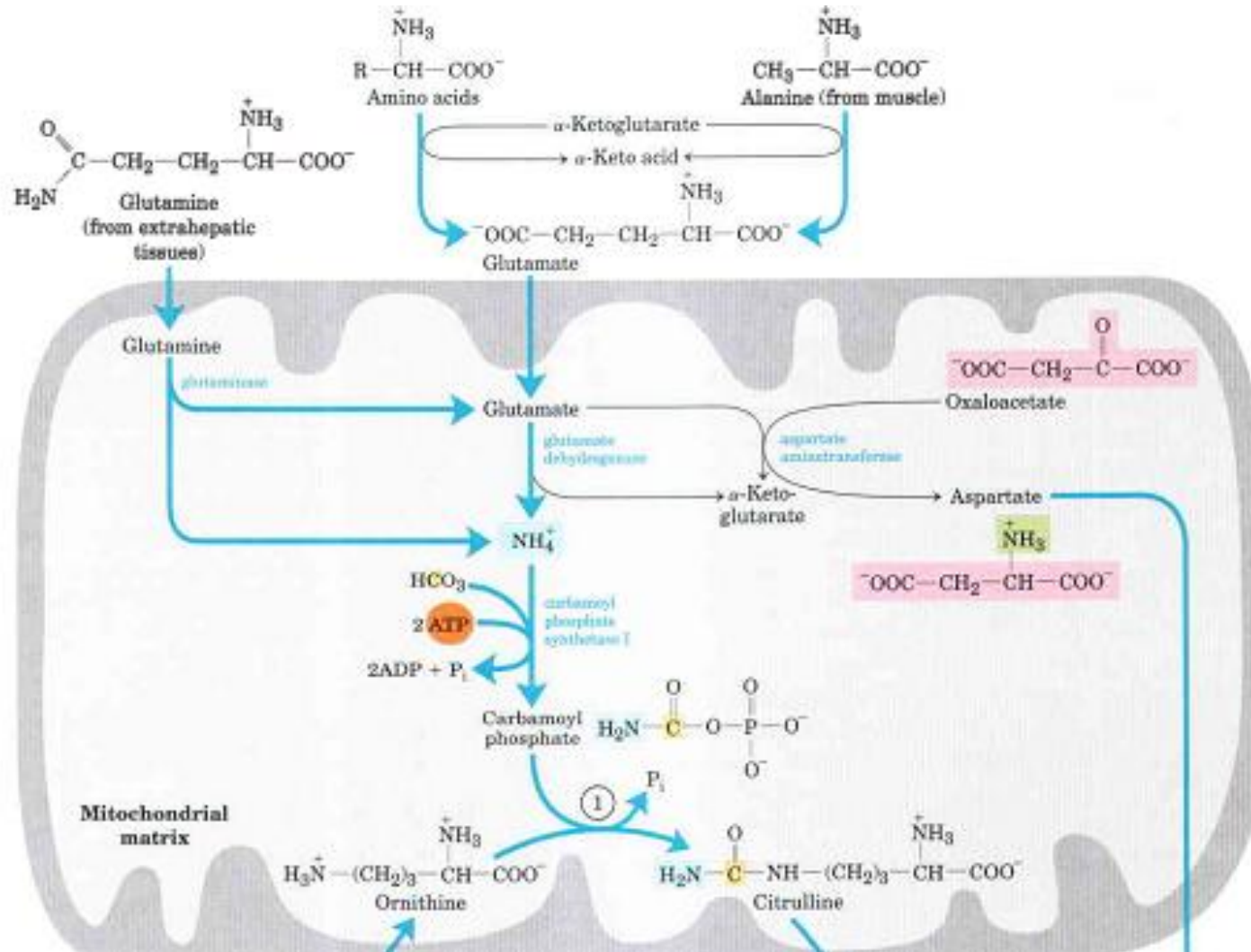
Transport and excretion of ammonium ions

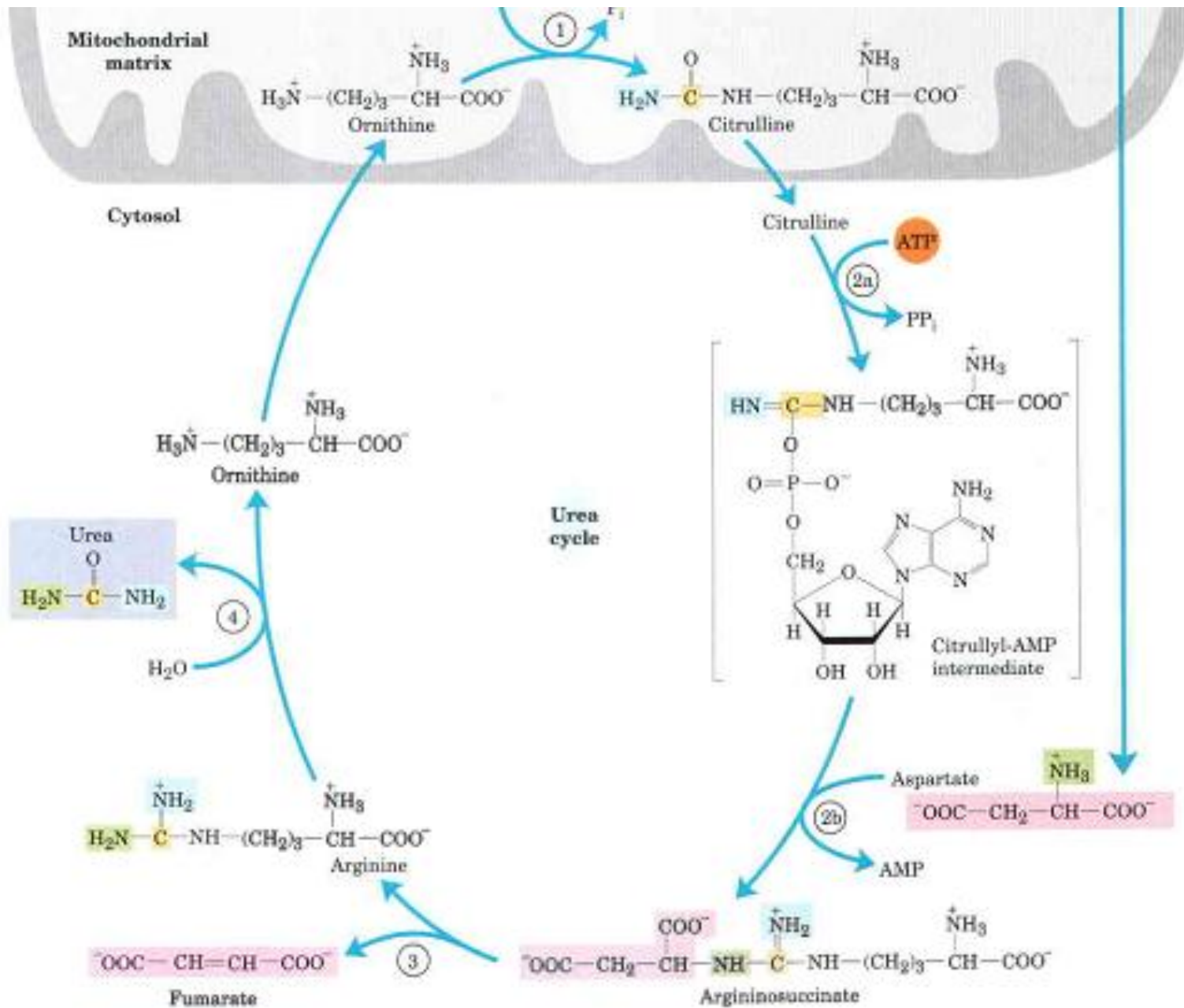
Glucose-alanine cycle



- Alanine plays a special role in transporting amino groups to the liver in a nontoxic form, via a pathway called the glucose-alanine cycle
- Alanine serves as a carrier of ammonia and of the carbon skeleton of pyruvate from skeletal muscle to liver.
- The ammonia is excreted and the pyruvate is used to produce glucose, which is returned to the muscle

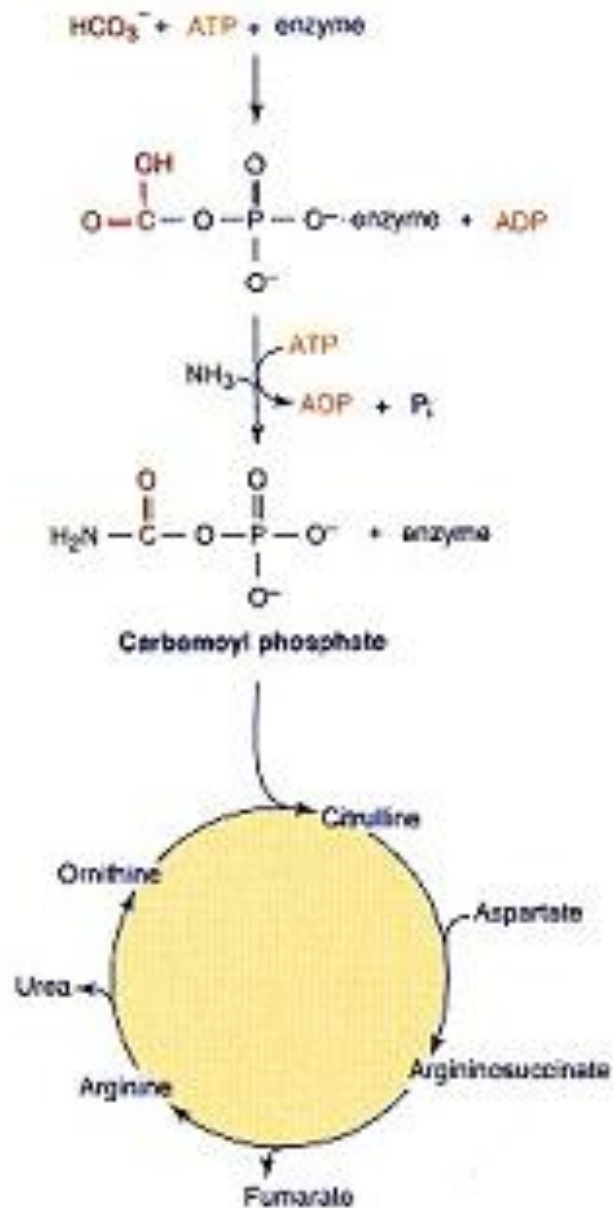
Urea cycle





- In humans and some other terrestrial animals toxic ammonium ions are excreted as urea. The two nitrogens of urea are derived from free ammonia and the amino group of aspartate.
- Ammonia (first nitrogen of urea) enters the cycle after condensation with bicarbonate (HCO_3^-) at the expense of two(2) ATPs to form carbamoyl phosphate which reacts with ornithine to form citrulline.
- The reaction of carbamoyl phosphate formation is catalyzed by carbamoyl phosphate synthetase I which occurs in the mitochondrial matrix. Another enzyme with similar activity is cytosolic and is used in pyrimidine synthesis.

Synthesis of carbamoyl phosphate and entry in urea cycle



Differences between Carbamoyl phosphate synthetase I and II

Carbamoyl Phosphate synthetase I	Carbamoyl Phosphate synthetase II
1. Occurs in mitochondrial matrix	Occurs in cytosol
2. Uses ammonia as nitrogen donor	Uses amide group of glutamine
3. Absolutely dependent on N-acetylglutamate for activity	Not affected by N-acetylglutamate

Step1

- Carbamoyl phosphate condenses with ornithine in the mitochondrial matrix to form citrulline which is transported to the cytosol where other reactions occur. Formation of citrulline is catalyzed by ornithine transcarbamoylase.

Step2

- Citrulline reacts with aspartate to form argininosuccinate in a reaction that requires hydrolysis of ATP to AMP and P_{pi}. This reaction is catalyzed by argininosuccinate synthetase.

Step 3

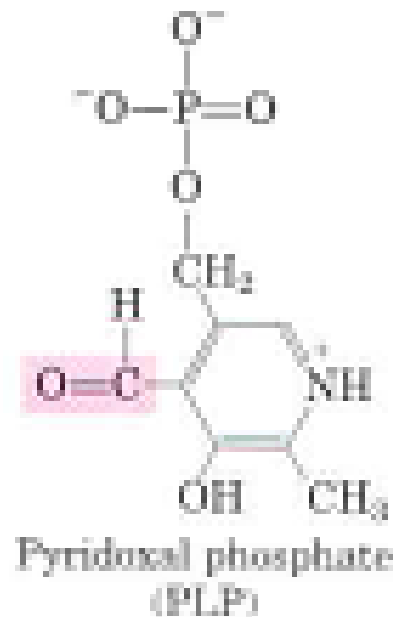
- Cleavage of argininosuccinate by argininosuccinate lyase to produce fumarate and arginine.

Step 4

- Arginine is cleaved by arginase to produce urea and ornithine. Ornithine reenters mitochondria for another turn of the urea cycle while urea is excreted.

Biosynthesis of neurotransmitters from amino acids

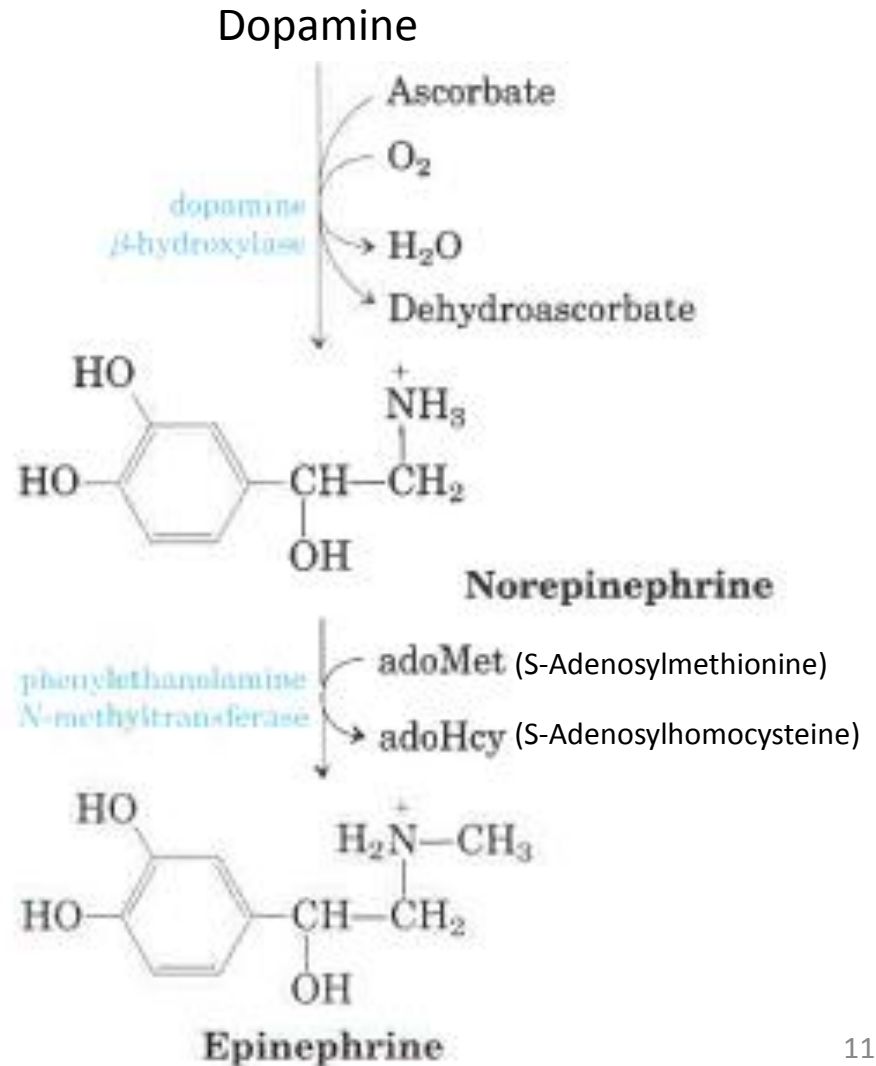
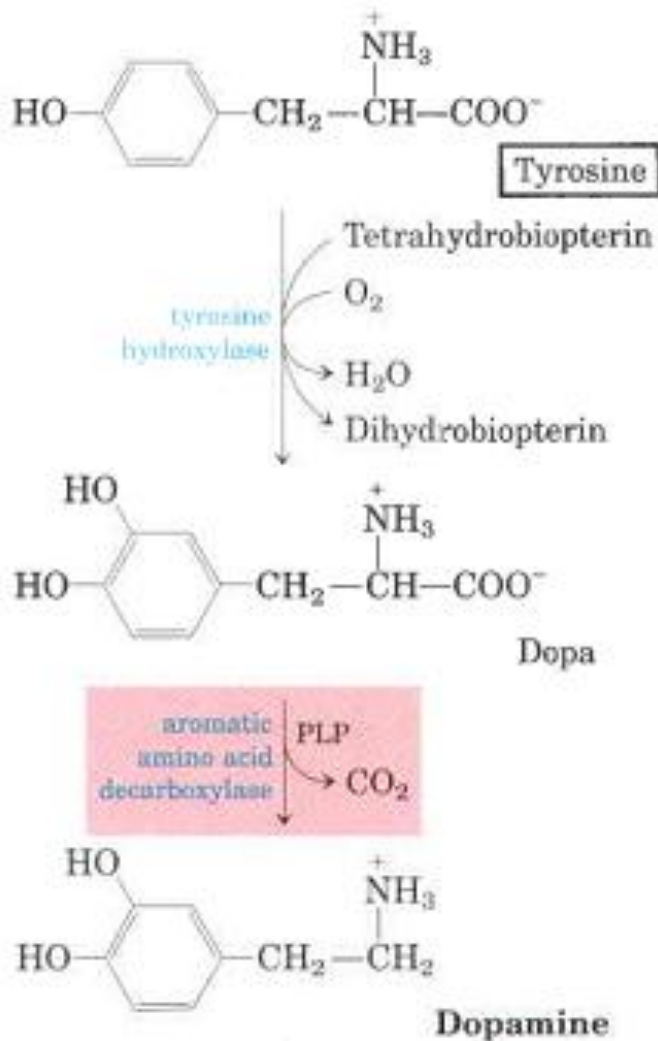
- Many important neurotransmitters are primary or secondary amines, derived from amino acids in simple pathways.
- A common denominator of many of these pathways is amino acid decarboxylation, a reaction that requires pyridoxal phosphate (PLP), the coenzyme form of pyridoxine (vitamin B₆).



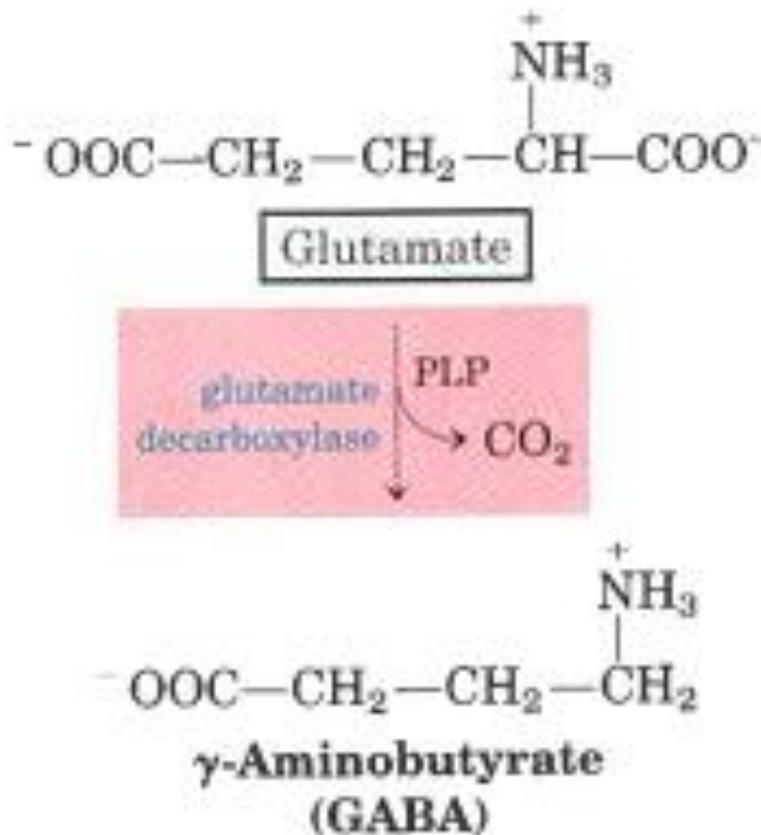
Synthesis of epinephrine

- Epinephrine is a neurotransmitter catecholamine derived from tyrosine. Tyrosine gives rise to other catecholamines that include dopamine and norepinephrine.
- Levels of catecholamine are correlated with, among other things, changes in blood pressure.
- The neurological disorder Parkinson's disease is associated with an underproduction of dopamine, and it has traditionally been treated by administering L-DOPA.
- Overproduction of dopamine in the brain may be linked to psychological disorders such as schizophrenia.

Steps in the synthesis of Epinephrine from Tyrosine



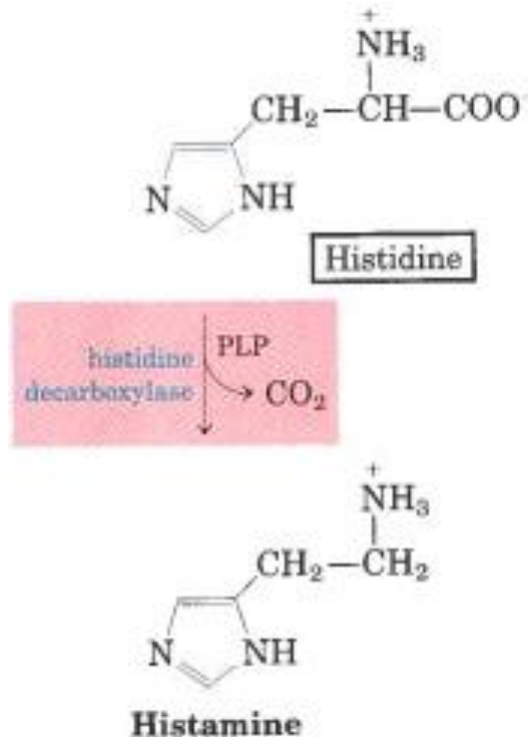
γ -amino-butyric acid (GABA)



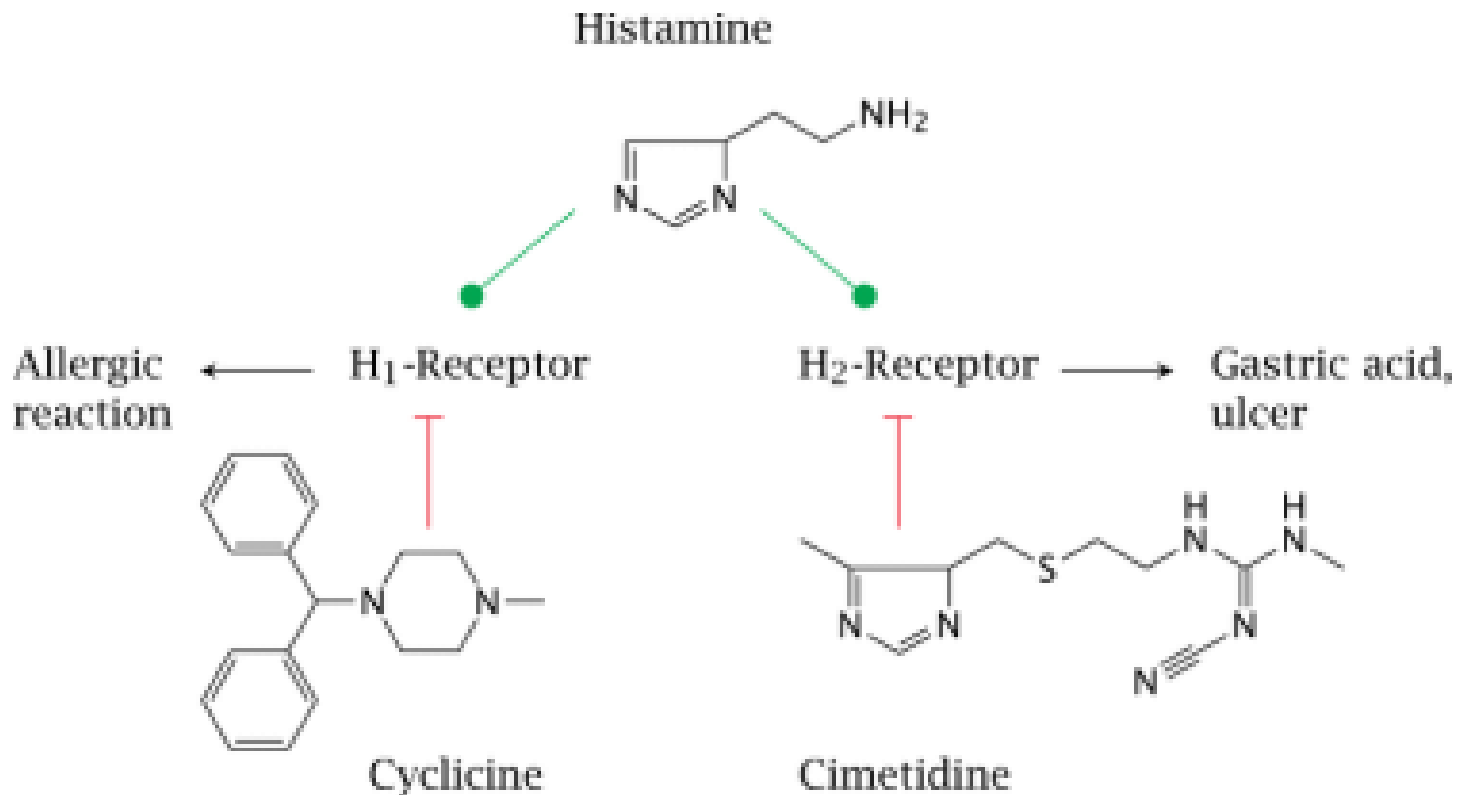
- Glutamate undergoes a decarboxylation reaction in the presence of glutamate decarboxylase to give rise to γ -amino-butyrate (GABA), an inhibitory neurotransmitter.
- Its underproduction is associated with epileptic seizures.
- GABA analogs are used in the treatment of epilepsy and hypertension.
- Levels of GABA can also be increased by administering inhibitors of the GABA-degrading enzyme GABA aminotransferase,

Histamine

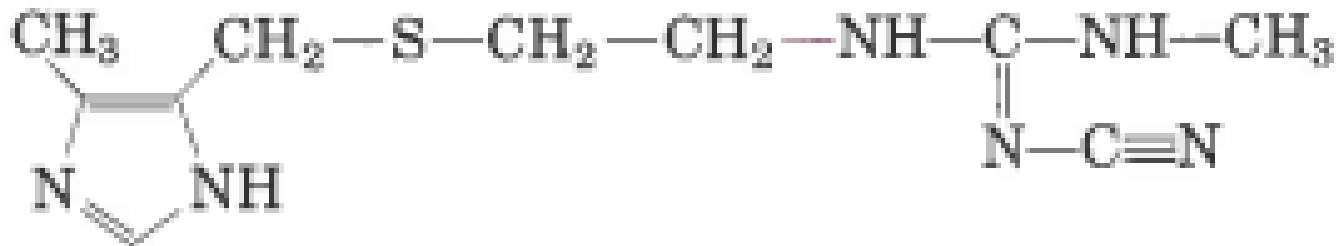
- Histidine undergoes decarboxylation to histamine, a powerful vasodilator in animal tissue.
- Histamine is released in large amounts as part of the allergic response, and it also stimulates acid secretion in the stomach.



Histamine mode of action



- Pharmaceutical products have been designed to interfere with either the synthesis or the action of histamine.
- Cimetidine, a structural analog of histamine, is a histamine receptor antagonist (i.e. H₂-receptor blocker) that promotes the healing of duodenal ulcers by inhibiting secretion of gastric acid



Cimetidine

Serotonin (5-Hydroxy-tryptamine)

- Serotonin (a vasoconstrictor) is derived from tryptophan in a two-step pathway.

