Biosynthesis of the Nutritionally Nonessential Amino Acids part 1

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Biomedical Importance

- Amino acid deficiency states include **kwashiorkor,** which results when a child is weaned onto a starchy diet poor in protein; and **marasmus,** in which both caloric intake and specific amino acids are deficient.
- Patients with short bowel syndrome unable to absorb sufficient quantities of calories and nutrients suffer from significant nutritional and metabolic abnormalities.
- Both the nutritional disorder **scurvy,** a dietary deficiency of vitamin C, and specific genetic disorders are associated with an impaired ability of connective tissue to form hydroxyproline and hydroxylysine. The resulting conformational instability of collagen results in bleeding gums, swelling joints, poor wound healing, and ultimately in death.
- **As well as** the deficiency of copper, which is an essential cofactor for lysyl oxidase, an enzyme that functions in formation of the covalent cross-links that strengthen collagen fibers**.**

Nutritionally essential & nutritionally nonessential amino acids

As applied to amino acids, the terms "essential" and "nonessential" are misleading since all 20 common amino acids are essential to ensure health. Of these 20 amino acids, 8 must be present in the human diet, and thus are best termed "nutritionally essential." The other 12 amino acids are "nutritionally nonessential" since they need not be present in the diet. The distinction between these two classes of amino acids was established in the 1930s by feeding human subjects purified amino acids in place of protein.

Table 27–1. Amino Acid Requirements of Humans

Nutritionally Essential	Nutritionally Nonessential
Arginine[1] Histidine	Alanine Asparagine
Isoleucine	Aspartate
Leucine	Cysteine
Lysine Methionine	Glutamate Glutamine
Phenylalanine	Glycine
Threonine	Hydroxyproline[2]
Tryptophan Valine	Hydroxylysine[2] Proline
	Serine
	Tyrosine

1Nutritionally "semiessential." Synthesized at rates inadequate to support growth of children.

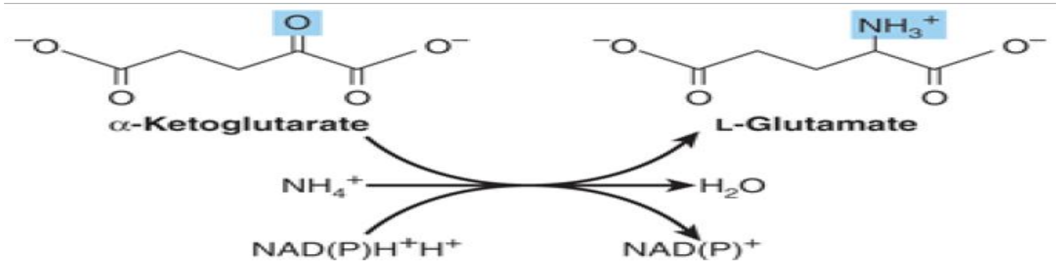
2Not necessary for protein synthesis, but is formed during post-translational processing of collagen.

Glutamate Dehydrogenase, Glutamine Synthetase, & Aminotransferases Play Central Roles in Amino Acid Biosynthesis

The combined action of the enzymes glutamate dehydrogenase, glutamine synthetase, and the aminotransferases converts ammonium ion into the -amino nitrogen of amino acids.

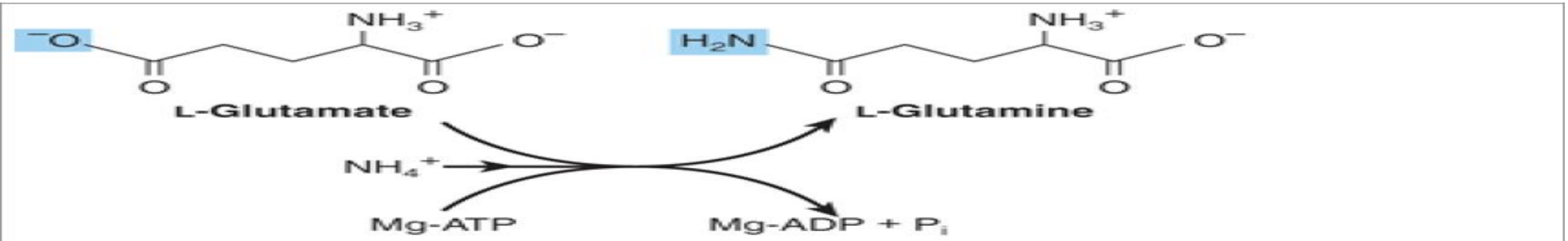
Glutamate

Reductive amidation of α-ketoglutarate is catalyzed by glutamate dehydrogenase. This reaction constitutes the first step in biosynthesis of the "glutamate family" of amino acid



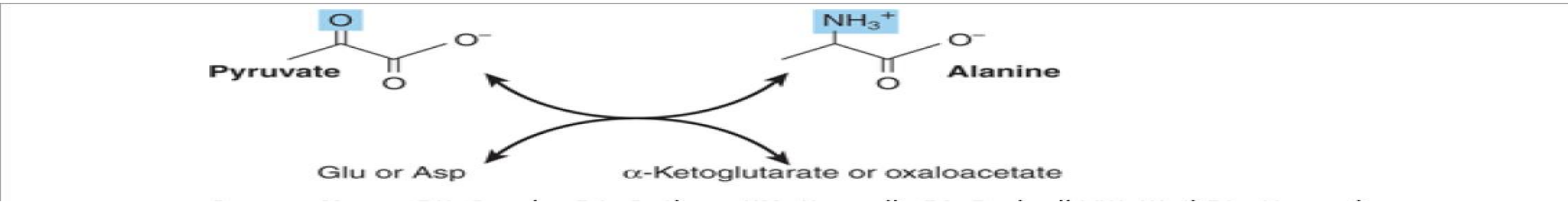
Glutamine

The amidation of glutamate to glutamine catalyzed by glutamine synthetase involves the intermediate formation of -glutamyl phosphate. Following the ordered binding of glutamate and ATP, glutamate attacks the -phosphorus of ATP, forming -glutamyl phosphate and ADP. NH4+ then binds, and as NH3, attacks -glutamyl phosphate to form a tetrahedral intermediate. Release of Pi and of a proton from the -amino group of the tetrahedral intermediate then facilitates release of the product, glutamine.



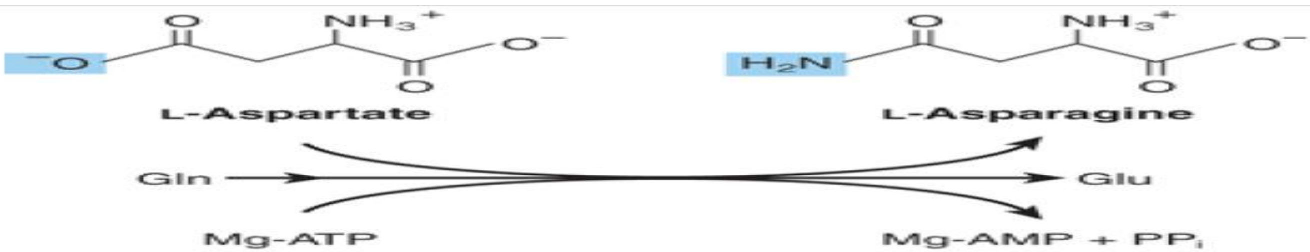
Alanine & Aspartate

Transamination of pyruvate forms alanine . Similarly, transamination of oxaloacetate forms aspartate.



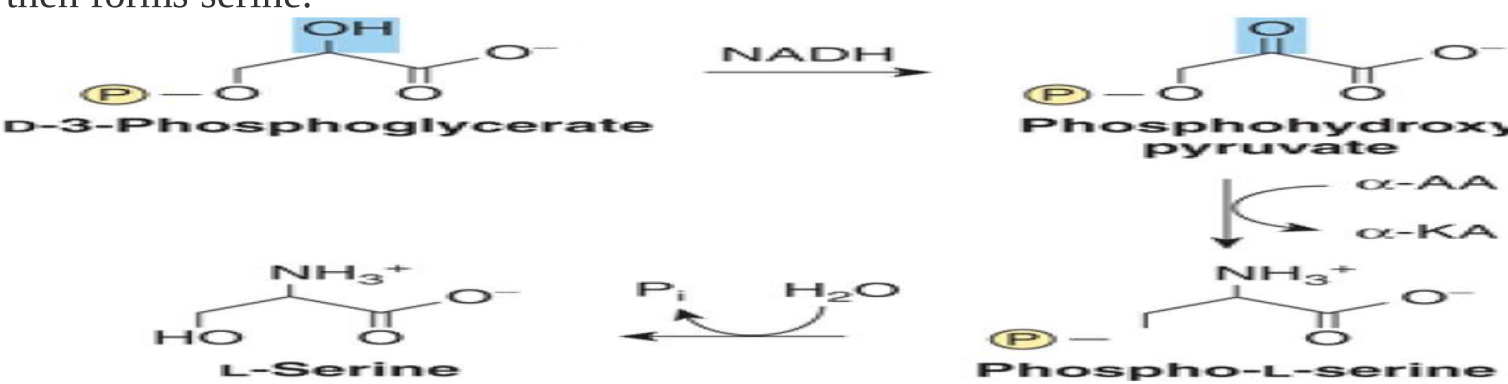
Asparagine

The conversion of aspartate to asparagine, catalyzed by asparagine synthetase, resembles the glutamine synthetase reaction, but glutamine rather than ammonium ion, provides the nitrogen.



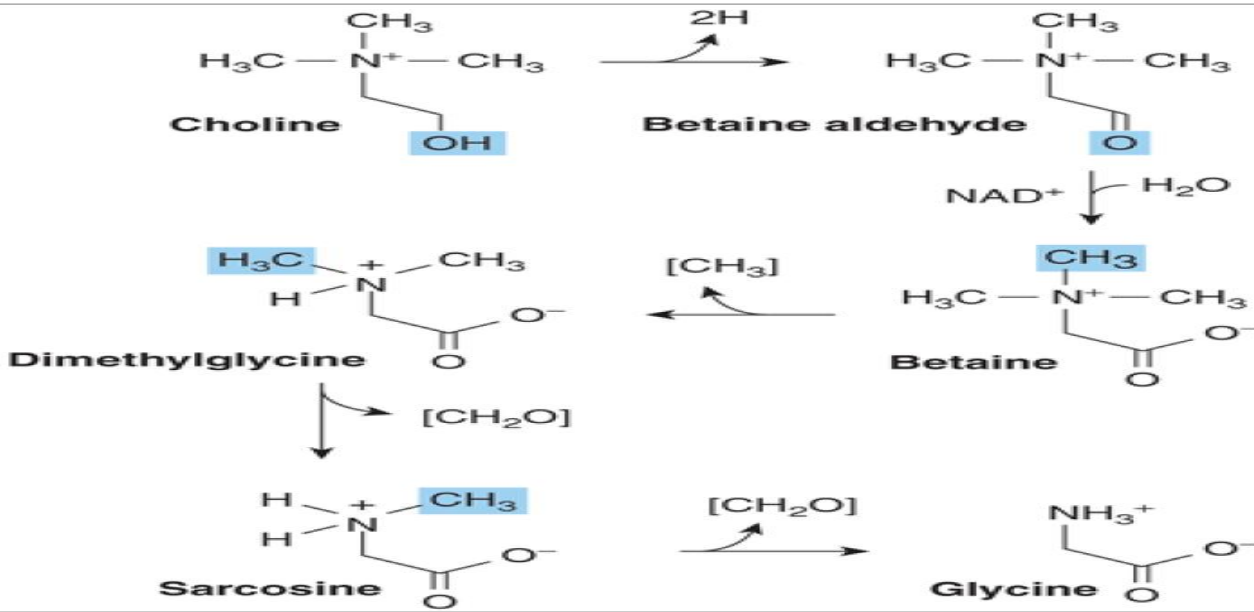
Serine

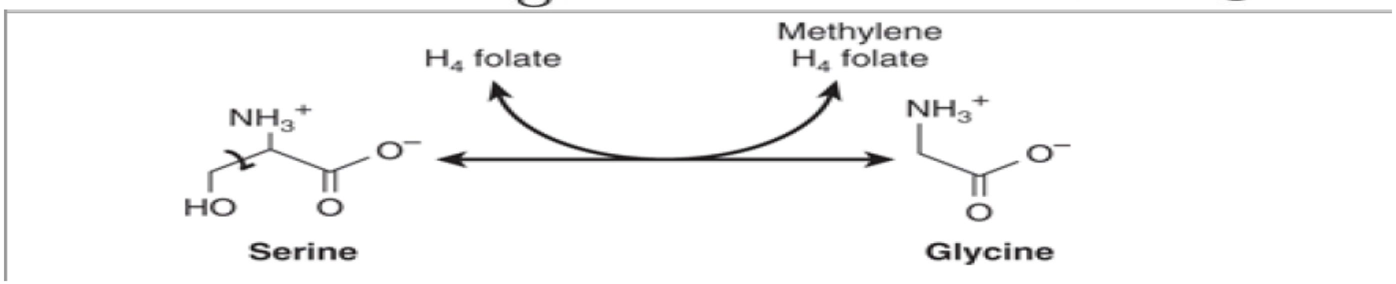
Oxidation of the -hydroxyl group of the glycolytic intermediate 3-phosphoglycerate by 3-phosphoglycerate dehydrogenase converts it to 3-phosphohydroxypyruvate. Transamination and subsequent dephosphorylation then forms serine.



Glycine

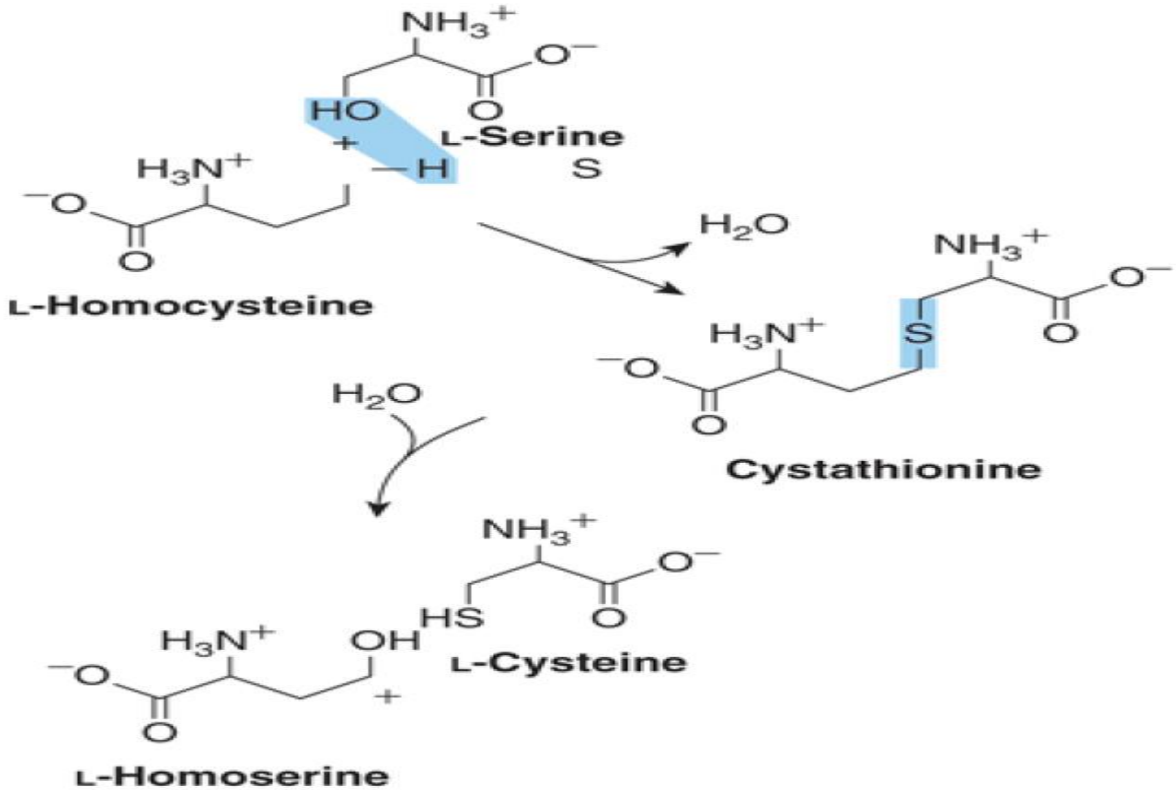
Glycine aminotransferases can catalyze the synthesis of glycine from glyoxylate and glutamate or alanine. Unlike most aminotransferase reactions, these strongly favor glycine synthesis. Additional important mammalian routes for glycine formation are from choline and from serine .





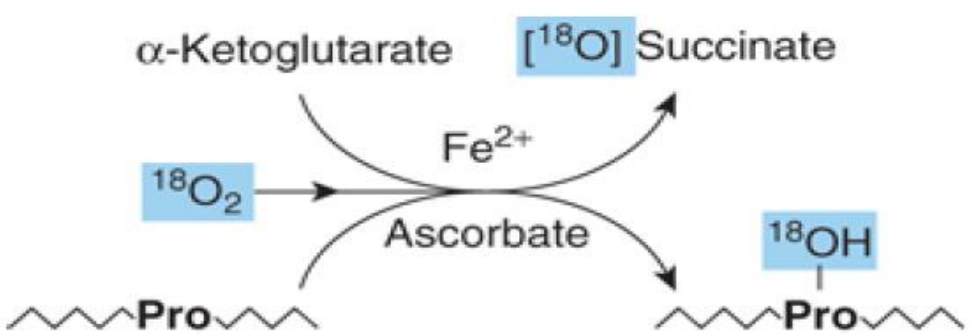
Cysteine

While not nutritionally essential, cysteine is formed from methionine, which is nutritionally essential. Following conversion of methionine to homocysteine, homocysteine and serine form cystathionine, whose hydrolysis forms cysteine and homoserine.



Hydroxyproline & Hydroxylysine

Hydroxyproline and hydroxylysine occur principally in collagen. Since there is no tRNA for either hydroxylated amino acid, neither dietary hydroxyproline nor hydroxylysine is incorporated during protein synthesis. Peptidyl hydroxyproline and hydroxylysine arise from proline and lysine, but only after these amino acids have been incorporated into peptides. Hydroxylation of peptidyl prolyl and lysyl residues, catalyzed by **prolyl hydroxylase** and **lysyl hydroxylase** of skin, skeletal muscle, and granulating wounds requires, in addition to the substrate, molecular O2, ascorbate, Fe2+, and -ketoglutarate . For every mole of proline or lysine hydroxylated, one mole of -ketoglutarate is decarboxylated to succinate. The hydroxylases are mixed-function oxygenases. One atom of O2 is incorporated into proline or lysine, the other into succinate .



Valine, Leucine, & Isoleucine

While leucine, valine, and isoleucine are all nutritionally essential amino acids, tissue aminotransferases reversibly interconvert all three amino acids and their corresponding -keto acids. These -keto acids thus can replace their amino acids in the diet.

Tyrosine

Phenylalanine hydroxylase converts phenylalanine to tyrosine. If the diet contains adequate quantities of the nutritionally essential amino acid phenylalanine, tyrosine is nutritionally nonessential. But since the phenylalanine hydroxylase reaction is irreversible, dietary tyrosine cannot replace phenylalanine. Catalysis by this mixed-function oxygenase incorporates one atom of O2 into the para position of phenylalanine and reduces the other atom to water. Reducing power, provided as tetrahydrobiopterin, derives ultimately from NADPH.