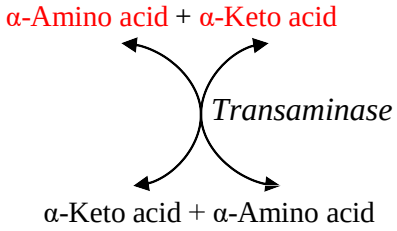
Biosynthesis of Nonessential Amino Acids

Humans do not have the ability to synthesize 10 of the proteogenic amino acids and must obtain them from the diet. These 10 are termed the nutritionally essential amino acids.

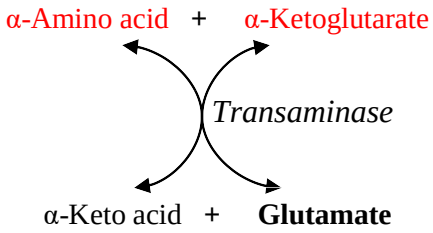
The number of enzymes required by cells to synthesize the nutritionally essential amino acids is large in relation to the number of enzymes required to synthesize the nutritionally nonessential amino acids. This suggests that there is a positive survival advantage in retaining the ability to manufacture 'easy' amino acids while losing the ability to make 'difficult' amino acids.

The 10 nonessential amino acids are formed by 3 general mechanisms:

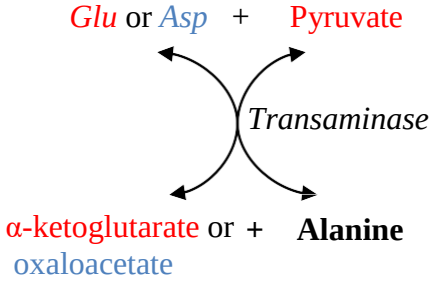
I) Transamination:



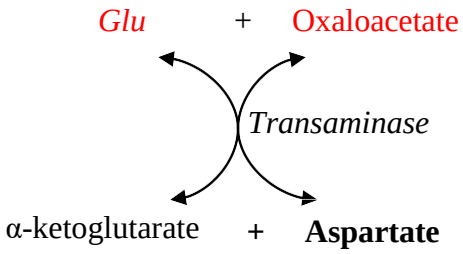
- **Glutamate:** can be synthesized by transamination of the corresponding α -keto acid, α – ketoglutarate. The amino donor may be any amino acid (except lysine, threonine, proline, hydroxylysine and hydroxyproline).



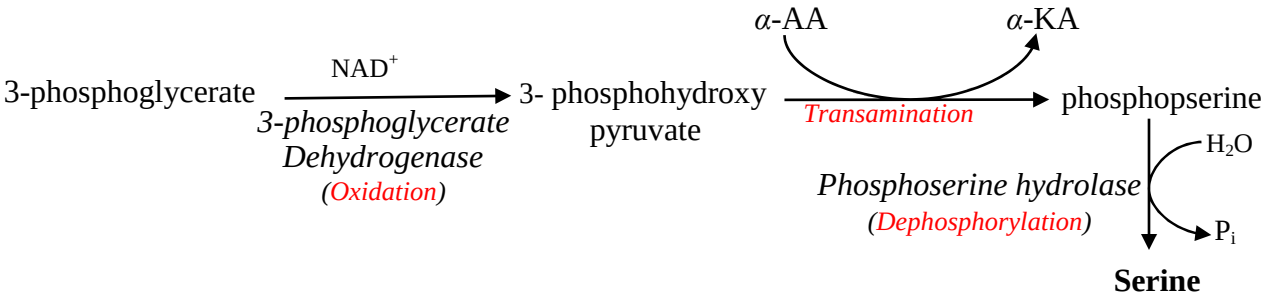
- **Alanine:** transamination of pyruvate forms alanine. The amino donor may be glutamate or aspartate. The other product thus is α-ketoglutarate or oxaloacetate.



- **Aspartate:** can be synthesized by transamination of oxaloacetate to form aspartate and α-ketoglutarate. The amino donor is glutamate.



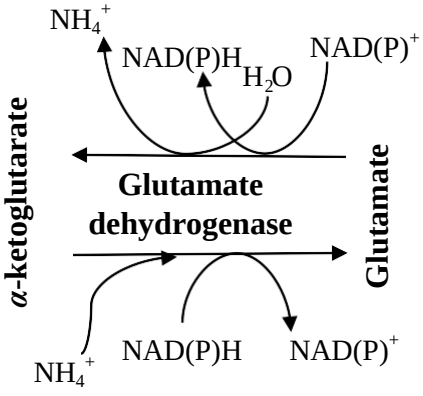
- **Serine** is synthesized by the oxidation, transamination and subsequent dephosphorylation of 3-phosphogylcerate, an intermediate of glycolysis.



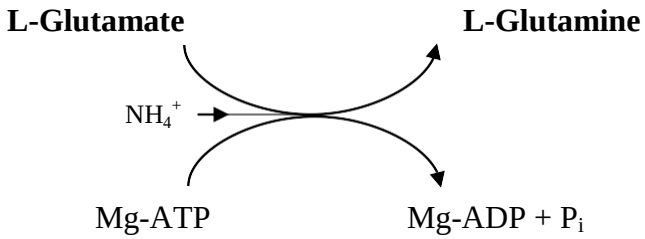
NOTE
In all of the transamination reactions, pyridoxal phosphate PLP (**vitamin B6**) acts as an intermediate carrier of the amino group that is being transferred.

II) Assimilation of free ammonia:

- **Glutamate:** Formation of glutamate from free ammonia and α-ketoglutarate is catalyzed by glutamate dehydrogenase. This reaction is **reversible** and plays a role in both synthesis and breakdown of glutamate. Both NADPH and NADH can serve as the source of reducing equivalents used in this reaction.

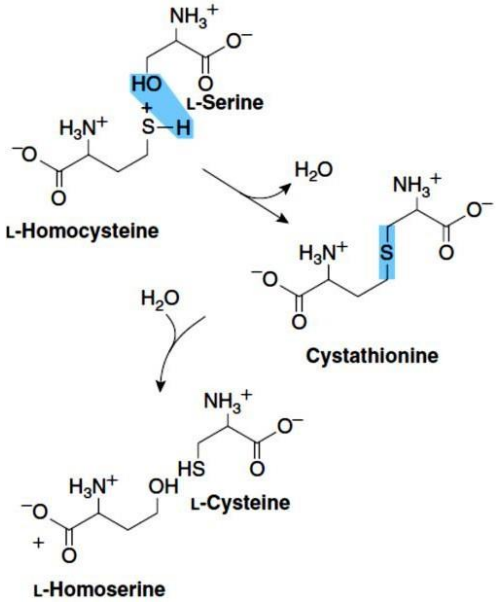


- **Glutamine:** Glutamine synthetase catalyzes the ATP-dependent formation of glutamine, using glutamate and ammonia as substrates.



III) Modification of the carbon skeletons of existing amino acids.

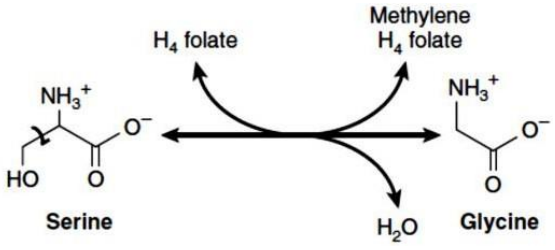
- **Cysteine**: Cysteine contains atoms donated by both methionine and serine. Following conversion of methionine to homocysteine, homocysteine and serine form cystathionine, a thioether (RSR′), the reaction is catalyzed by cystathionine β-synthase. Hydrolysis of cystathionine by cystathionine lyase forms cysteine.



While cysteine is nutritionally nonessential, it is formed from methionine, which is nutritionally essential.

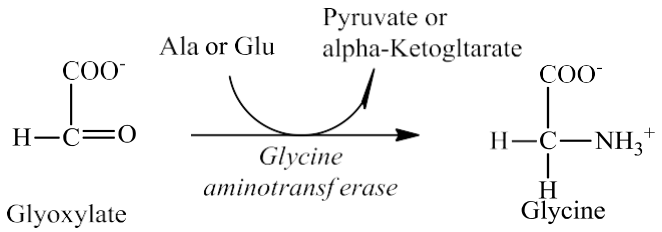
- **Glycine:** three mammalian routes for glycine formation

✓ From serine which is converted to glycine by the removal of its hydroxymethyl group. The reaction is freely **reversible** and catalyzed by **serine hydroxymethyl transferase**



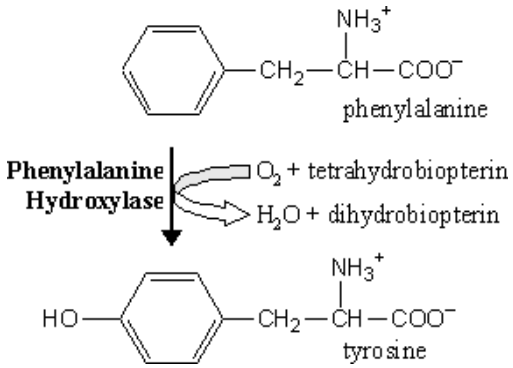
Interconversion of serine and glycine, catalyzed by serine hydroxymethyltransferase (H_4 folate:tetrahydrofolate, cofactor)

- ✓ From glyoxylate and glutamate or alanine catalyzed by **glycine aminotransferase** (**irreversible**, unlike other transamination reactions)



- ✓ From choline

- **Tyrosine:** Phenylalanine is hydroxylated to form tyrosine a reaction catalyzed by phenylalanine hydroxylase.

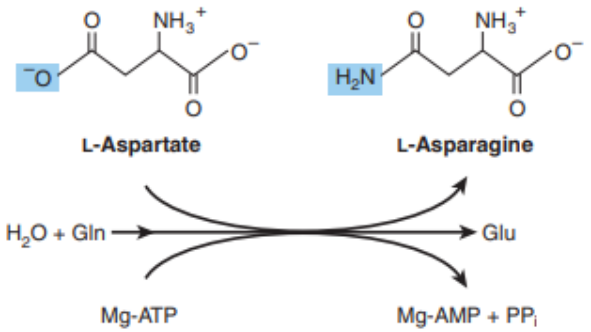


NOTE

- ✓ Provided that the diet contains adequate nutritionally essential phenylalanine, tyrosine is nutritionally nonessential.
- ✓ Since the reaction is **irreversible**, dietary tyrosine cannot replace phenylalanine.

- **Proline:** Glutamate is reduced and cyclized to form proline.

- **Asparagine:** Asparagine is synthesized from aspartate catalyzed by asparagine synthetase. Coupled hydrolysis of pyrophosphate (PP_i) to P_i by pyrophosphatase ensures that the reaction is strongly favored. (Note similarities to and differences from the glutamine synthetase reaction)

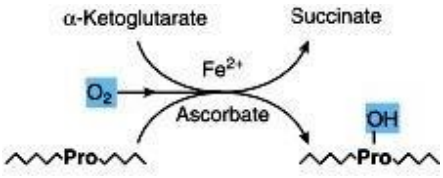


Hydroxyproline & Hydroxylysine

Hydroxyproline and hydroxylysine occur principally in collagen. Since there is no tRNA for either hydroxylated amino acid, neither dietary hydroxyproline nor dietary 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 peptidyl lysyl residues, catalyzed by prolyl hydroxylase and lysyl hydroxylase of skin, skeletal muscle, and granulating wounds requires, in addition to the substrate, molecular O_2 , ascorbate, Fe^{2+} , and α -ketoglutarate.

For every mole of proline or lysine hydroxylated, one mole of α –ketoglutarate is decarboxylated to succinate.

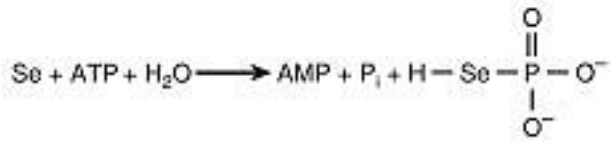
A deficiency of ascorbate required for these two hydroxylases results in **scurvy**, in which bleeding gums, swelling joints, andimpaired wound healing result from the impaired stability of collagen.



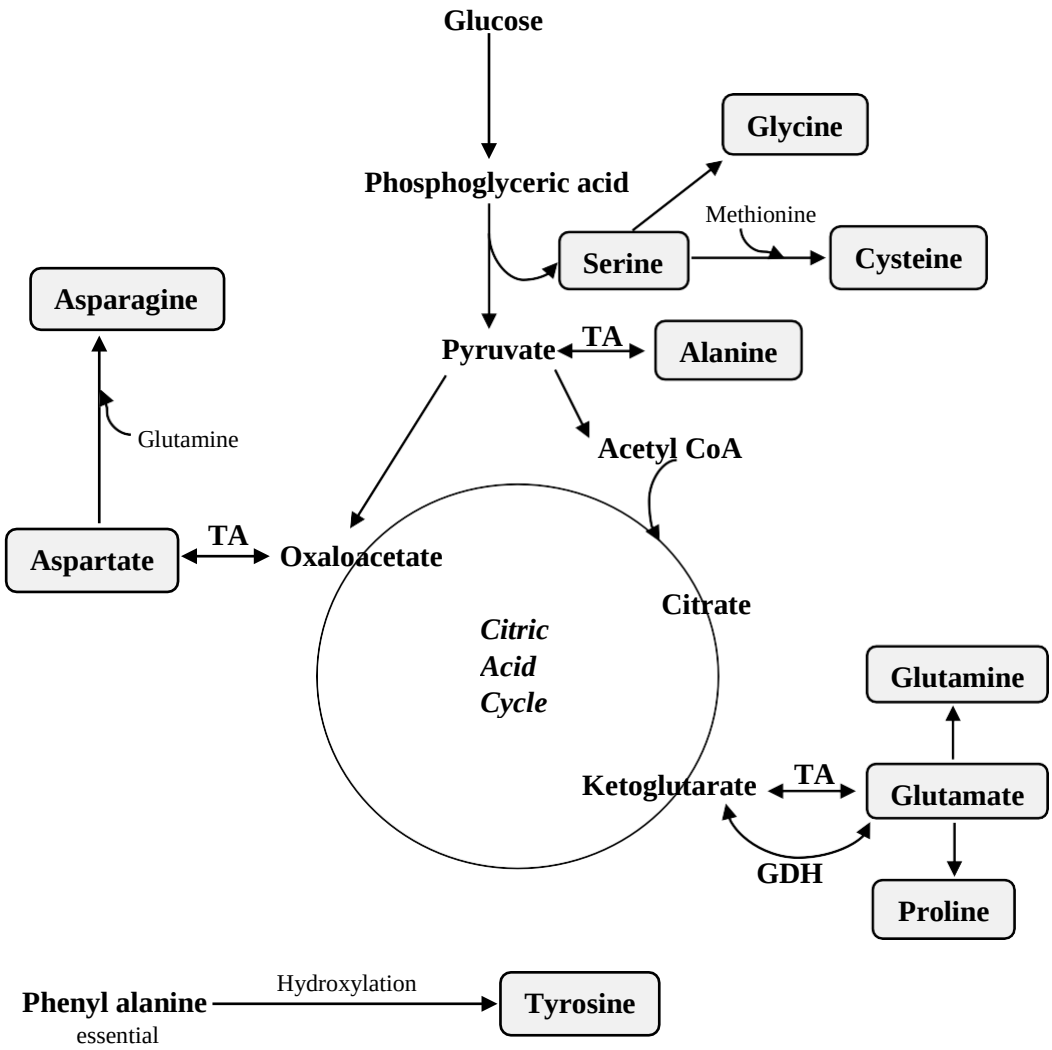
Selenocysteine, the 21st Amino Acid

While the occurrence of selenocysteine in proteins is uncommon, at least 25 human selenoproteins are known. Selenocysteine is present at the active site of several human enzymes that catalyze redox reactions. Examples include thioredoxin reductase, glutathione peroxidase, and the deiodinase that converts thyroxine to triiodothyronine. Where present, selenocysteine participates in the **catalytic mechanism** of these enzymes. Significantly, the replacement of selenocysteine by cysteine can actually impair catalytic activity. Impairments in human selenoproteins have been implicated in tumorigenesis and atherosclerosis, and are associated with selenium deficiency cardiomyopathy (Keshan disease). Unlike hydroxyproline or hydroxylysine, selenocysteine arises **cotranslationally** during its incorporation into peptides.

Biosynthesis of **selenocysteine** requires serine, selenite ($SeO4^{2-}$), ATP, a specific tRNA, and several enzymes. Serine provides the carbon skeleton of selenocysteine. Selenophosphate, formed from ATP and selenite (catalyzed by selenophosphate synthetase), serves as the selenium donor.



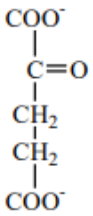
The specific $tRNA^{Ser}$ is first charged with serine by the ligase that charges $tRNA^{Ser}$. Subsequent replacement of the serine oxygen by selenium from selenophosphate. The formed **selenocysteine** can then be incorporated into proteins.



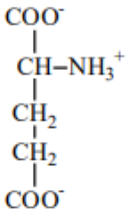
Biosynthesis of nonessential amino acids

TA: Transamination

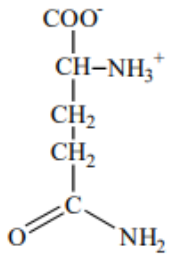
GDH: Glutamate dehydrogenase



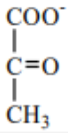
α-Ketoglutarate



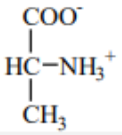
Glutamate



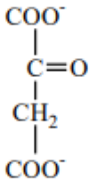
Glutamine



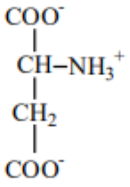
Pyruvate



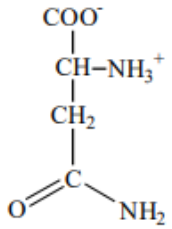
Alanine



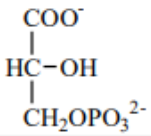
Oxaloacetate



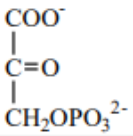
Aspartate



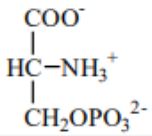
Asparagine



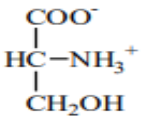
3-phosphoglycerate



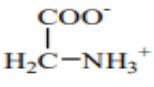
3-phosphohydroxypyruvate



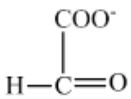
Phosphoserine



Serine



Glycine



Glyoxylate