Amino acid Catabolism

Amino acids:
1. There are 20 different amino acid, they are monomeric constituents of proteins.
2. They act as precursors of other nitrogen containing biologically important compounds, like hormones, neurotransmitters etc.
3. Can be used as energy source.

We will be discussing just the catabolism of the amino acids (AAs), to generate energy.

There are three major steps in catabolism of AAs.

1. Removal of amino group: deamination by
   i. Transamination: Transfer of amino gp to α-ketoglutarate yielding glutamate
   ii. Oxidative deamination: removal of amino gp from glutamate to release ammonia
   iii. Other deamination processes.

2. Urea Cycle: Conversion of NH₃ to urea for excretion

3. Metabolic breakdown of carbon skeleton to generate common intermediates that can be catabolized to CO₂ or used in anabolic pathways to be stored as glucose or fat.

Excretory forms of Nitrogen

Transamination: Transfer of amino group to α-ketoglutarate. There are several aminotransferases specific to different amino acids. In this step amino group from all the amino acids are transferred to α-ketoglutarate and they exist as glutamate.

Transaminases or aminotransferases require pyridoxal 5'-phosphate PLP (vitamin B₆ derivative)

PLP is very important cofactor for many enzymatic reactions.
Pyridoxal phosphate as carrier of amino group (a) and its enzyme-bound form (b) through Schiff’s base.

Oxidative deamination: In liver the amino gp of glutamate is released as ammonia, regenerating a-ketoglutarate, by an enzyme glutamate dehydrogenase. Glutamate dehydrogenase requires NAD+ or NADP+ as cofactor. This is the only enzyme known that has specificity for both type of cofactor. This enzyme is allosterically inhibited by GTP and activated by ADP.

Transport of excess ammonia by glutamine: Excess ammonia is toxic to animal tissues. Other than amino acid catabolism in tissues ammonia is also produced as a result of nucleic acid degradation. Glutamine synthase catalyses the synthesis of glutamine by adding the ammonia to glutamate at the expense of ATP hydrolysis. Glutamine is a non-toxic carrier of ammonia. It is transported to liver or kidney via blood. In liver or kidney mitochondria, the glutamine is converted to glutamate and ammonia. Ammonia is incorporated in urea cycle in liver to be excreted.

Glucose-Alanine cycle: Amino group from excess glutamate produced in muscle as a result of amino acid catabolism, is transferred to pyruvate resulting in the formation of alanine. Alanine is another safe way to transport ammonia from muscle to liver via blood. In liver alanine aminotransferase transfers the amino gp to glutarate and pyruvate regenerated is used in gluconeogenesis. Glucose produced by gluconeogenesis is transported to muscle where it enters the glycolysis. Thus the excess puruvate and ammonia generated in muscle are safely transported to liver.

Carbamoyl phosphate synthase-I Reaction: Ammonia released from the oxidative deamination is incorporated in carbamoyl phosphate by using ATP and bicarbonate. N-acetyl glutamine is a positive regulator of this enzyme. Carbamoyl phosphate enters the urea cycle in the mitochondria.
Possible therapies for the patients with defect in urea cycle:

1. Defined diet containing just the minimum amount of essential amino acids.

2. Feeding the patients with Benzoate or phenylacetalate: These compound react with glycine and glutamine respectively forming non-toxic compounds that are excreted in urine. Thus the body runs low in glycine and glutamine and starts synthesizing these AA using the ammonia available in system. Thus clearing the system of excess ammonia.

3. In the patients with N-acetylglutamate synthase deficiency, Carbamoyl glutamate can act as activator of carbamoyl phosphate synthase.
Regulation of urea cycle:
1. Enzymes involved in urea cycle are synthesized at higher levels when proteins are utilized for energy production (starvation, or availability of fat and carbohydrate-free diet).
2. The carbamoyl phosphate synthase is allosterically activated by N-acetylglutamate.

Entry of the carbon skeleton of AAs in citric acid cycle:

Some of the cofactors involved in amino acid metabolism:
Catabolic pathway of Glycine, serine, threonine, cysteine, alanine and tryptophan

Metabolic fates of Glycine

Catabolic pathways of Aspartic acid and asparagine

Catabolic pathways for Arg, His, Pro, Glu, Gln

Catabolic pathway of Tryptophan, tyrosine, phenyl alanine, lysine and lucine

Tryptophan as a precursor of other important compound

Niacinate, vitamin, a precursor of NAD and NADP
Sildenafil, a pde5 inhibitor
Serotonin, a neurotransmitter
Catabolism of Phenylalanine and tyrosine

Role of tetrahydrobiopterine in phenylalanine hydroxylase reaction

Alternative pathways for the catabolism of phenylalanine in patients with phenylketonuria
The end product phenylpyruvate accumulates in liver, blood and urine.
Phenylacetate and phenylactate are also found in urine.

Catabolic pathways of three branched chain amino acids

Met, Ile, Thr, Val catabolism

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*Essential in young, growing animals but not in adults.