**Nitrogen Metabolism**

**18.1 Nitrogen Fixation and Assimilation**

**Nitrogenase**

* Gaseous N2 is unusable for synthesis of biomolecules
* Biological productivity is limited by the availability of fixed N2
* Diazotrophs: marine cyanobacteria and root nodule bacteria that make nitrogenase
* Nitrogenase: reduces N2 to NH3
* Fe-S clusters; Fe and molybdenum cofactor
* Highly endergonic reaction breaks triple bond between nitrogen atoms
* Requires strong reducing agent (ferredoxin) as e- donor
* N2 fixation is anaerobic (O2 inactivates nitrogenase)

**The Nitrogen Cycle**

* Nitrate (from water and soil) is also source of useful nitrogen
* Reduced to NH3 by plants, fungi and bacteria; also produced from NH4+ = **nitrification**
* Conversion of NO3- to N2 = **dentrification**

**Glutamine Synthetase**

* Microorganisms: metabolic entry point for fixed N2
* Animals: absorbs excess NH3 (toxic)
* Step 1: phosphoryl group donated by ATP to glutamate
* Step 2: P*i* displaced by NH4+ to produce glutamine
* Glu and Gln = amino group carriers (present at high concentration)
* Activity is tightly regulated to maintain supply of amino groups

**Glutamate Synthase**

* Provides substrate (glu) for glutamine synthetase in bacteria and plants
* Exchanges amine group between Glutamine and a-Ketoglutarate
* Combined reactions (gln synthetase and glu synthase) assimilate fixed nitrogen as NH4+ into organic compound (a-Ketoglutarate = CAC intermediate) to produce amino acid

**Transaminase**

* Amino group transfer from amino acid to a-keto acid (or reverse)
* Requires PLP prosthetic group for transient attachment
* Amino acid displaces enzyme to form amino acid-PLP Schiff base intermediate
* Enzyme Lys residue acts as acid-base catalyst

**18.2 Amino Acid Biosynthesis**

**Essential/Nonessential Amino Acids**

* Intermediates from glycolysis, CAC and PPP; nitrogen carriers glutamate and glutamine
* Sources of essential a.a. vary (plants, microorganisms)
* Transaminations of pyruvate, oxaloacetate, and a-ketoglutarate produce alanine, aspartate, and glutamate
* Amidation of glutamate produces glutamine
* Asparagine is produced from glutamine amino-group transfer to aspartate
* Glutamate converted to proline and arginine
* Serine derived from 3-phosphoglycerate (glycolysis)
* Serine converted to glycine using PLP and tetrahydrofolate (one C carrier)

**Neurotransmitters**

* Glycine, glutamate, GABA, catecholamines (tyrosine derivatives), serotonin, melatonin, NO

**18.3 Amino Acid Catabolism**

**Amino Acids as Metabolic Fuels**

* Intestinal cells use a.a. as primary fuel source (glutamate, aspartate, glutamine)
* Liver (and other tissues) catabolizes dietary and recycled amino acids
* Fasting: amino acids mobilized from muscle tissue breakdown
* alpha-amino groups removed (transamination) and carbon skeletons enter CAC
* Partial oxidation leaves glucogenic or ketogenic substrates

**Catabolic Fates of Amino Acids**

* Alanine, aspartate, glutamate: transaminated to gluconeogenic substrates **pyruvate**, **oxaloacetate**, **a-ketoglutarate**
* Asparagine deamidated to aspartate, transaminated to **oxaloacetate**
* Glutamine deamidated to glutamate, dehydrogenated to **a-ketoglutarate**
* Serine converted to **pyruvate** via amino group release
* Arginine, proline and histidine catabolized to **glutamate**
* Cysteine converted to **pyruvate** by amino group and sulfur release
* Threonine oxidized and cleaved to **acetyl-CoA** (ketogenesis) and **glycine** (gluconeogenesis or disposal)

**Coenzyme A in Degradation**

* Valine: succinyl-CoA
* Isoleucine: succinyl-CoA and acetyl-CoA
* Lysine: acetyl-CoA and acetoacetate
* Methionine: succinyl-CoA

**Phenylalanine Hydroxylase**

* Phenylalanine, tyrosine, tryptophan yield acetoacetate and either alanine or fumarate
* Phenylketonuria: lacking phenylalanine hydroxylase

**18.4 Nitrogen Disposal: The Urea Cycle**

**The Glutamate Dehydrogenase Reaction**

* Glutamate = nitrogen supplier
* Redox reaction to release NH4+ and alpha-KG
* Uses either NAD(P)H
* Glutamate dehydrogenase deaminates glutamate to a-ketoglutarate, releasing NH4+ to urea cycle
* Glx DH is allosterically regulated

**The Carbamoyl Phosphate Synthetase Reaction**

* Generates starting material (carbamoyl phosphate) for urea cycle
* Activation of bicarbonate, followed by condensation with ammonia yields carbamoyl phosphate
* Consumes two ATP molecules
* NH4+ from glutamate dehydrogenase (or other ammonia supplier)
* Bicarbonate = urea carbon
* Stimulated by N-Acetylglutamate (glutamate and Acetyl-CoA signal amino acid transamination/catabolism to increase disposal via flux through urea cycle)

**The Urea Cycle**

* Disposal of NH4+ as urea
* Production of arginine (not sufficient for growing children)
* Fumarate > oxaloacetate > gluconeogenesis
* Amino groups donated by transaminated amino acids via glutamate and aspartate
* Steps 2-4 cytosolic (citrulline xfer from mitochondria; ornithine xfer from cytosol)
* Rate controlled by carbamoyl phosphate synthetase, as donor for starting material