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Medical relevance of amino acid metabolism pathways:

What is nitrogen balance, and what affects it?

Role of vitamins: pyridoxamine (VitB₆), folic acid

Understanding a critical function of the liver: nitrogen metabolism

Which amino acids are essential?

Inborn errors of metabolism: amino acid breakdown, urea cycle

Pharmacologic manipulation of neurotransmitters (e.g. Parkinson's Syndrome)

I. Protein degradation/Nitrogen balance

A. Cells constantly turn over proteins

It's a normal process, balanced by protein intake.

Proteins can be degraded if they are:

- damaged by free radicals
- oxidative damage
- misfolded
- no longer needed.

B. "Nitrogen Balance" expresses the balance between anabolism and catabolism

1. Measured by assessing dietary N intake vs urinary N output (as urea)

2. "Positive" nitrogen balance (net storage of nitrogenous compounds):
 - childhood growth
 - pregnancy
 - muscle building
 - healing

3. "Negative" nitrogen balance (net breakdown of stored nitrogenous compounds):
 - illness
 - uterine resorption
 - starvation
 - amino acid deficiency
 - wounding

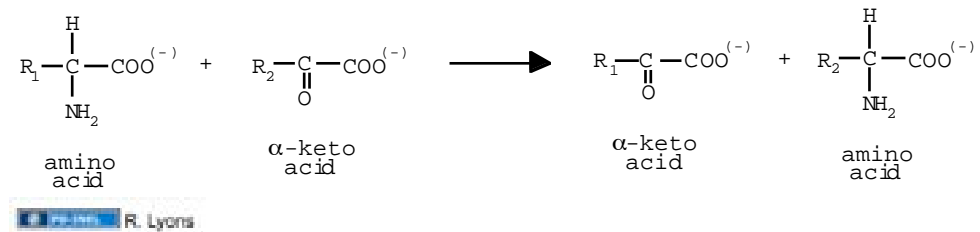
4. In negative nitrogen balance, the liver may be taxed in handling excess nitrogenous waste.
We will revisit this when we discuss pathologies of the nitrogen disposal pathways.

II. AA catabolism - Separate the amino moiety, carbon skeleton:

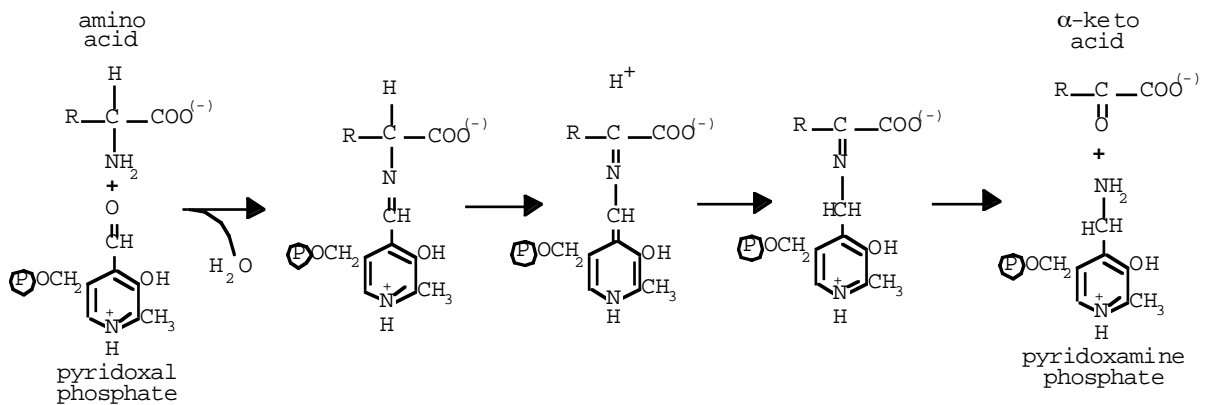
A. Dealing with the amine: convert to urea or re-utilize:

1. transaminated to α -ketoglutarate forming an α -keto acid and glutamate.

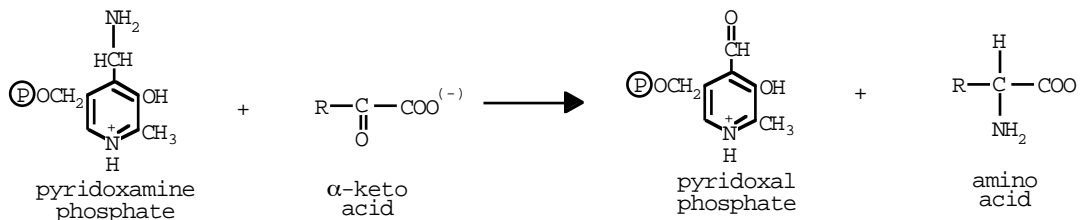
Simplified version:



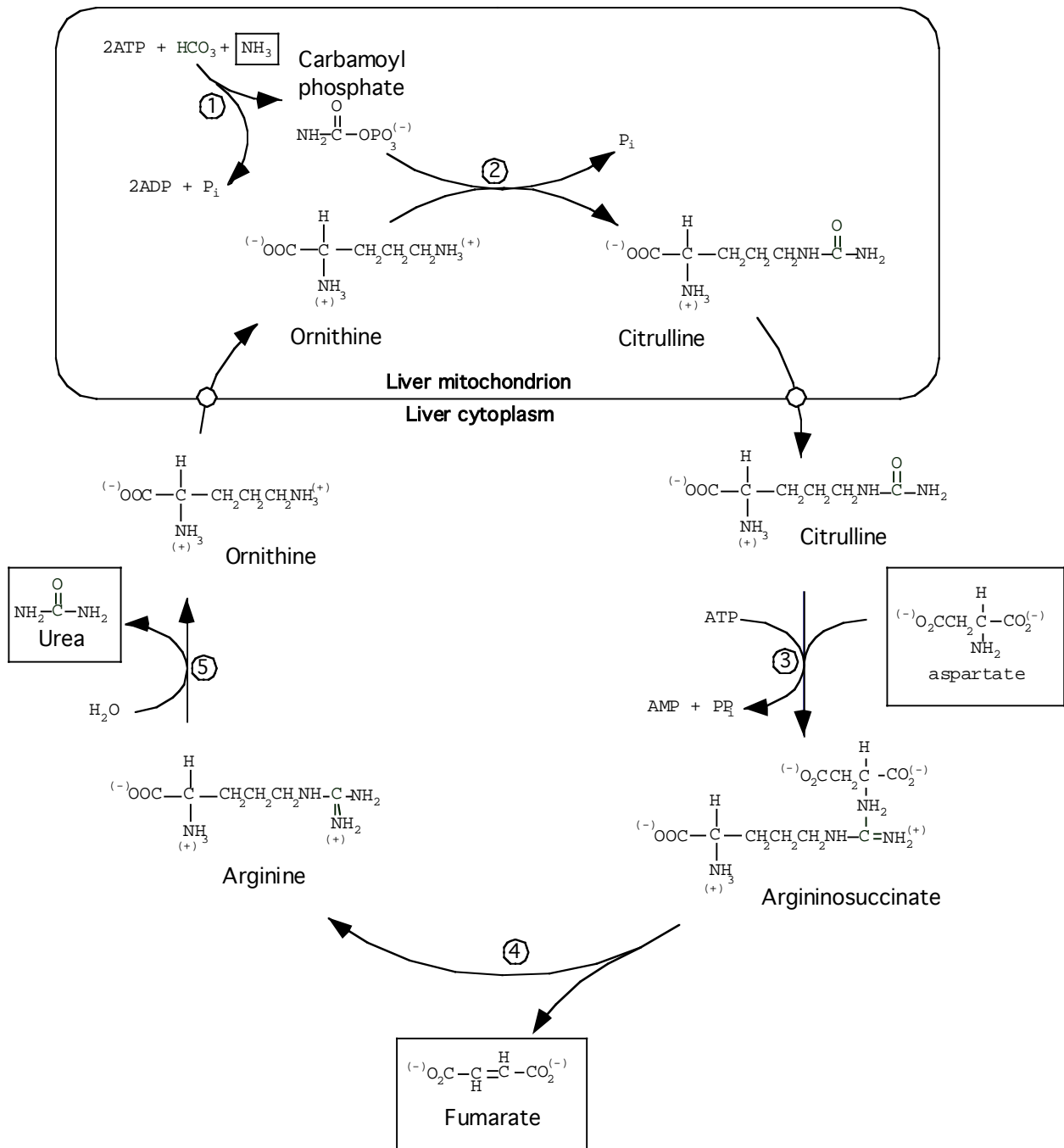
Complicated version, step 1: Transfer amine to pyridoxal phosphate (PLP)



Complicated version, step 2: Transfer amine to acceptor α -keto acid:



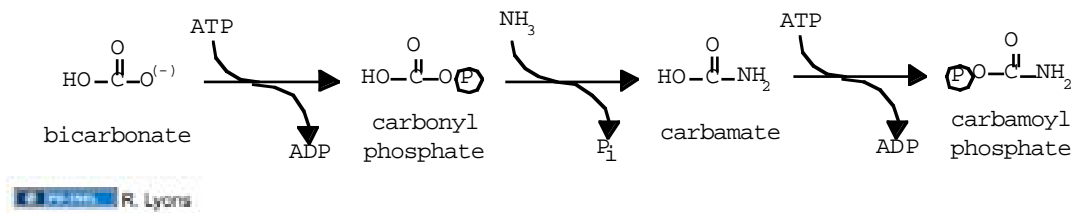
In peripheral tissues, catabolism of amino acids tends to form glutamate (i.e. α -ketoglutarate is the preferred N-acceptor)



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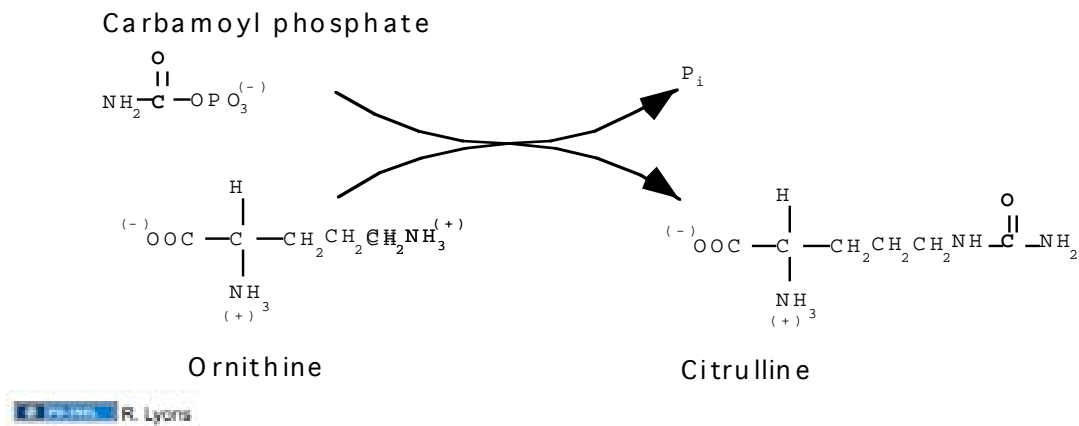
Step 1: Formation of carbamoyl phosphate.

Catalyzed by Carbamoyl Phosphate Synthetase I (CPS I), in liver mitochondria



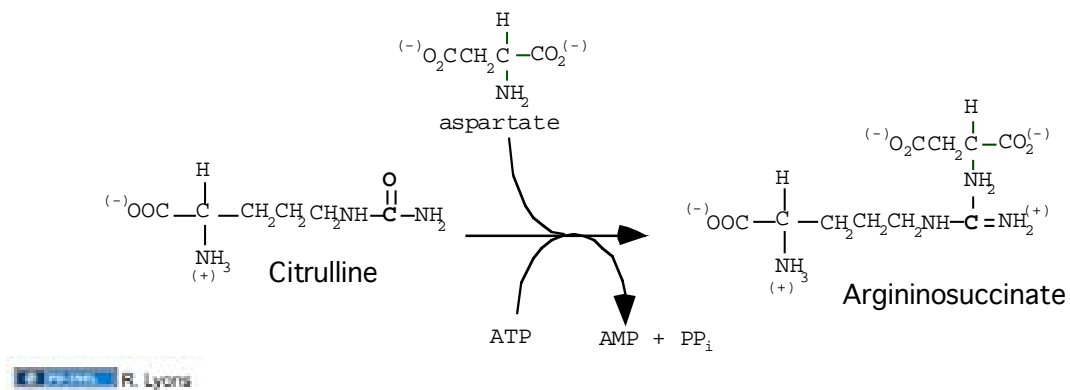
Step 2: Formation of Citrulline

Catalyzed by Ornithine Trans-Carbamoylase (OTC), in liver mitochondria



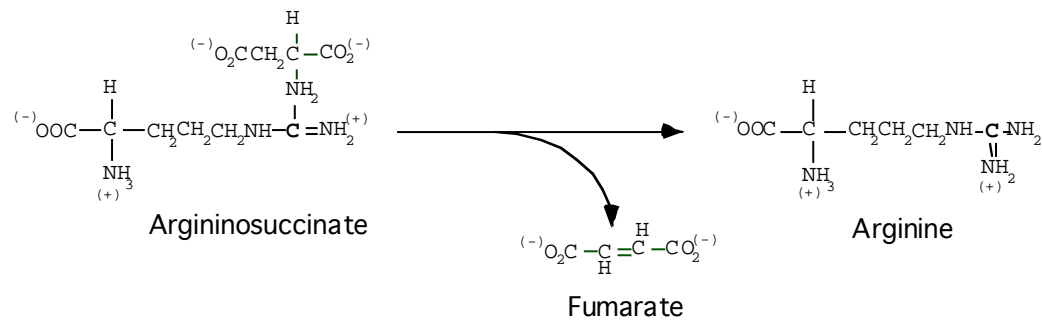
Step 3: Formation of Argininosuccinate

Catalyzed by Argininosuccinate Synthetase (AS), in liver cytoplasm



Step 4: Cleavage to form Arginine

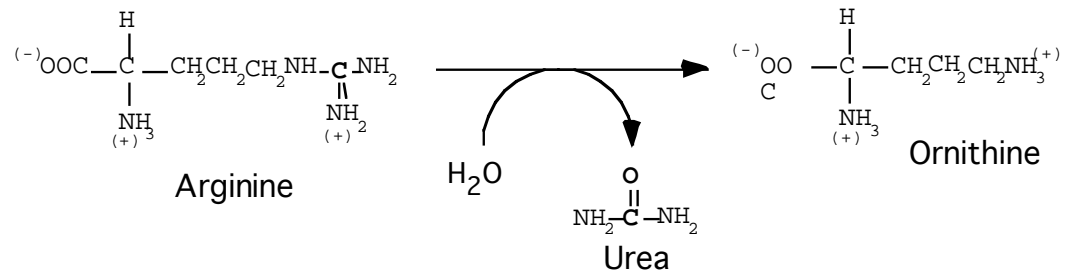
Catalyzed by Argininosuccinase, a.k.a. Argininosuccinate Lyase (AL), liver cytoplasm



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Step 5: Cleavage to release Urea

Catalyzed by Arginase (no abbreviation); liver cytoplasm



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f. Regulation and energetics of the urea cycle

(i) Rule of thumb: Any reaction that creates a new C-N bond costs one ATP.

- one ATP spent to put the amine on carbamoyl phosphate
- one ATP spent to put the phosphate on CP, which drives the next reaction (formation of citrulline; OTC)
- one ATP (*two* Hi-E bonds) used to make argininosuccinate.

(ii) The urea cycle costs energy BUT it produces energy as well:

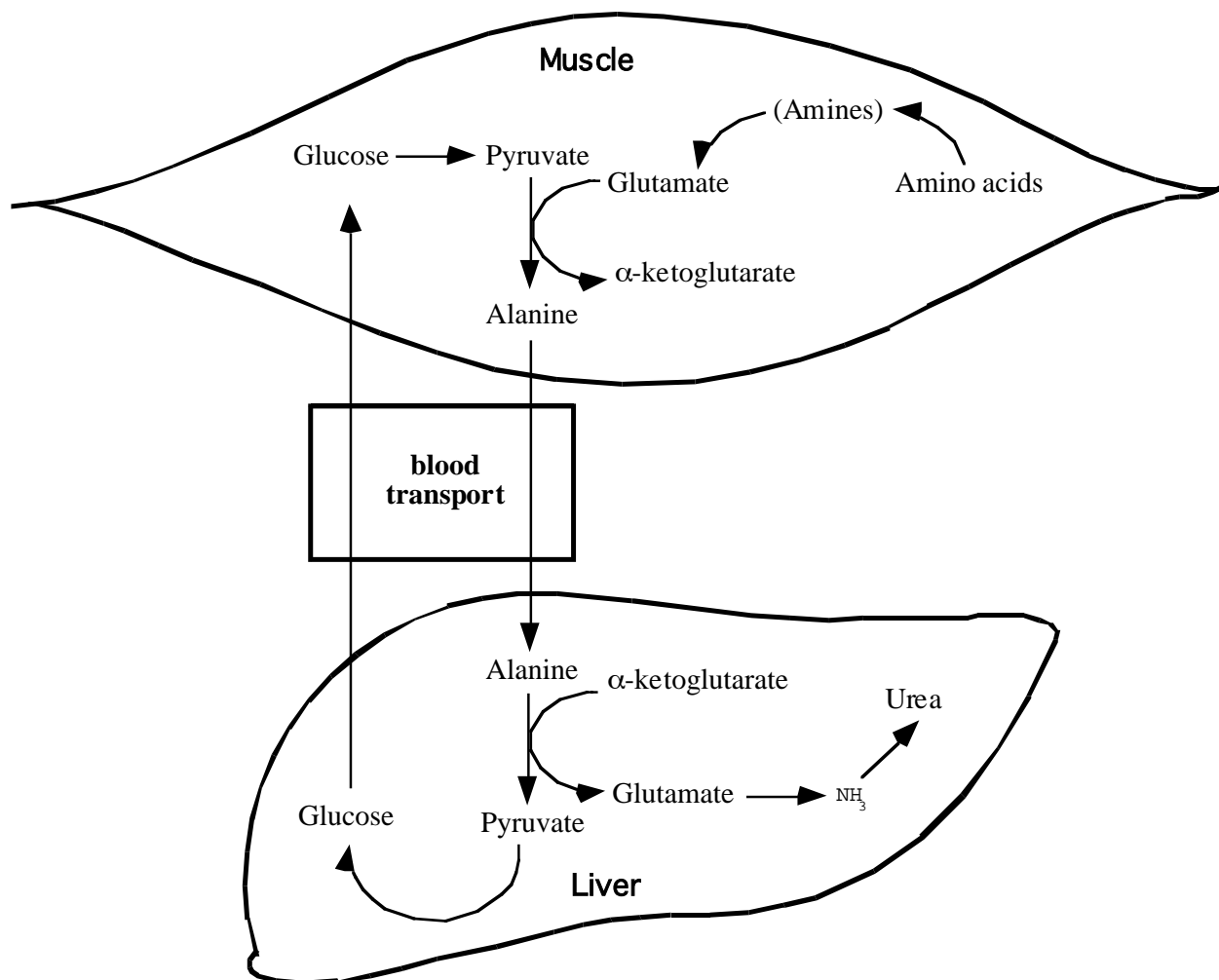
- Fumarate is oxidized in the Krebs cycle to Oxaloacetate, yielding one NADH (which can be used to make three ATP).
- The glutamate dehydrogenase reaction also yields NADH (also equivalent to three ATP).

g. Special role for alanine in energy metabolism in muscle: the **glucose-alanine cycle**.

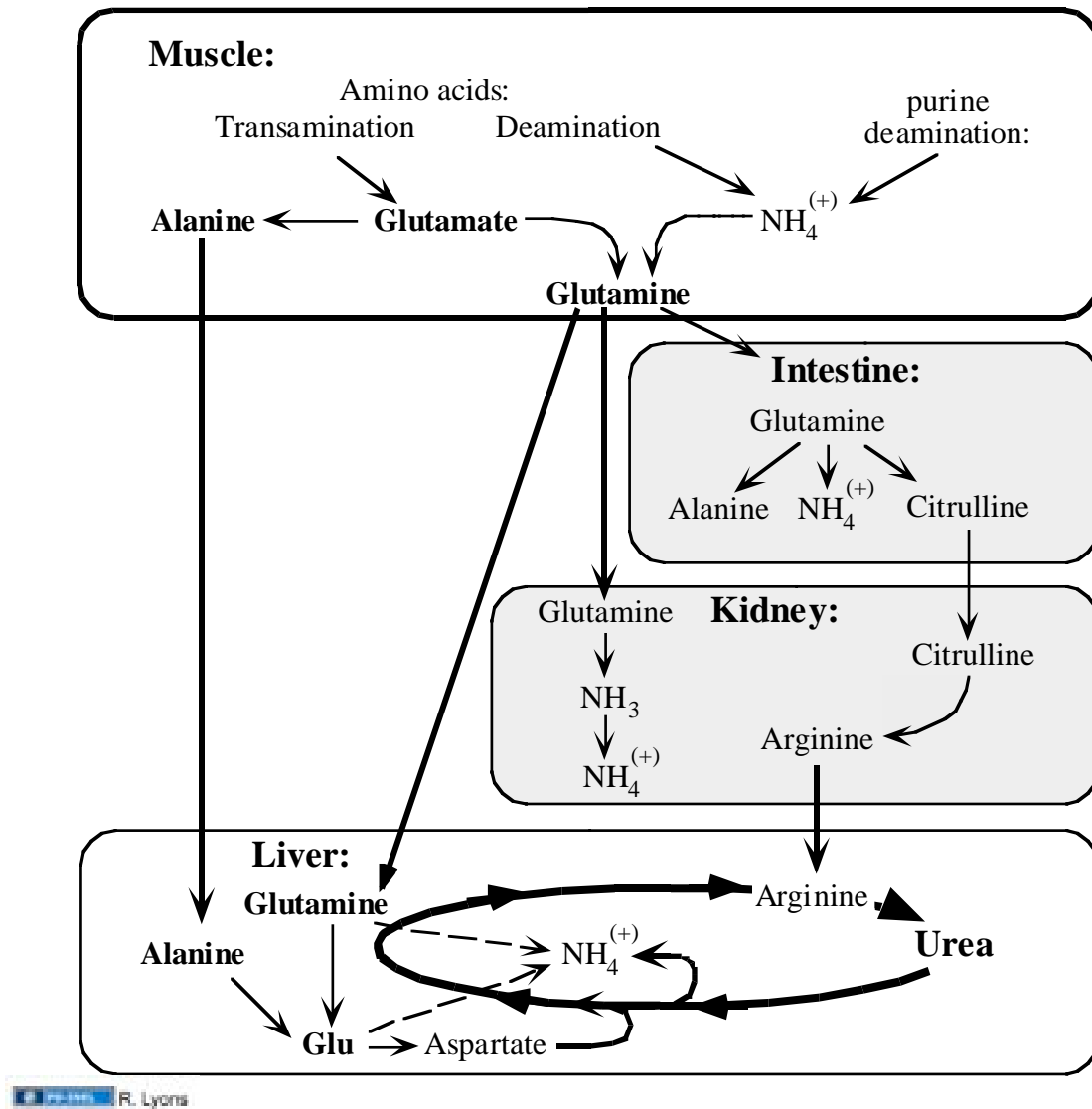
Muscles frequently utilize amino acids as energy sources, They are consequently particularly active for production of glutamine.

Under heavy energy demands, muscles convert to anaerobic energy production via simple glycolysis, producing excess pyruvate and lactate.

The excess pyruvate and ammonia can be converted to alanine and sent to the liver. There the amino groups are converted to urea and the pyruvate is used in gluconeogenesis to form glucose, which goes back to peripherals via blood.



h. Other organs involved in nitrogen metabolism:



i. Kidneys can break down glutamine:

- More acidic conditions increase that breakdown, less acid decreases it.
- The resulting ammonia is protonated to form ammonium ion, and excreted in the urine.
- This is thought to be a way to compensate for acidosis

ii. Kidneys and intestines jointly produce arginine

- Intestinal CPS 1 and OTC form citrulline, exported in the blood
- Kidneys take up citrulline, and forms arginine (using Argininosuccinate synthetase), which is again exported to the blood
- This mechanism is primarily used to synthesize Arg for purposes OTHER than ureagenesis, e.g. protein synthesis (see also other products of Arg, later).
- Massive resection of the small intestine can cause patients to become Arginine deficient

Sidebar: Why is ammonia toxic? (speculation only!)

Glutamate level is disturbed; and since it is a neurotransmitter, its levels may be critical to proper neural function.

Glutamate is recycled from post-synaptic neuron to pre-synaptic neuron as glutamine (via glutamine synthetase), and that step is probably disturbed by high ammonia levels.

Glutamate is also the precursor another neurotransmitter, gamma aminobutyric acid (GABA), which thus may be affected by hyperammonemia.

Alterations in glutamate levels may influence energetics. In addition, removing ammonia uses ATP (glutamine synthetase), also with potentially detrimental effects on energetics.

B. Inborn Defects of Nitrogen Metabolism (Urea Cycle)

1. Generalized features of urea cycle defects:

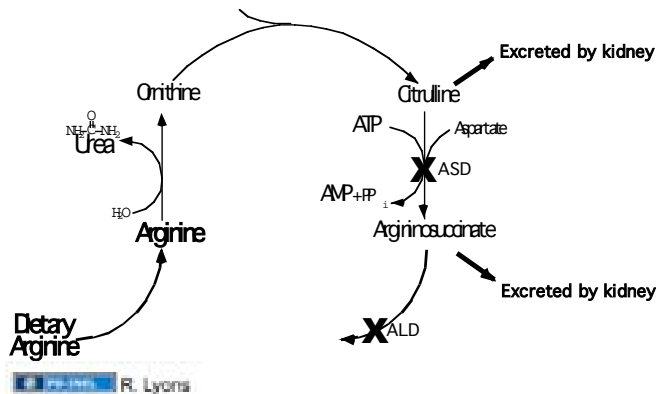
- a. Loss of an enzyme causes substrate to build up
The pathway backs up all the way to ammonia, which is toxic
- b. Complete absence of any of these enzymes causes neonatal death
- c. Classic presentation:
Infant displaying irritability, hypotonia, lethargy, vomiting, ataxia, delayed growth
Older child or adult displays similar symptoms after precipitating event (e.g. feast). If untreated, progresses to spasticity, mental retardation, coma, death.

2. Diagnosis:

- a. All of the deficiencies may present with hyperammonemia
- b. Determine which enzyme by substrate concentrations:
CPSD: only hyperammonemia; diagnose by elimination
OTCD: hyperammonemia with orotate in blood, urine
ASD: elevated citrulline in blood, urine
ALD: elevated argininosuccinate in blood, urine
AD: elevated arginine in blood, urine

3. Treatment:

- a. Dialysis to reduce the blood ammonia levels
- b. Intravenous sodium benzoate and phenylacetate to provide for nitrogen disposal (both compounds bind amino acids and are then excreted.)
- c. Supplementation of arginine



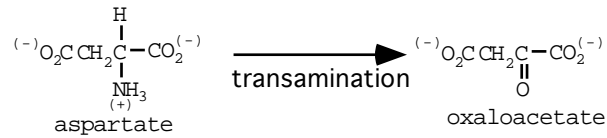
- d. Minimize gut production of ammonia - levulose or antibiotics
- e. Low protein diet (long-term solution)

C. Amino acid carbon backbone - degraded for metabolic fuel

1. Glucogenic versus ketogenic amino acids

2. Sometimes mere transamination can produce easily-degraded compounds:

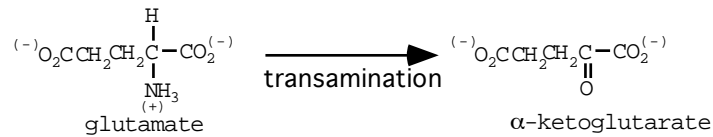
a) aspartate forms oxaloacetate



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(can also degrade via Urea cycle)

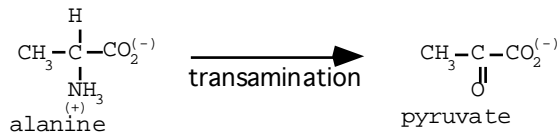
b) glutamate forms alpha-ketoglutarate



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(can also degrade via oxidative deamination)

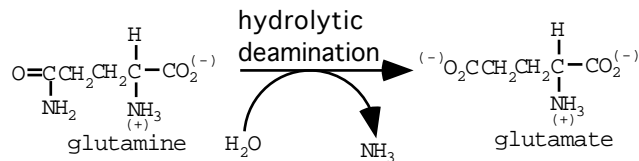
c) alanine forms pyruvate



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3. glutamine and asparagine deaminated to glutamate and aspartate (as above).

a) glutaminase reaction: glutamine + H₂O --> glutamate + NH₄⁺

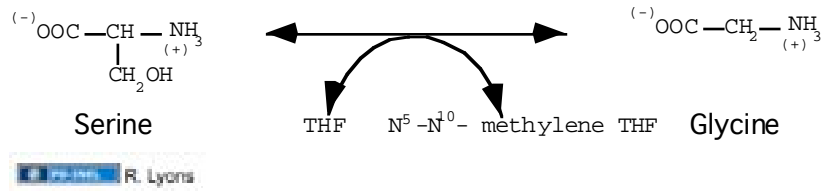


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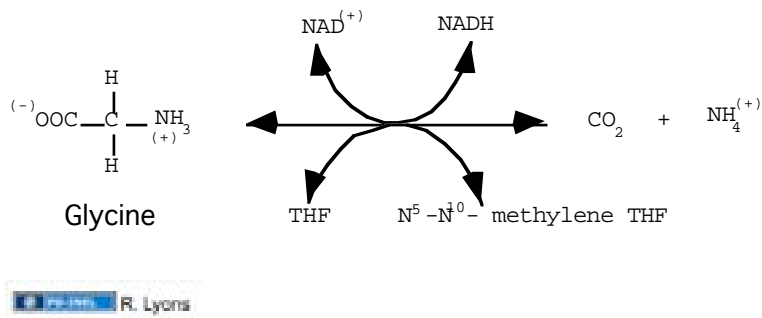
b) asparaginase reaction: similar to glutaminase, produces aspartate.

4. Other amino acids: see following figures:

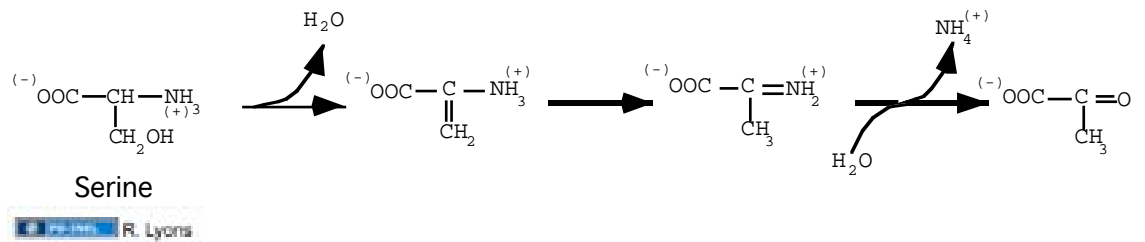
Serine hydroxymethyl transferase:



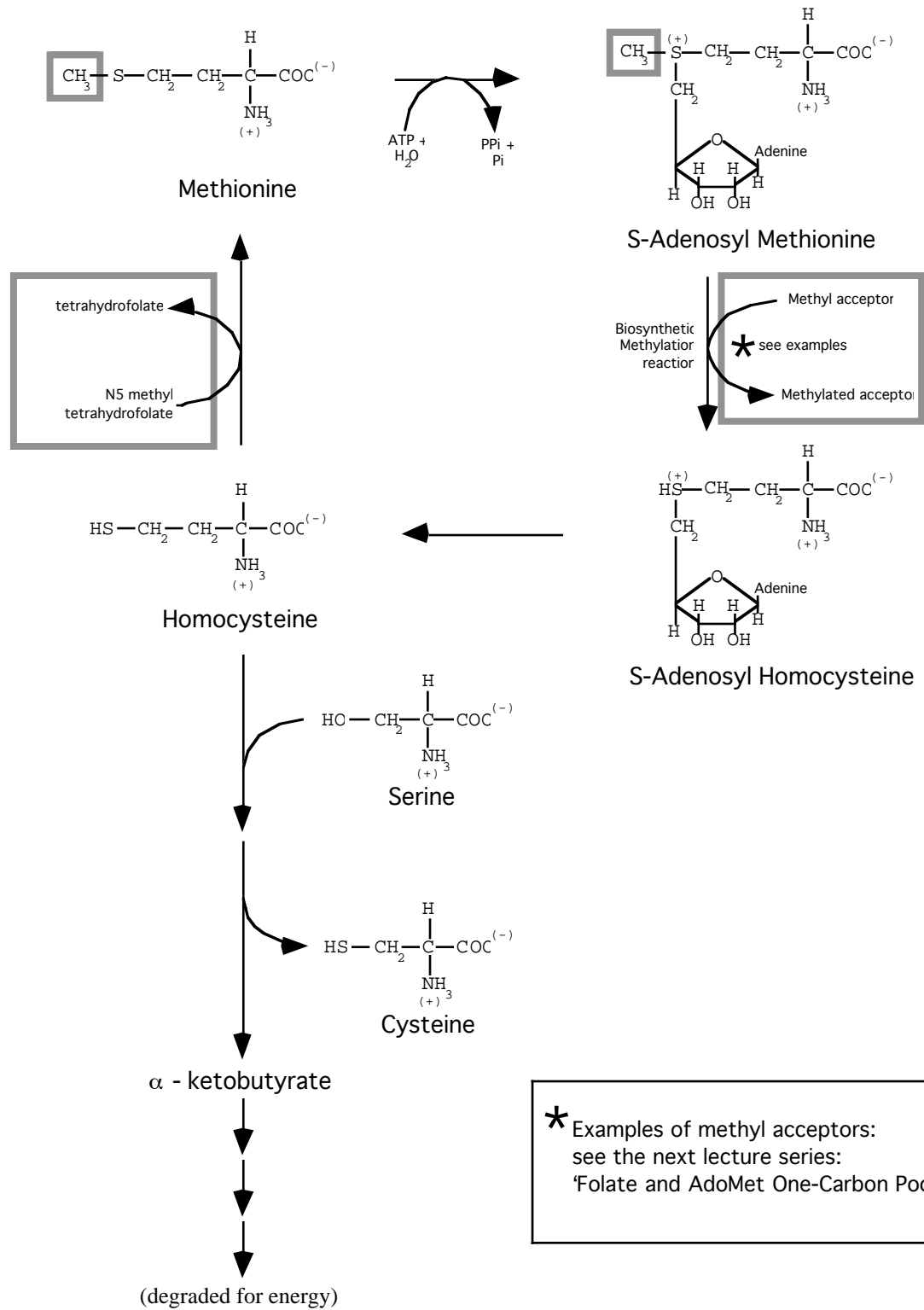
Glycine Synthase (a.k.a. Glycine Cleavage System):



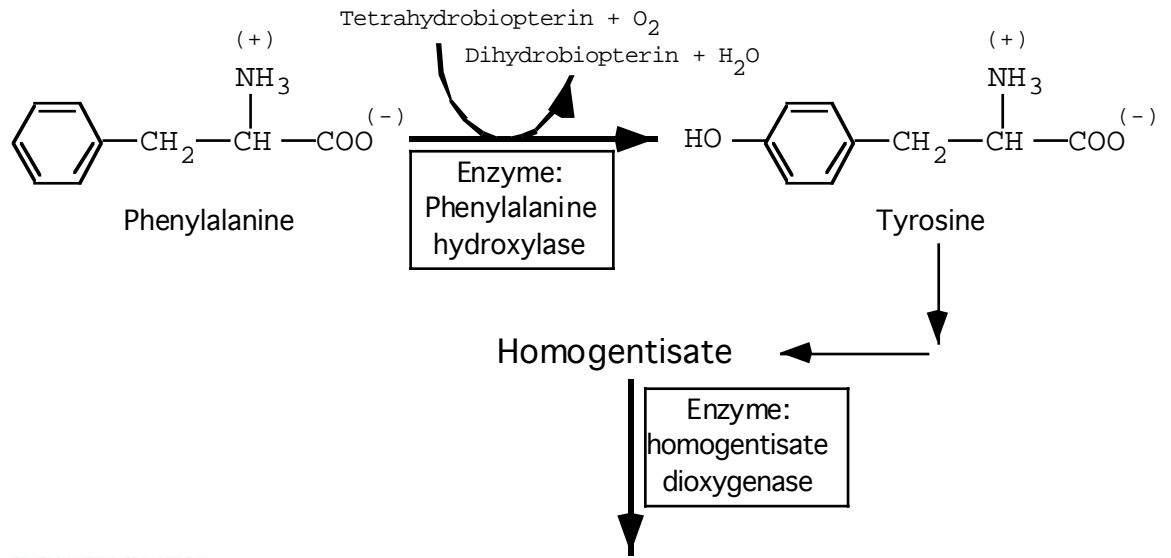
Serine dehydratase:



Methionine Cycle and Biological Methyl Groups

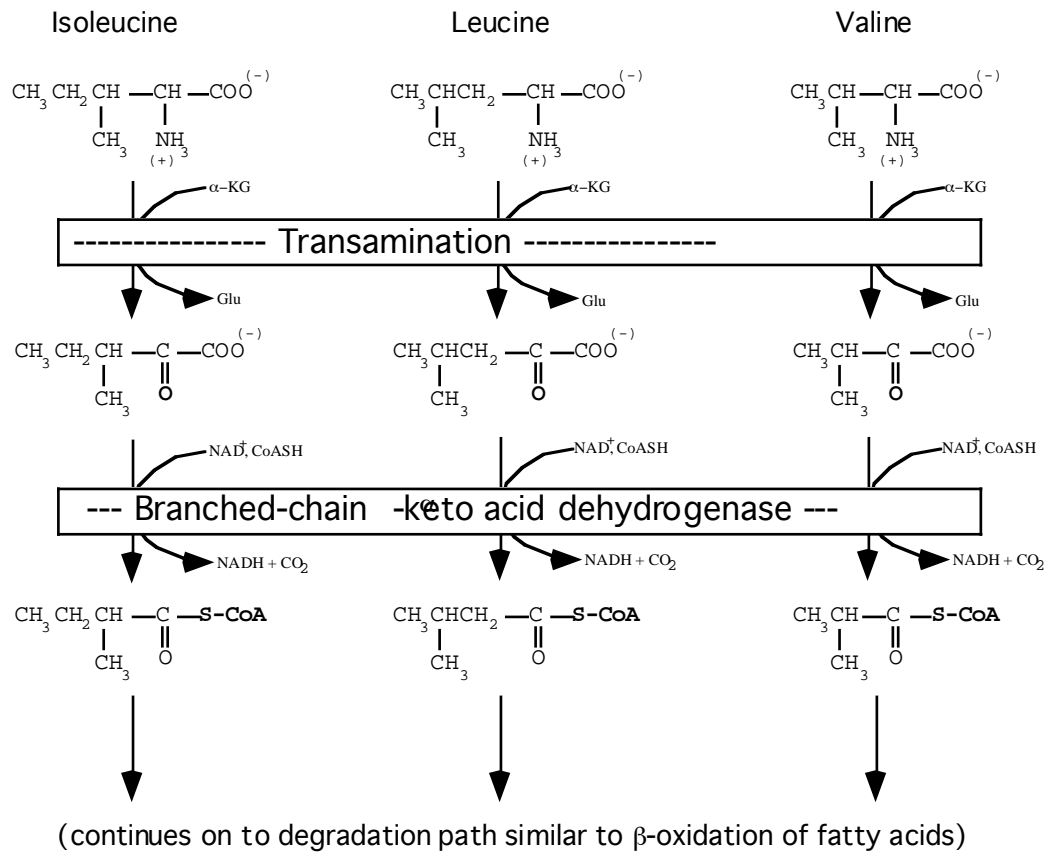


Degradation of Phenylalanine and Tyrosine:



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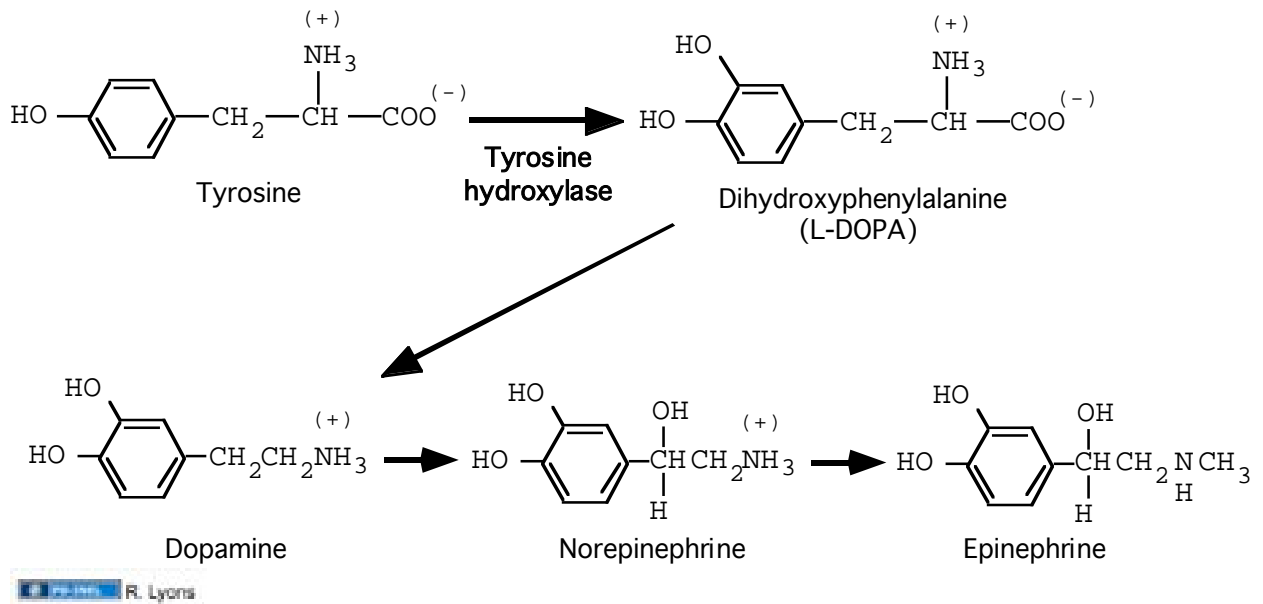
Branched-chain amino acids:



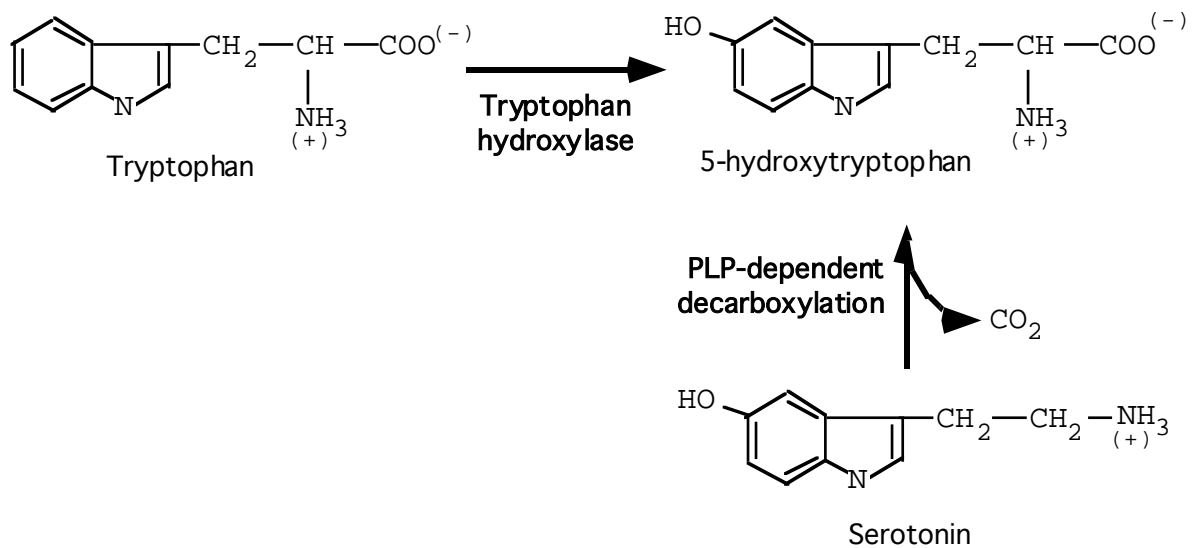
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D. Precursors for other important biomolecules - bioactive amines

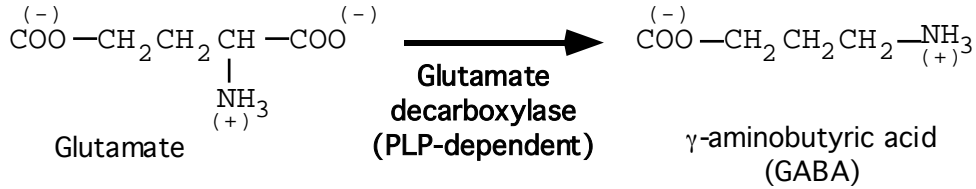
Tyrosine:



Tryptophan:

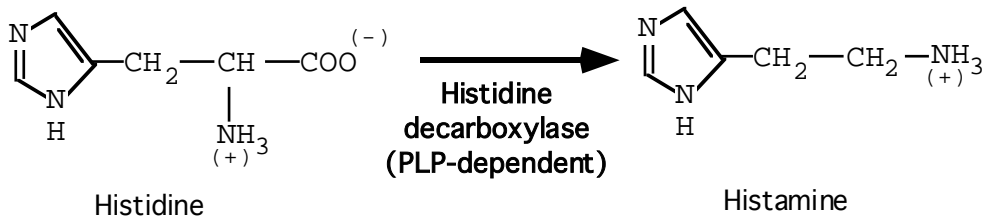


Glutamate:



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Histidine:



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E. A few other important products derived from amino acids:

- Arginine is converted to NO, Agmatine, creatine and creatinine
- Glutamine, cysteine and glycine are used to make glutathione
- Glycine is used in biosynthesis of heme
- Glutamine, glycine and aspartate contribute to purine nucleotide synthesis
- Aspartate is used in pyrimidine nucleotide biosynthesis

III. Amino acid biosynthesis

Essential vs. non-essential amino acids:

A. Non-essential - we can synthesize adequate amounts of:

Alanine, Glycine, Serine, Glutamate, Aspartate, Glutamine, Asparagine, Proline, (Cys, Tyr - usually considered non-essential, but it's semantics - depends on sufficient Met, Phe)

B. Essential: all the rest - Arginine (conditionally), Phenylalanine (enough to make Tyrosine, too), Methionine (enough to make Cysteine as well), Histidine, Isoleucine, Leucine, Lysine, Threonine, Valine, Tryptophan.

For each of the non-essential amino acids listed above, review the degradation pathways already discussed to identify the probable biosynthesis route (skip proline - that wasn't really covered).