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Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.

Nitrogen Metabolism (and Related Topics)

- Amino Acid Metabolism (Nitrogen metabolism)
- Folate Metabolism (“One-Carbon pathways”)
- Nucleotide Metabolism

Dr. Robert Lyons

Assistant Professor, Biological Chemistry

Director, DNA Sequencing Core

There are also PDF's of class handouts with supplemental information available in the table of contents for this course.

Supplementary study material on the Web:

<http://seqcore.brcf.med.umich.edu/mcb500>

Amino Acid metabolism

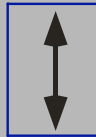
Amino acids



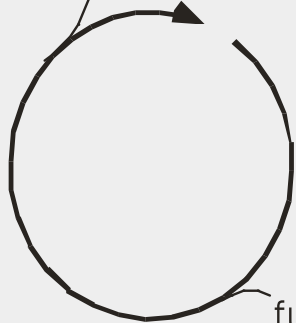
Glu, Gln,
Asp, NH₃



Urea



oxaloacetate



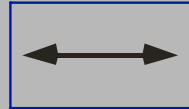
fumarate

TCA Cycle

Folate metabolism

Methylene
THF

Met
Cycle



Purines

DNA
RNA

Pyrimidines

Uric Acid

(energy)

Nucleic Acid metabolism

Protein Degradation:

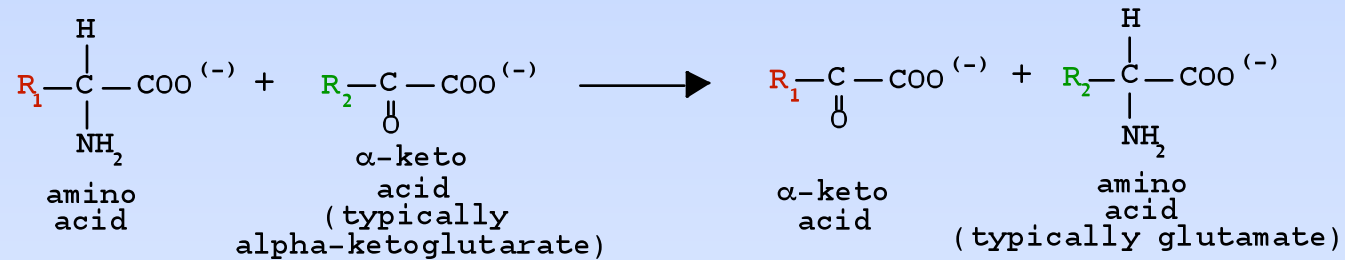
- Endogenous proteins degrade continuously
 - Damaged
 - Mis-folded
 - Un-needed
- Dietary protein intake - mostly degraded

Nitrogen Balance - expresses the patient's current status - are they *gaining* or *losing* net Nitrogen?

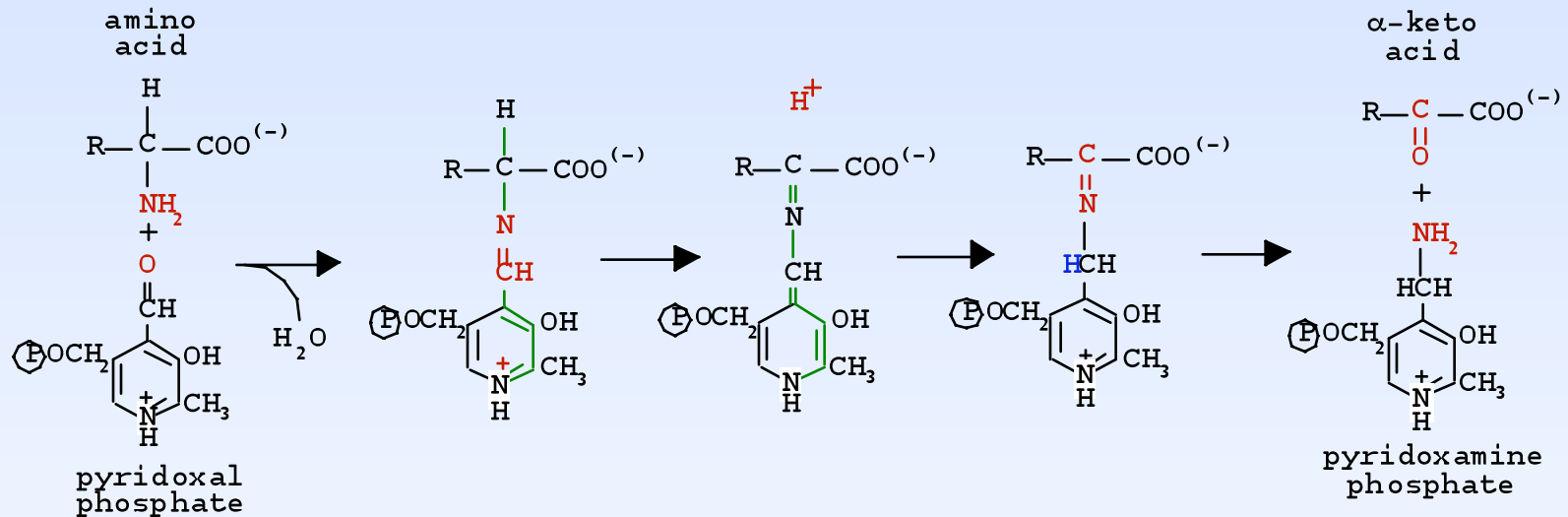
Transaminases

Collect Amines

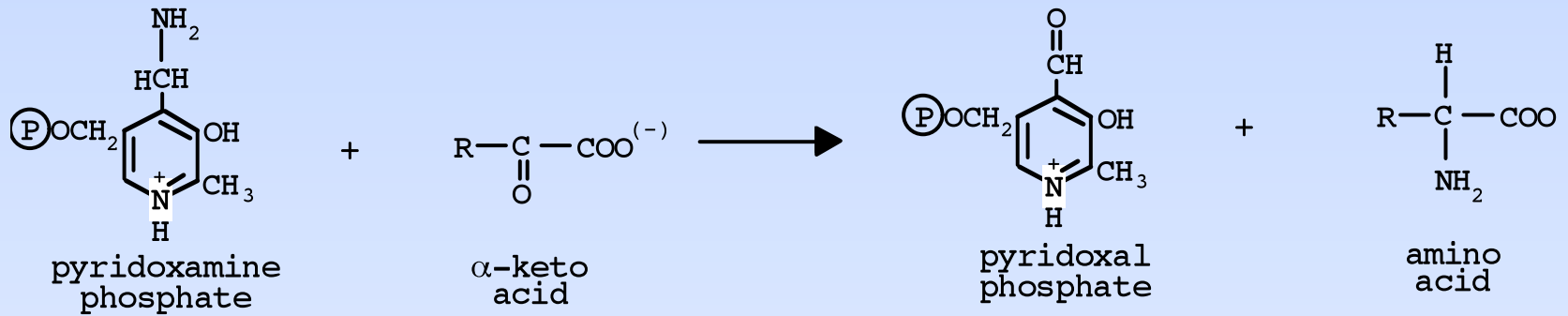
General reaction overview:



Details of reaction mechanism:



Transfer the amine back to an acceptor α -keto acid



In peripheral tissues, transaminases *tend* to form Glutamate when they catabolize amino acids

In other words, alpha-ketoglutarate is the preferred acceptor, and Glutamate is the resulting amino acid:

Some amino acid + α -ketoglutarate \rightarrow some alpha keto acid + Glutamate

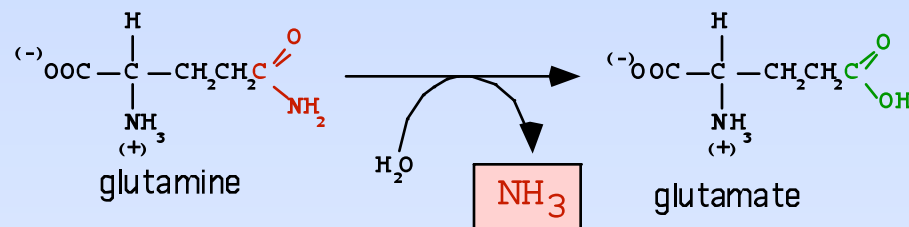
Glutamate can donate its amines to
form other amino acids as needed

A specific example - production of Aspartate in liver
(described a few slides from now):



In the Liver: Precursors for Urea Cycle

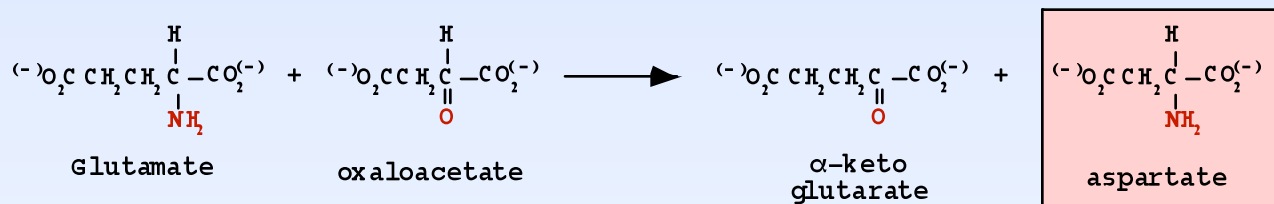
Glutamine is hydrolyzed to glutamate and ammonia:

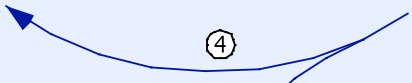
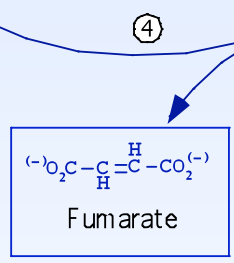
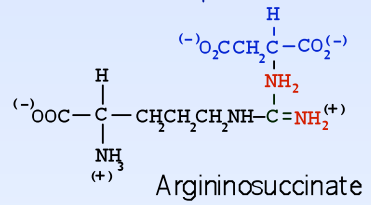
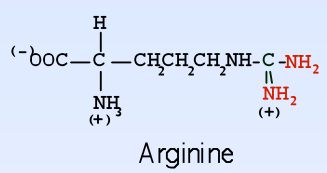
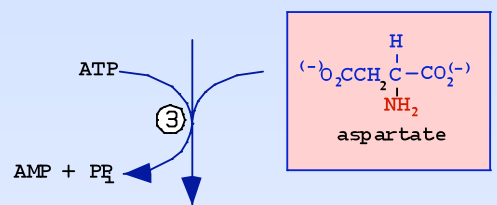
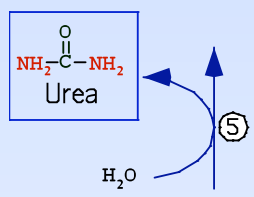
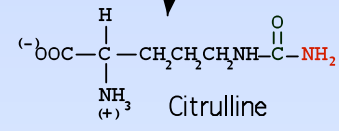
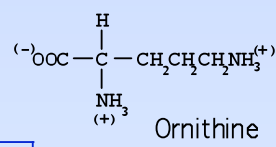
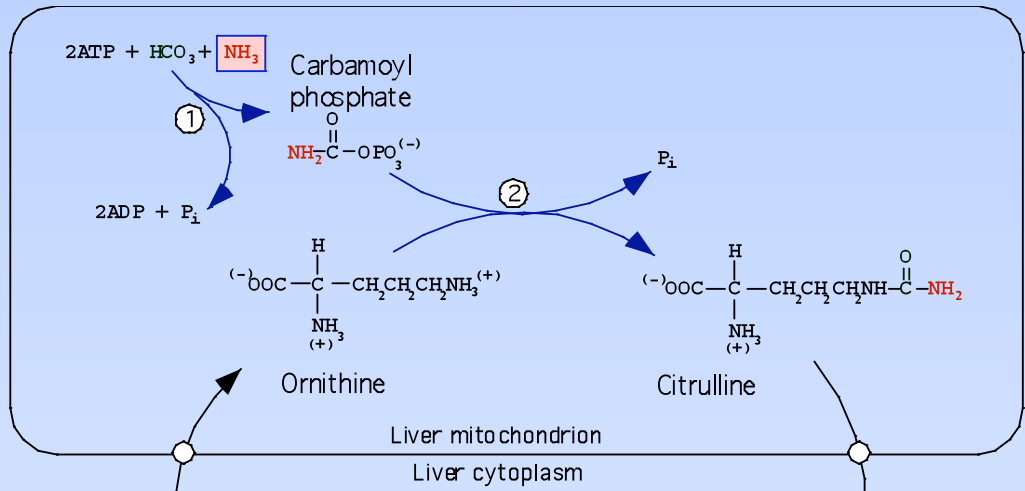


Ammonia can also be formed by the glutamate dehydrogenase reaction and several other reactions as well.

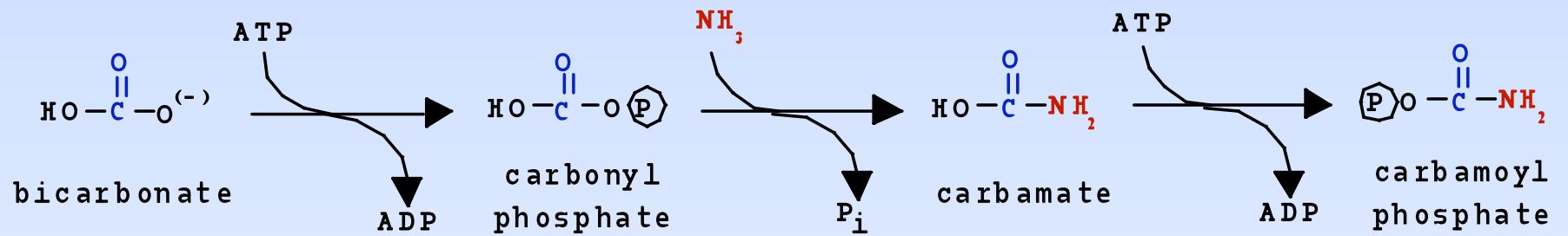
Glutamate donates its amino group to form aspartate:

Glutamate-aspartate aminotransferase:



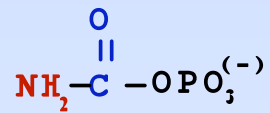


Carbamoyl phosphate synthetase I

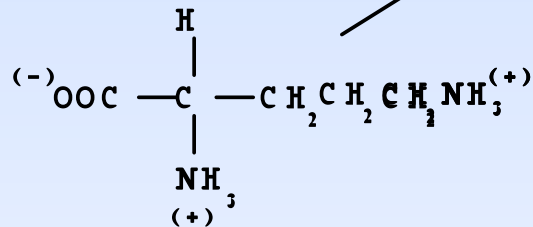


Ornithine Transcarbamoylase

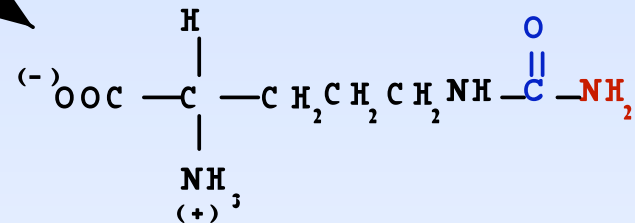
Carbamoyl phosphate



P_i

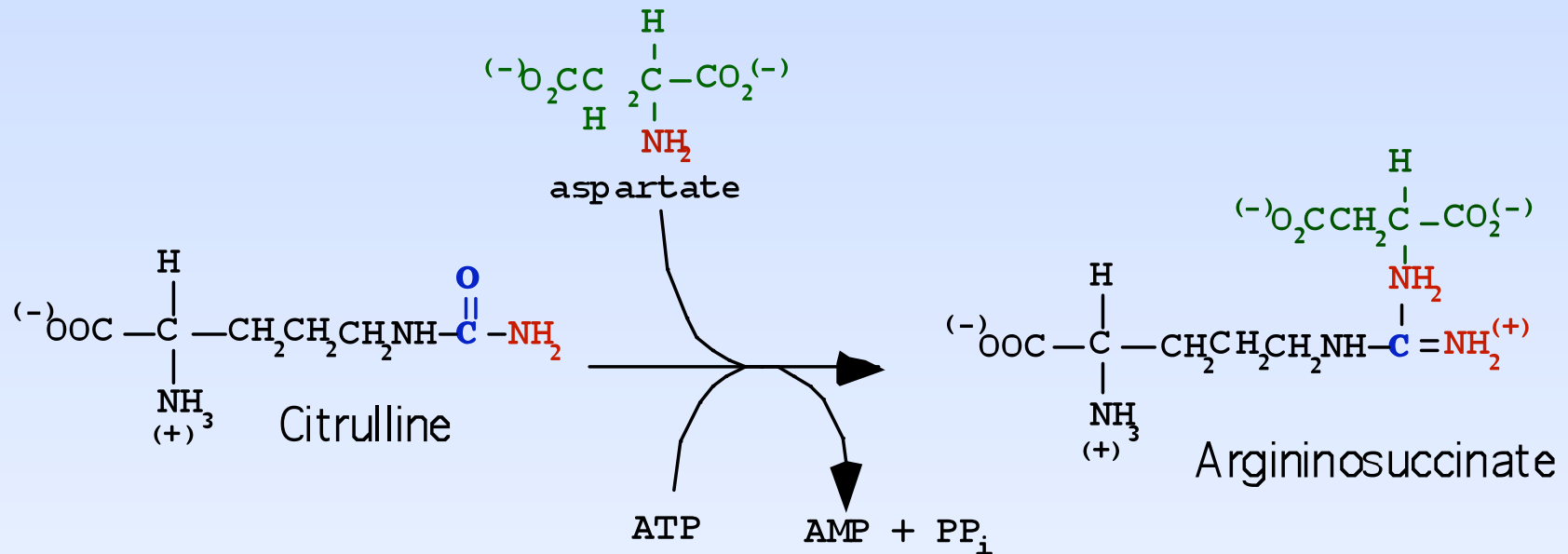


Ornithine

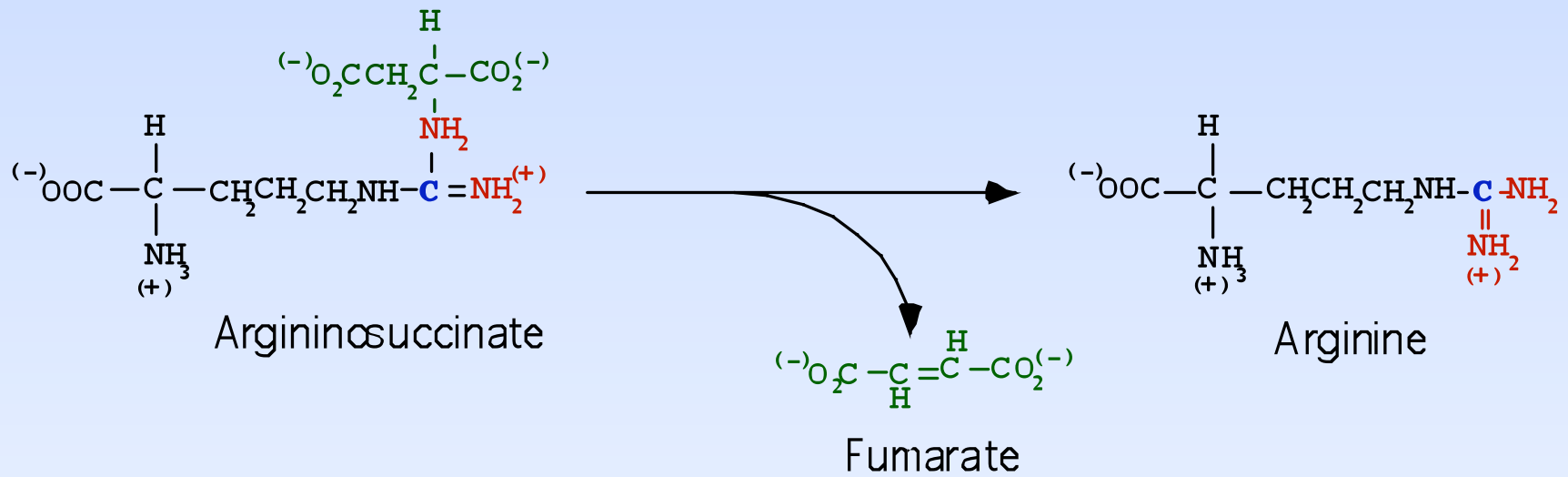


Citrulline

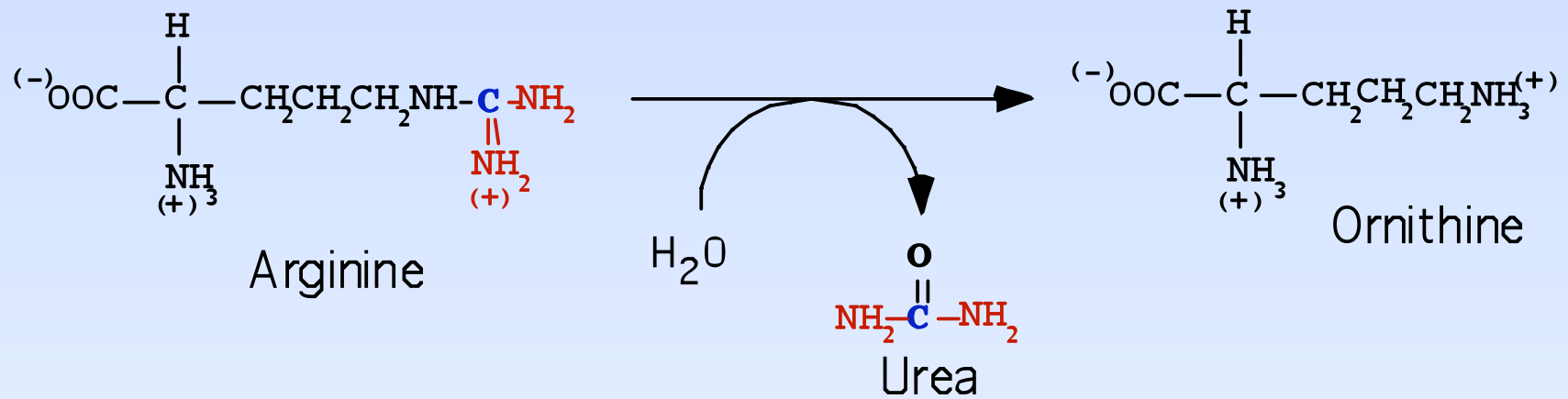
Argininosuccinate synthetase

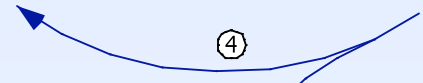
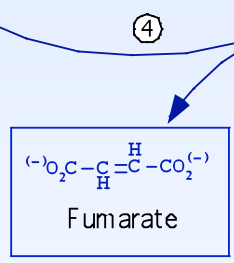
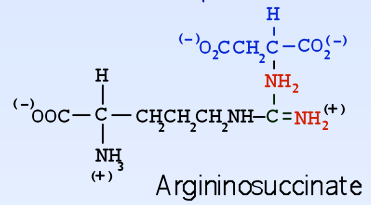
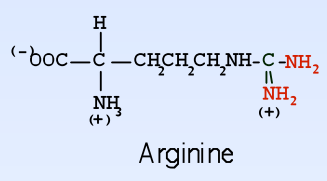
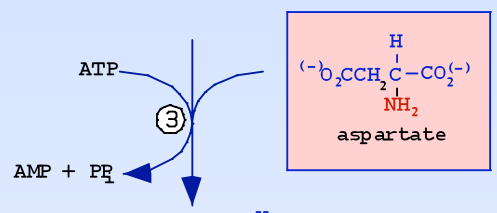
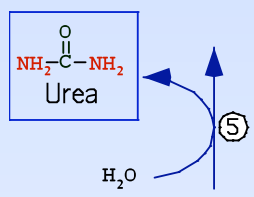
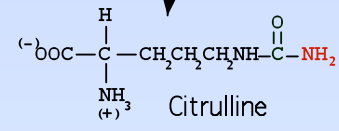
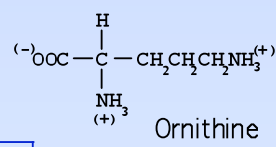
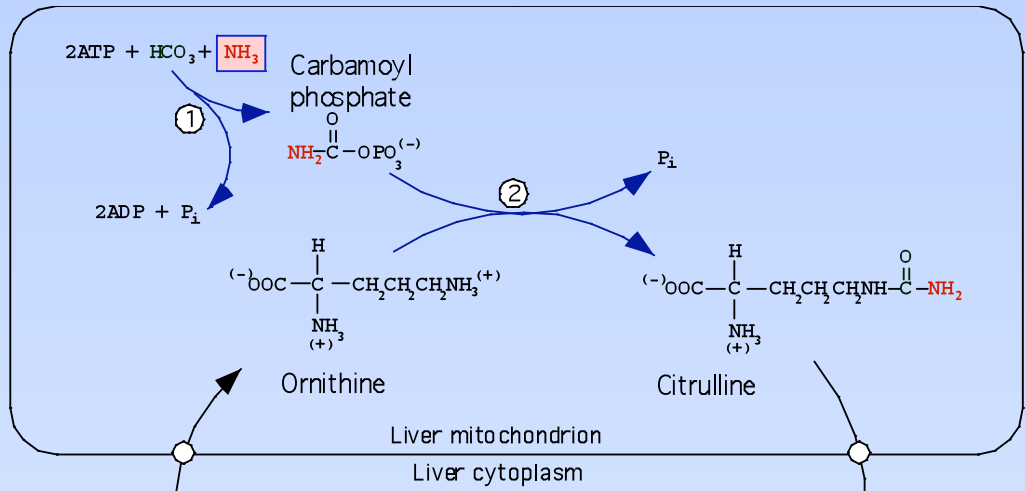


Argininosuccinate lyase

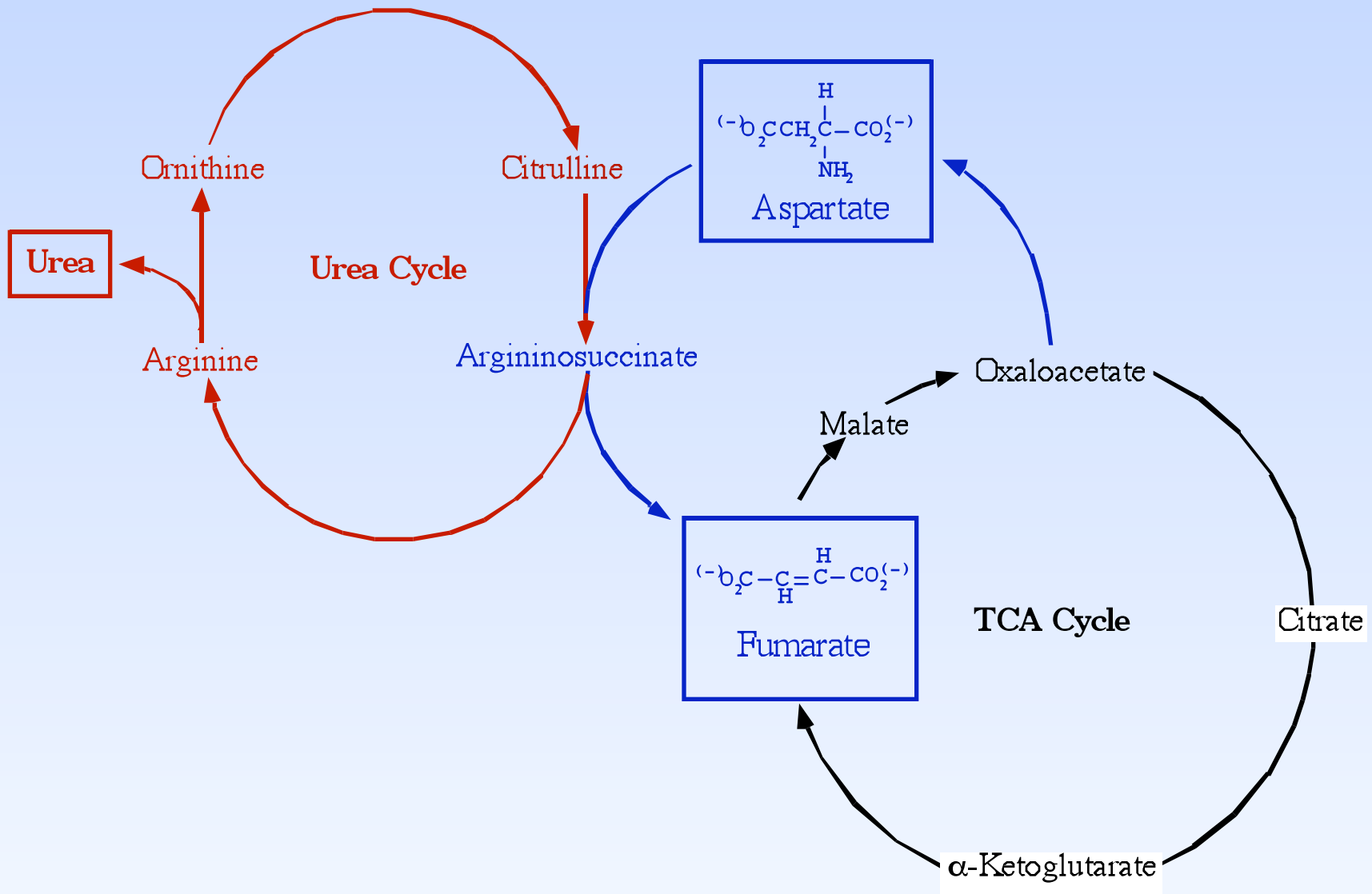


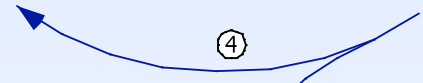
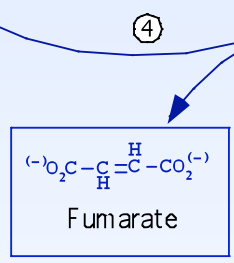
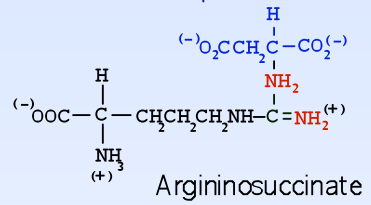
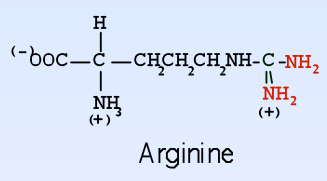
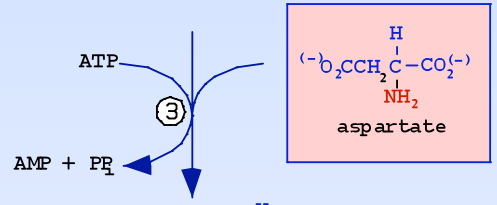
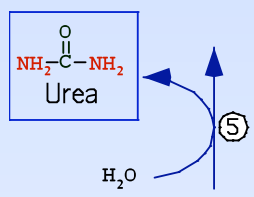
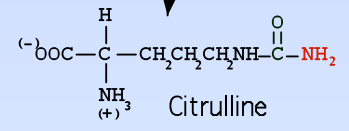
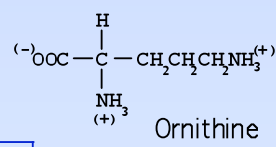
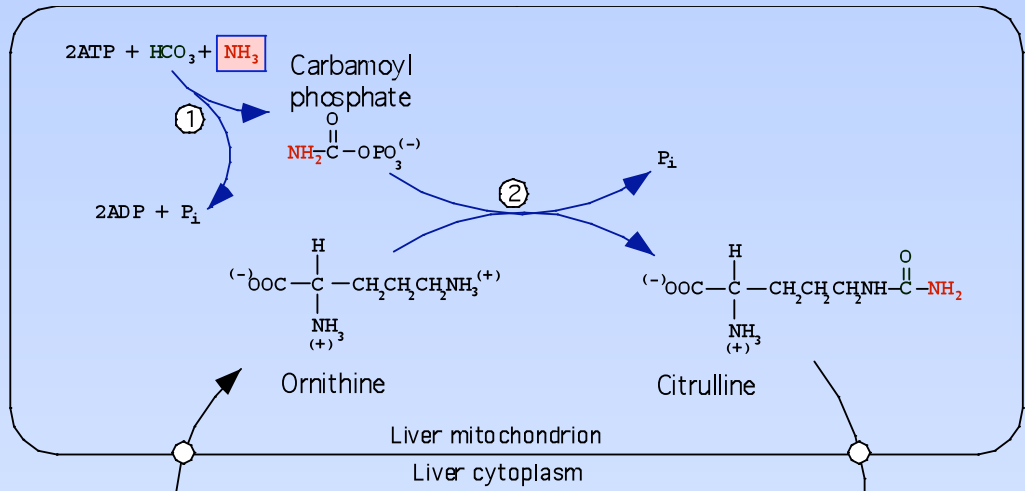
Arginase



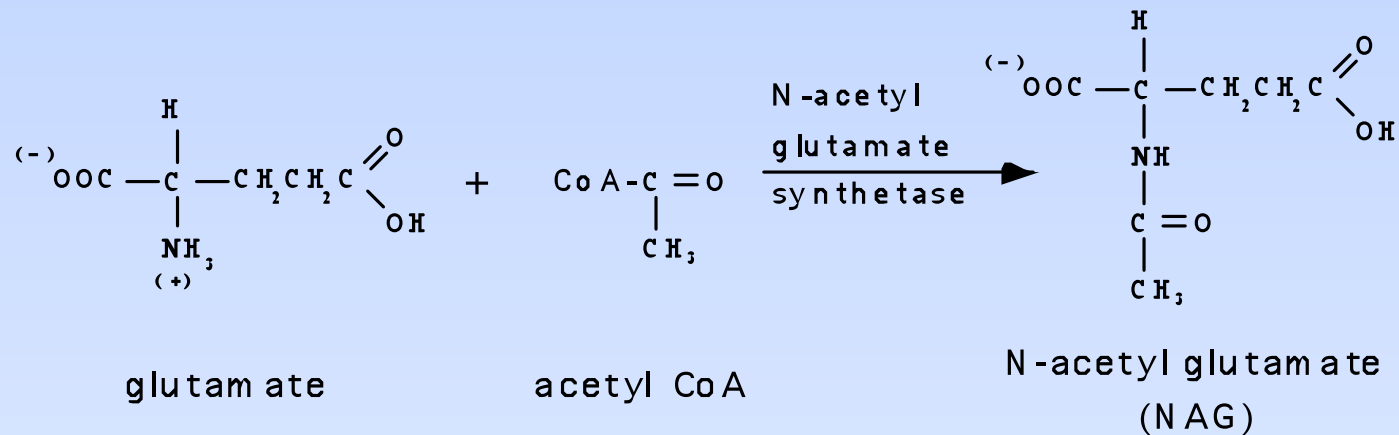


Urea Cycle Connects to TCA Cycle

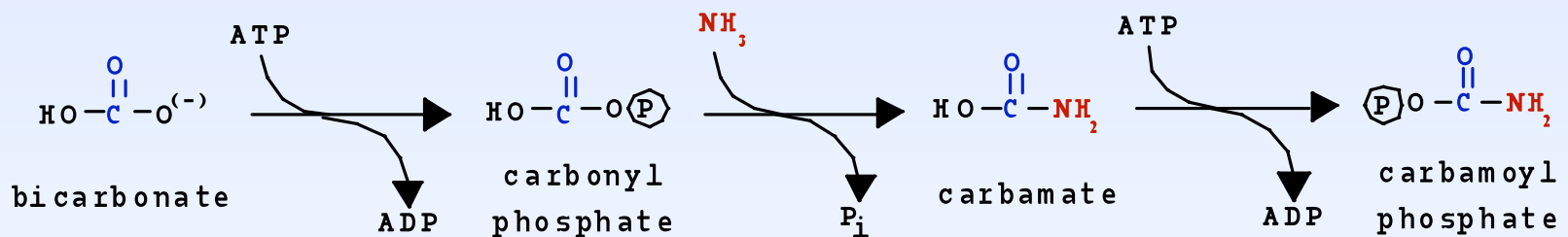


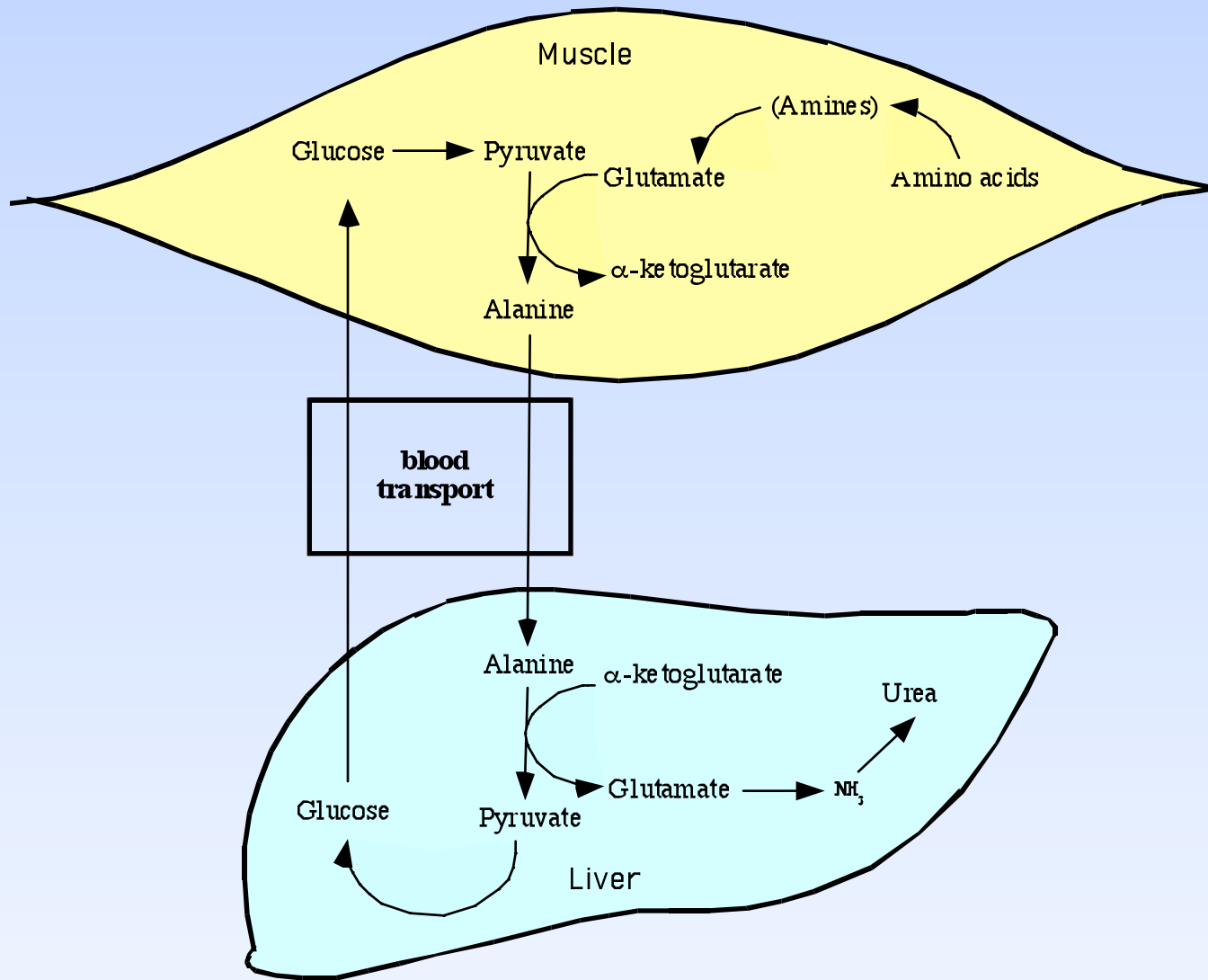


CPS I is Stimulated by NAG

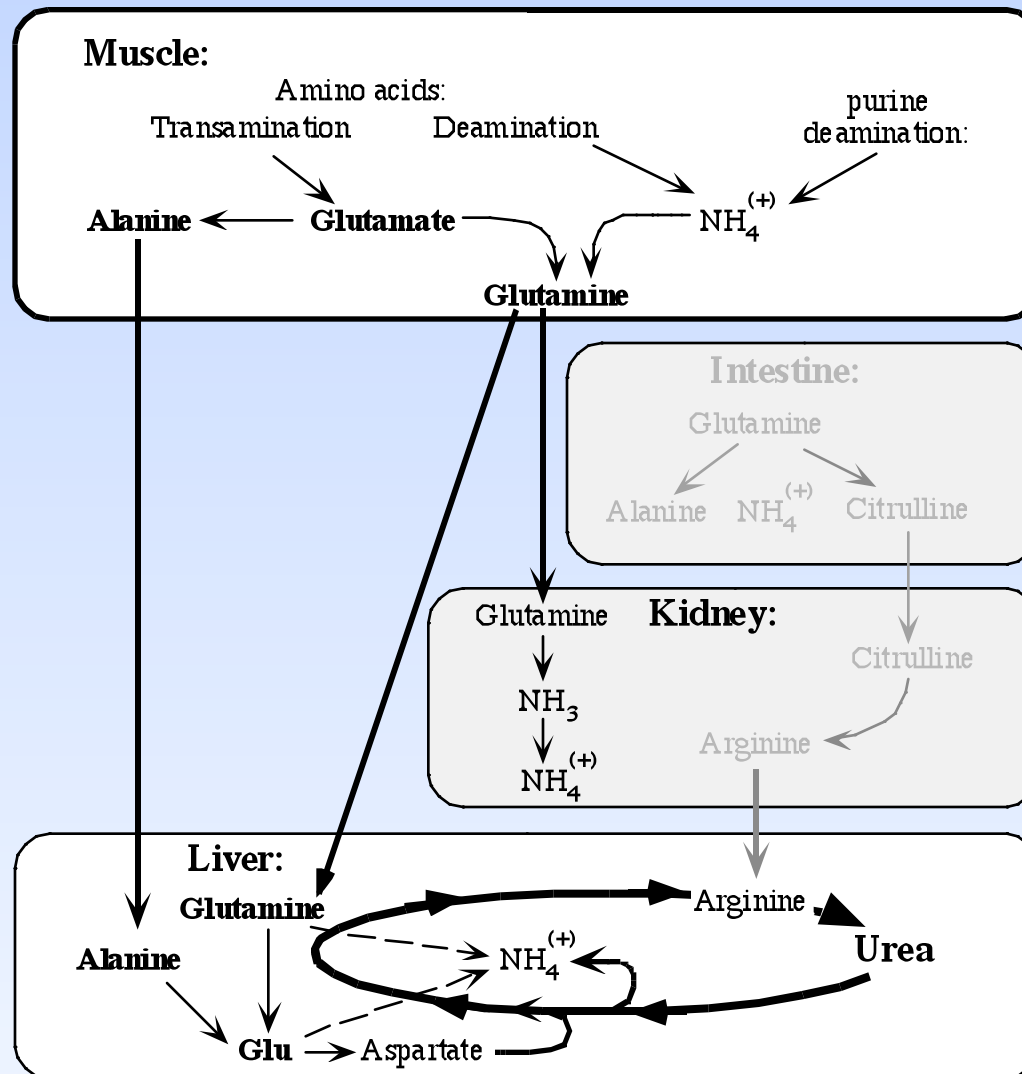


(repeating the figure from page 3 of your handout)





Complicating the picture: Other tissues may be involved



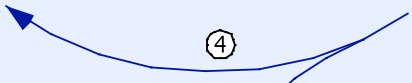
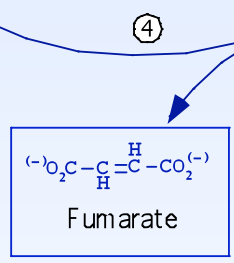
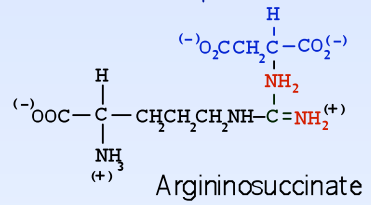
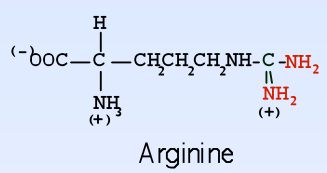
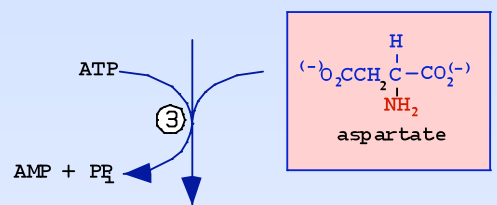
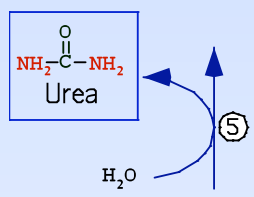
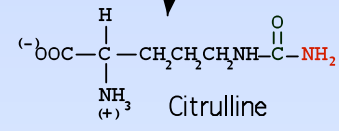
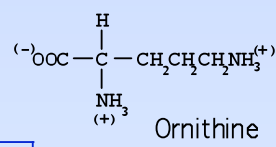
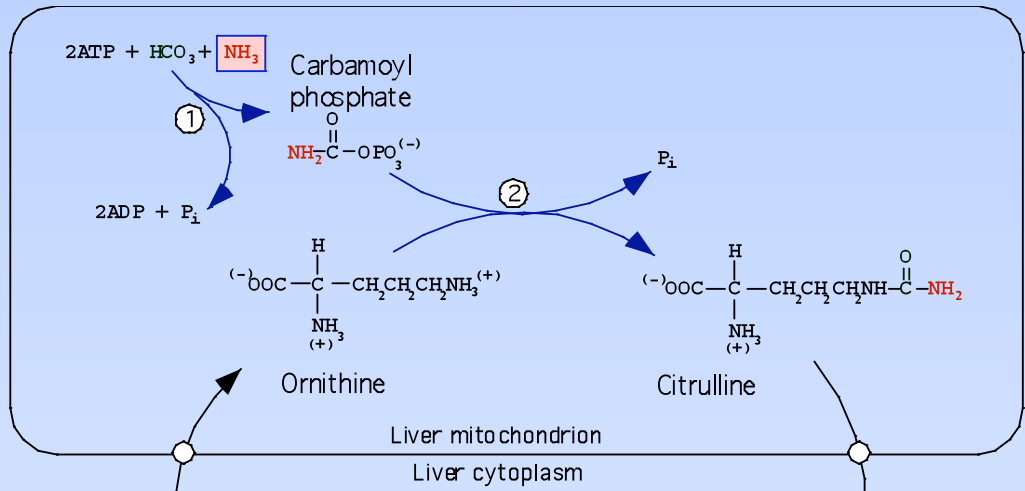
Why is Ammonia Toxic?

Why is Ammonia Toxic?

- Possible neurotoxic effects on glutamate levels (and also GABA)
(due to shifting equilibria of reactions involving these compounds)

Why is Ammonia Toxic?

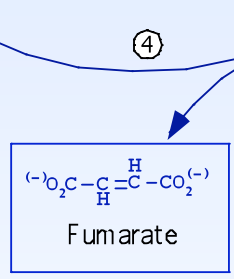
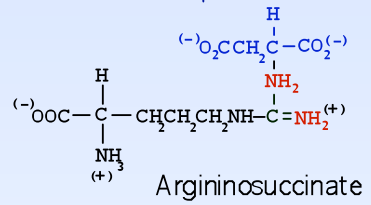
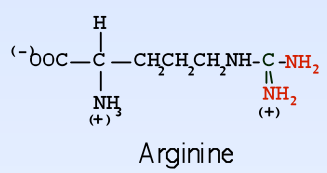
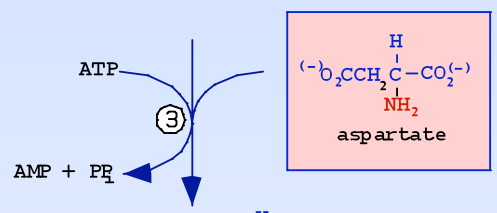
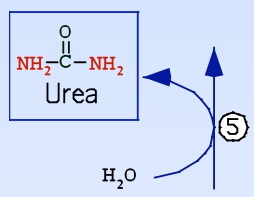
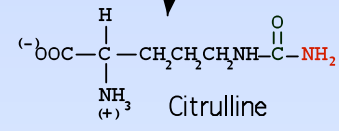
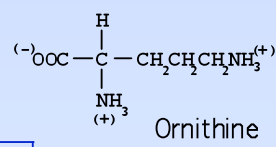
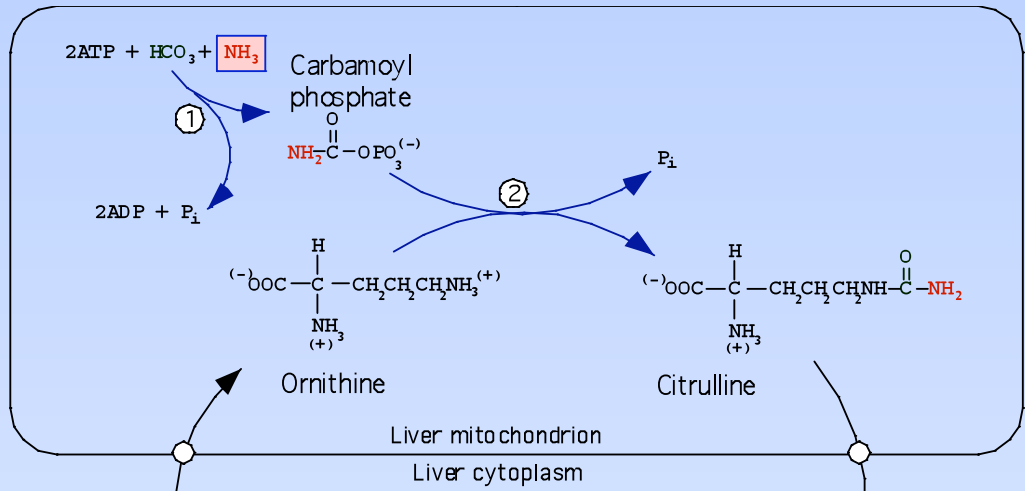
- Possible neurotoxic effects on glutamate levels (and also GABA)
(due to shifting equilibria of reactions involving these compounds)
- Possible metabolic/energetics effects:
 - alpha-ketoglutarate levels
 - glutamate levels
 - glutamine



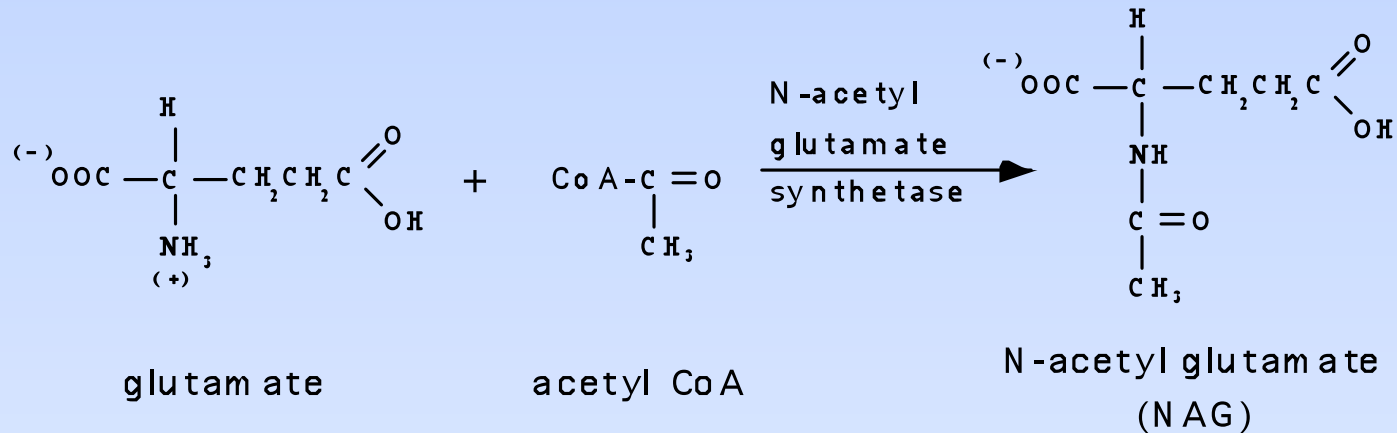
Inherited Defects of Urea Cycle Enzymes: Diagnosis

Defects are diagnosed based on the metabolites seen in the blood and/or urine.

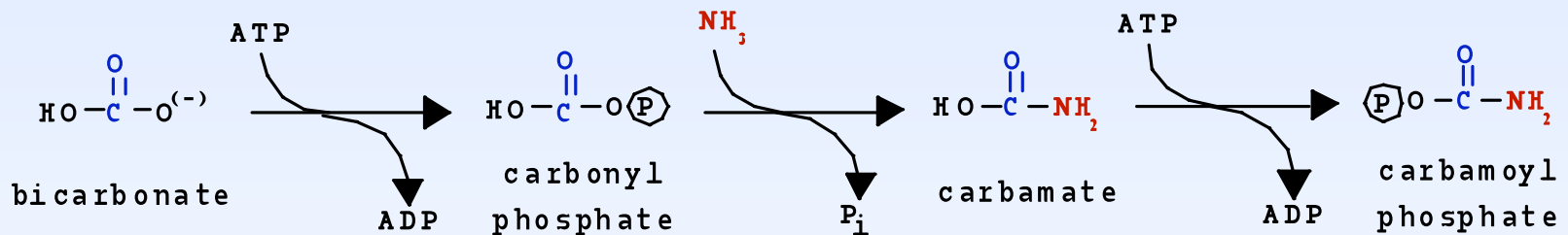
CPSD	No elevation except ammonia; diagnosed by elimination.
OTCD	Elevated CP causes synthesis of Orotate
ASD	Elevated citrulline
ALD	Elevated argininosuccinate
AD	Elevated arginine

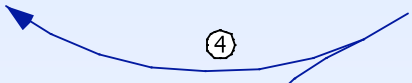
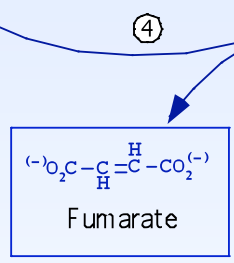
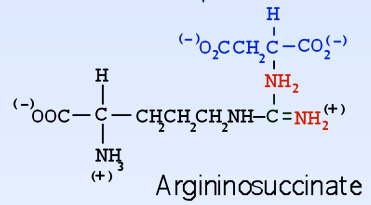
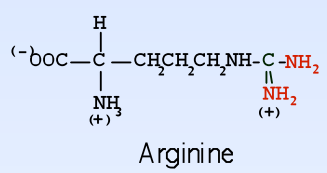
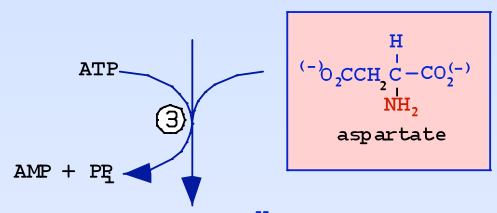
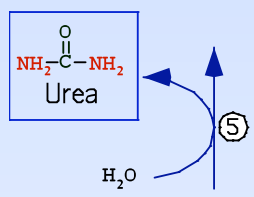
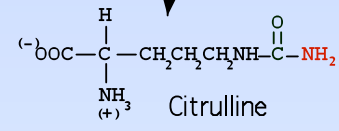
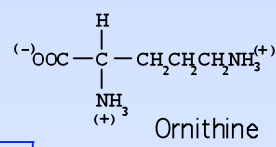
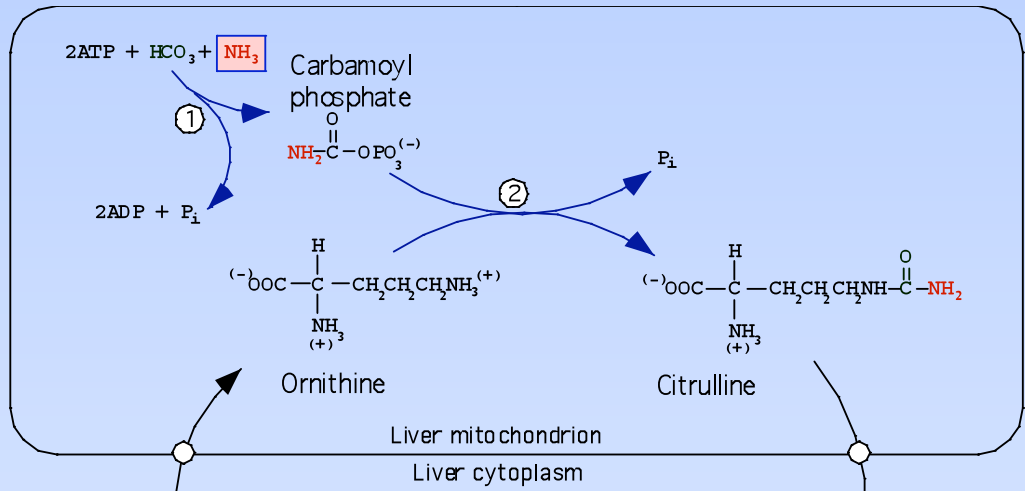


CPS I is Stimulated by NAG



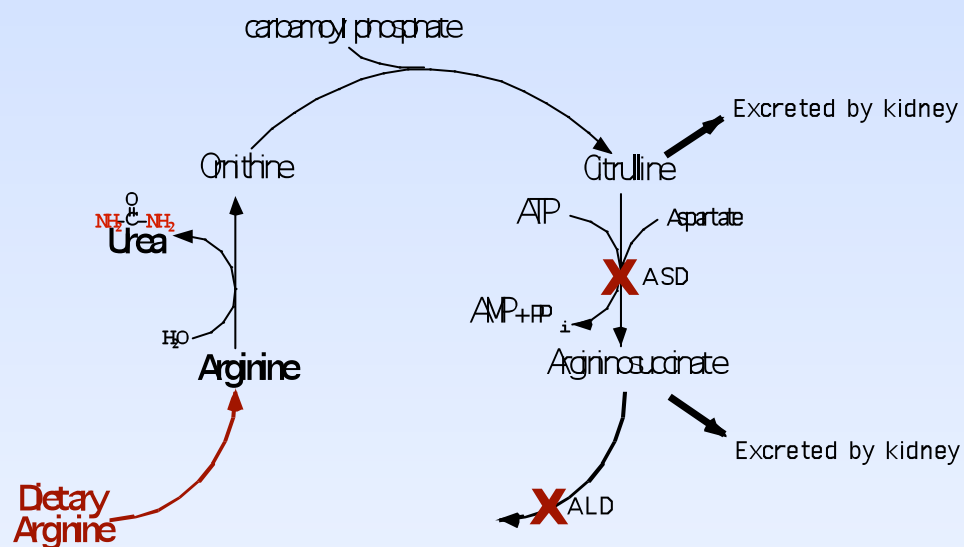
(repeating the figure from page 3 of your handout)





Clinical Management of Urea Cycle Defects

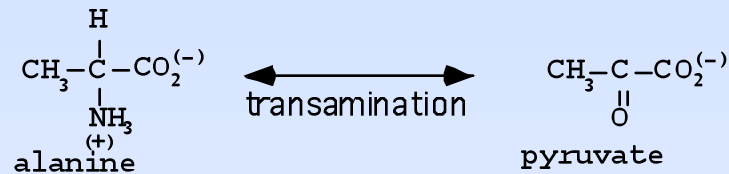
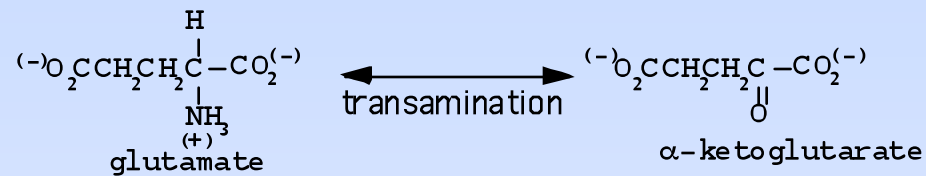
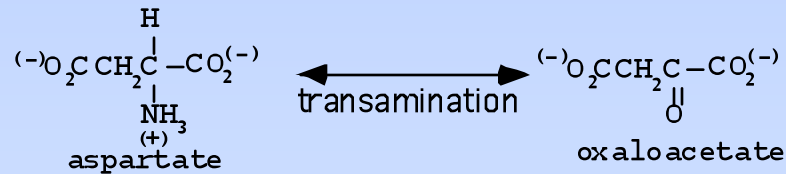
- Dialysis to remove ammonia
- Provide the patient with alternative ways to excrete nitrogenous compounds:
 - * Intravenous sodium benzoate or phenylacetate
 - * Supplemental arginine



- Levulose - acidifies the gut
- Low protein diet

Degrading the Amino Acid Carbon Backbone

Easily-degraded products after transamination:



We also already know how to degrade Glutamine:



...and by analogy, how to degrade Asparagine:



Amino Acids are categorized as 'Glucogenic' or 'ketogenic' or both.

Many amino acids are purely glucogenic:

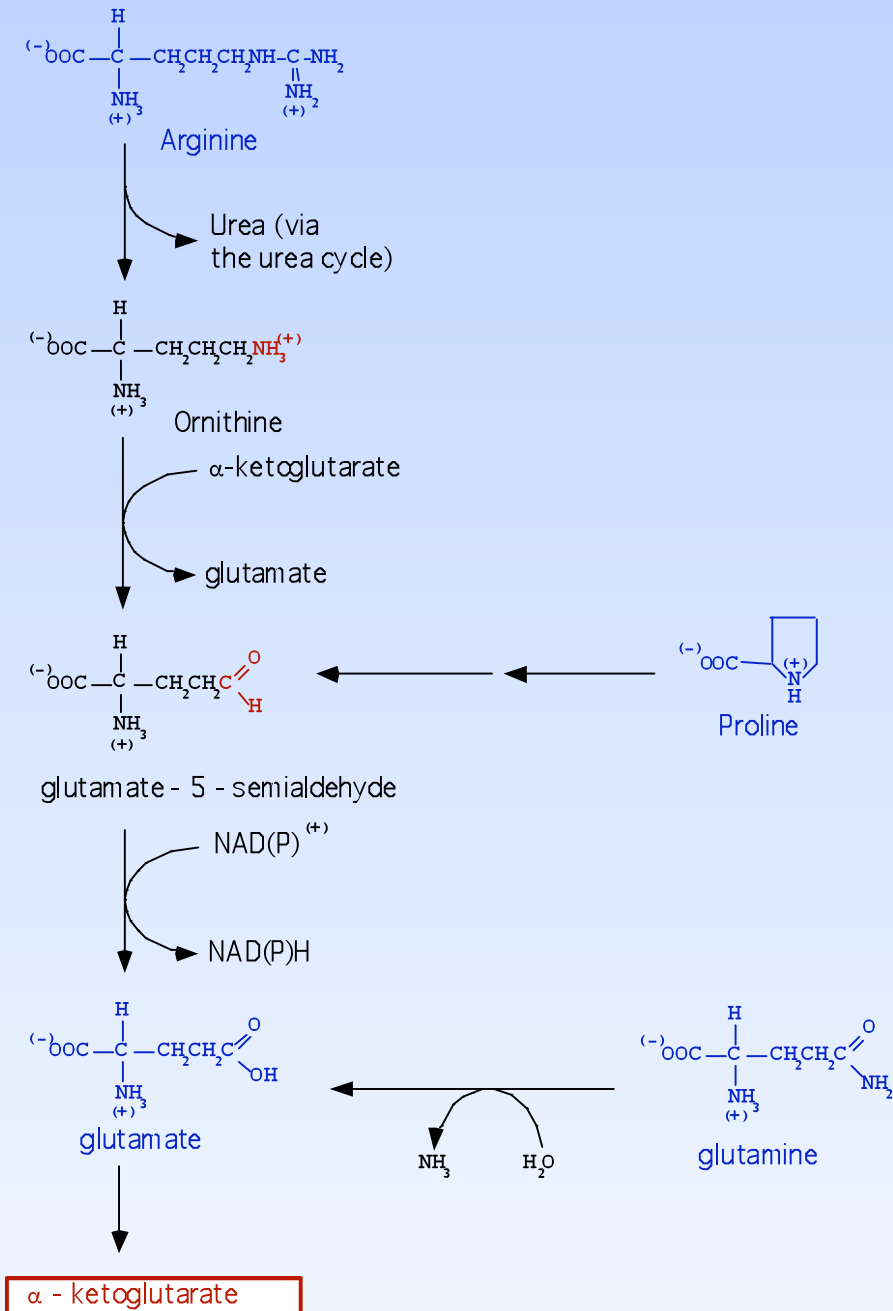
Glutamate, aspartate, alanine, glutamine, asparagine,...

Some amino acids are *both* gluco- and ketogenic:

Threonine, isoleucine, phenylalanine, tyrosine, tryptophan

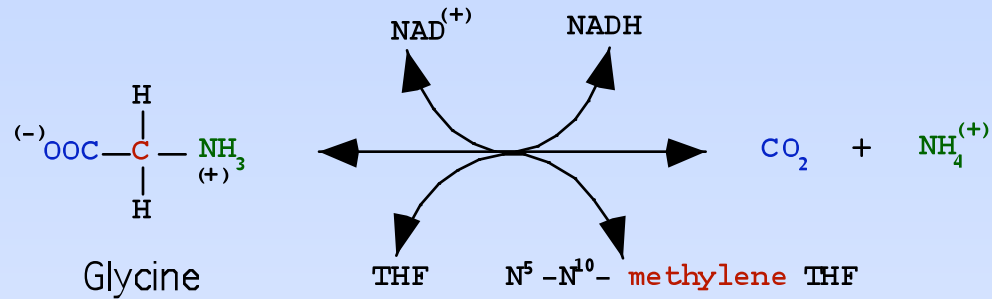
The only PURELY ketogenic Amino Acids
: leucine, lysine

Amino acids with 5-carbon backbones tend to form α -ketoglutarate

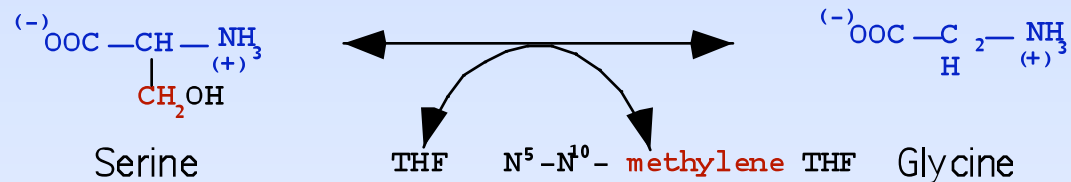


Degradation and Biosynthesis of Serine and Glycine

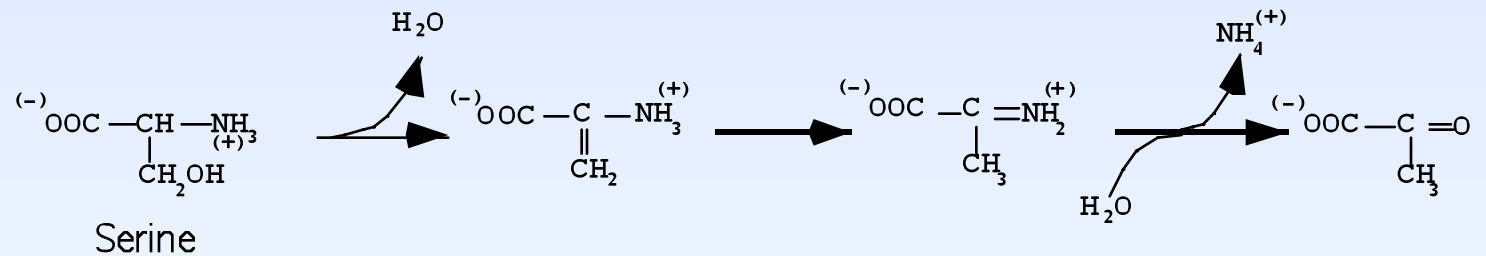
Glycine Synthase:



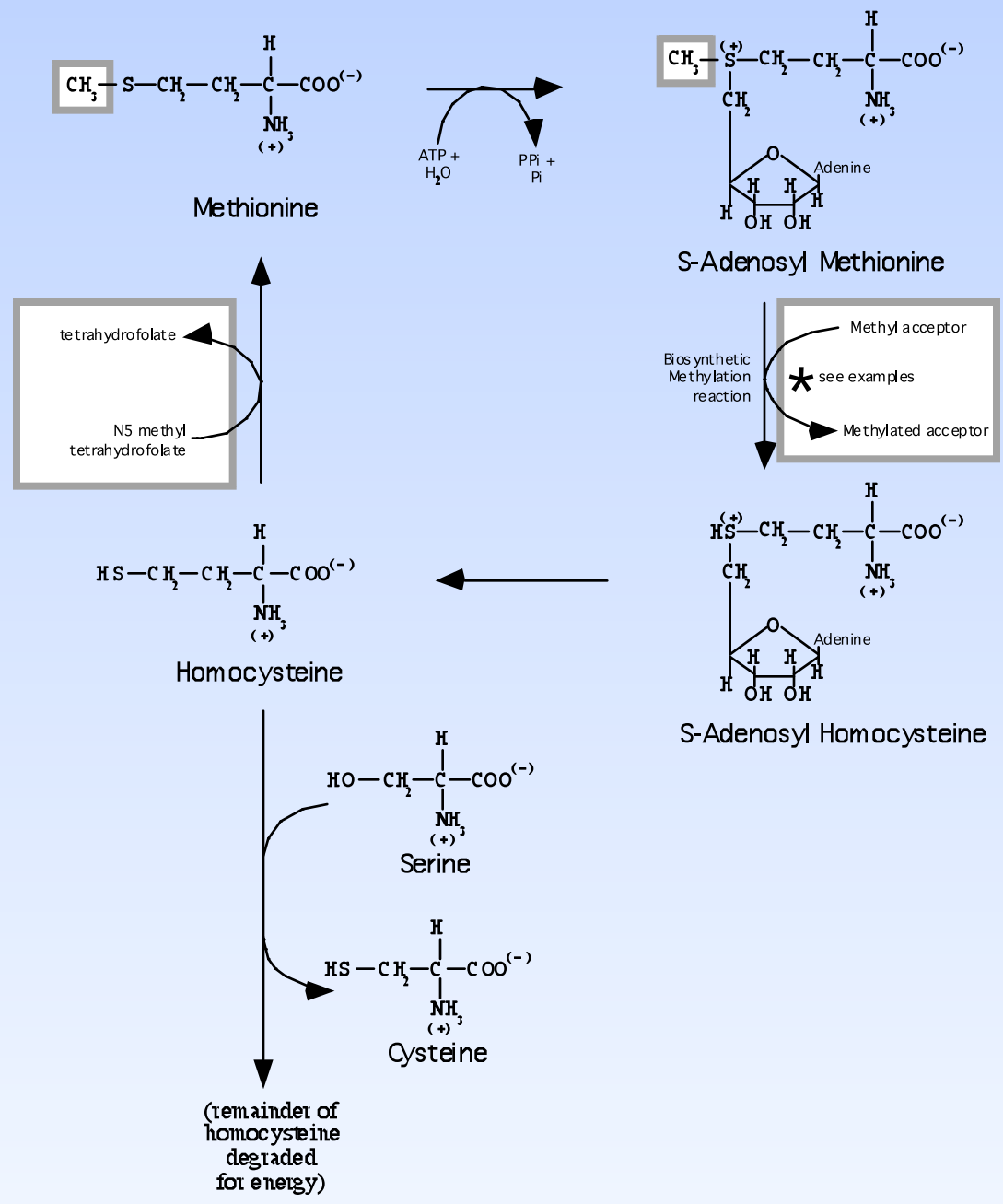
Serine Hydroxymethyltransferase:



Serine Dehydratase:

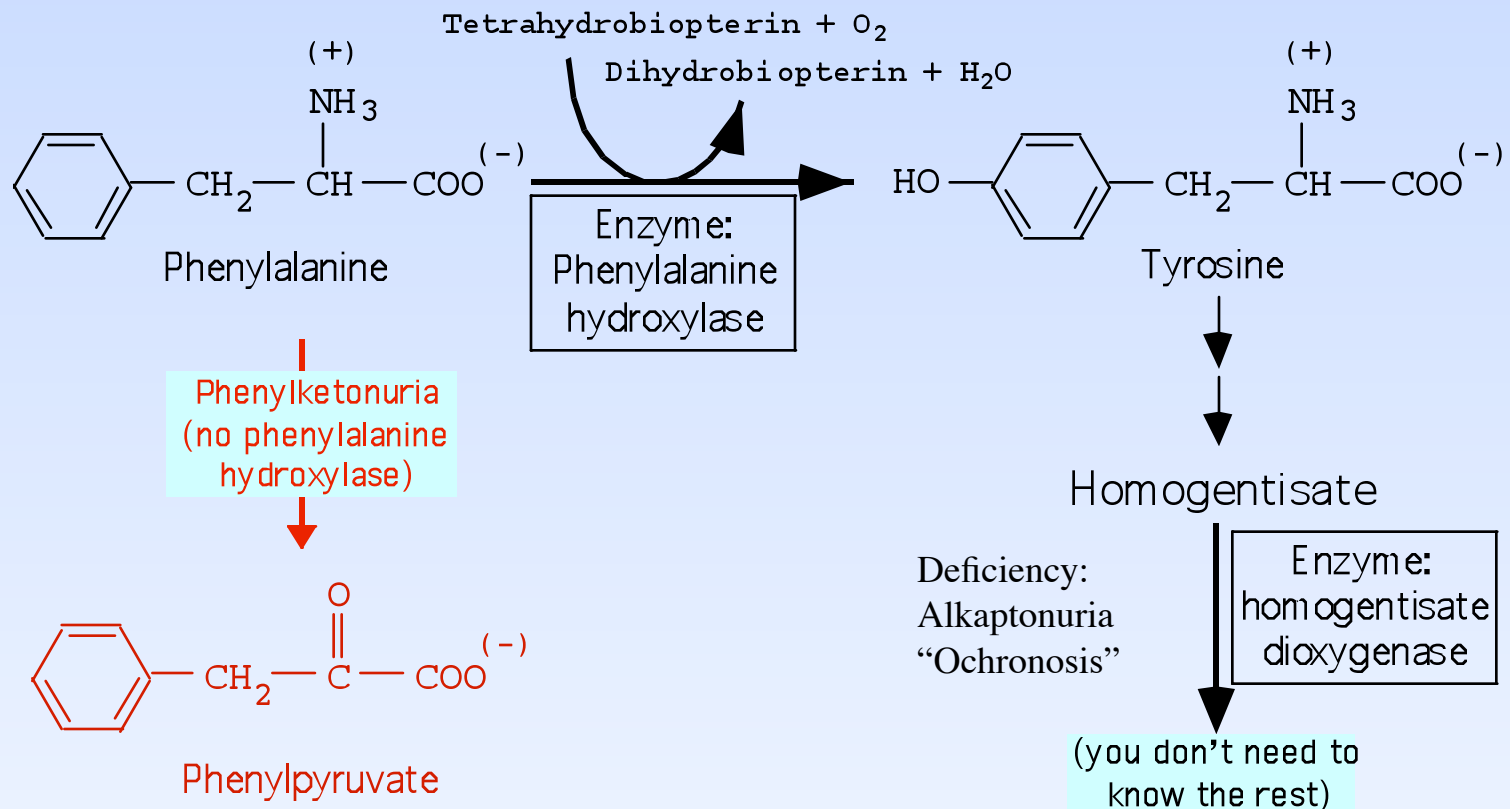


Methionine Cycle And Biological Methyl Groups

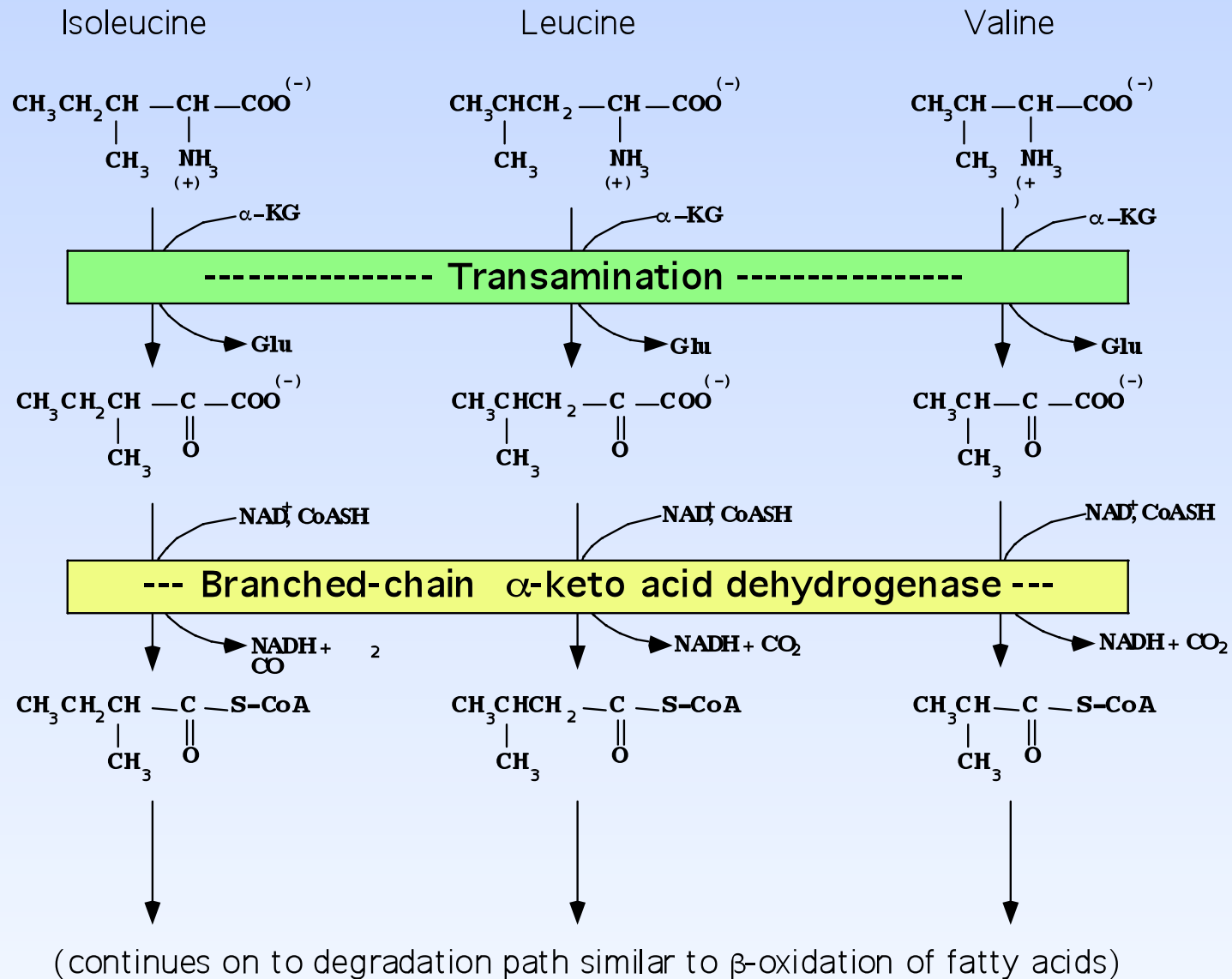


Phenylalanine and Tyrosine

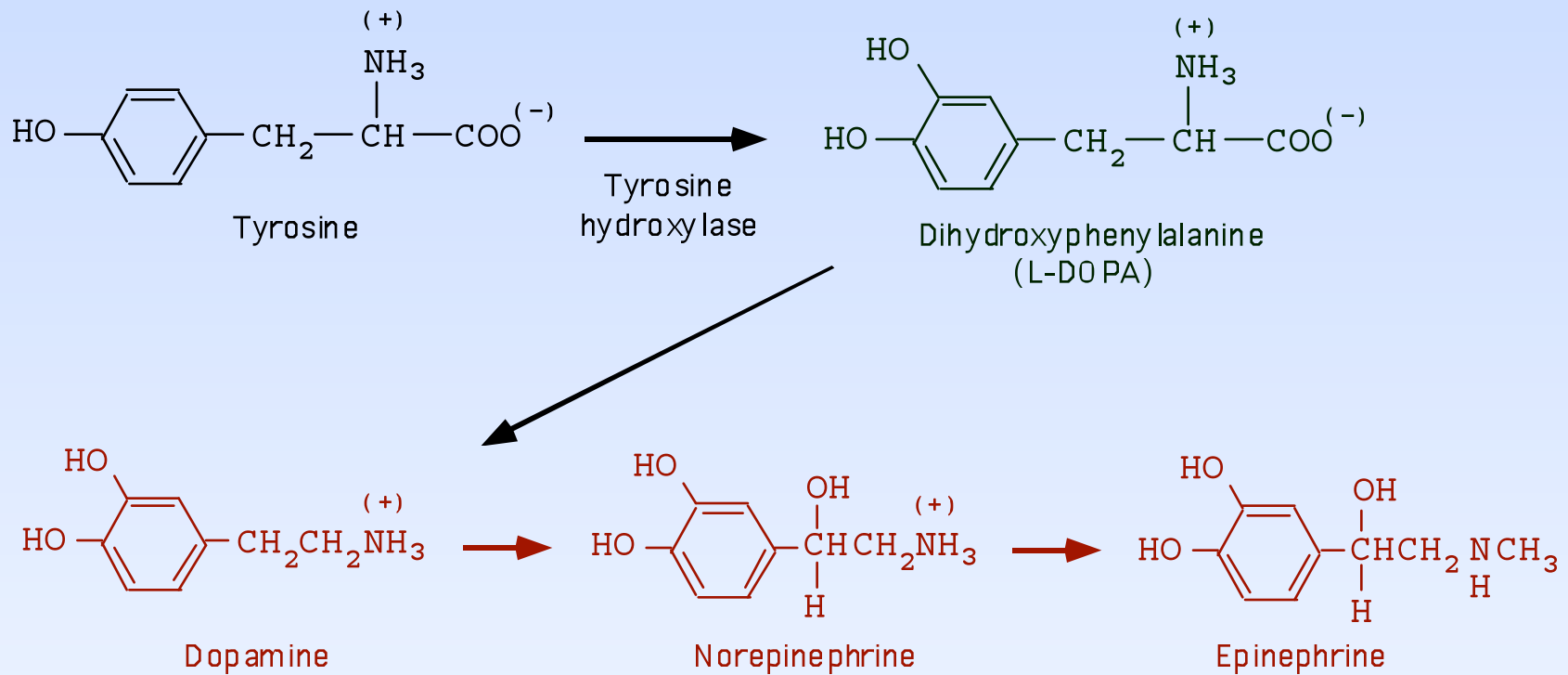
(Normal path shown in black, pathological reaction shown in red)



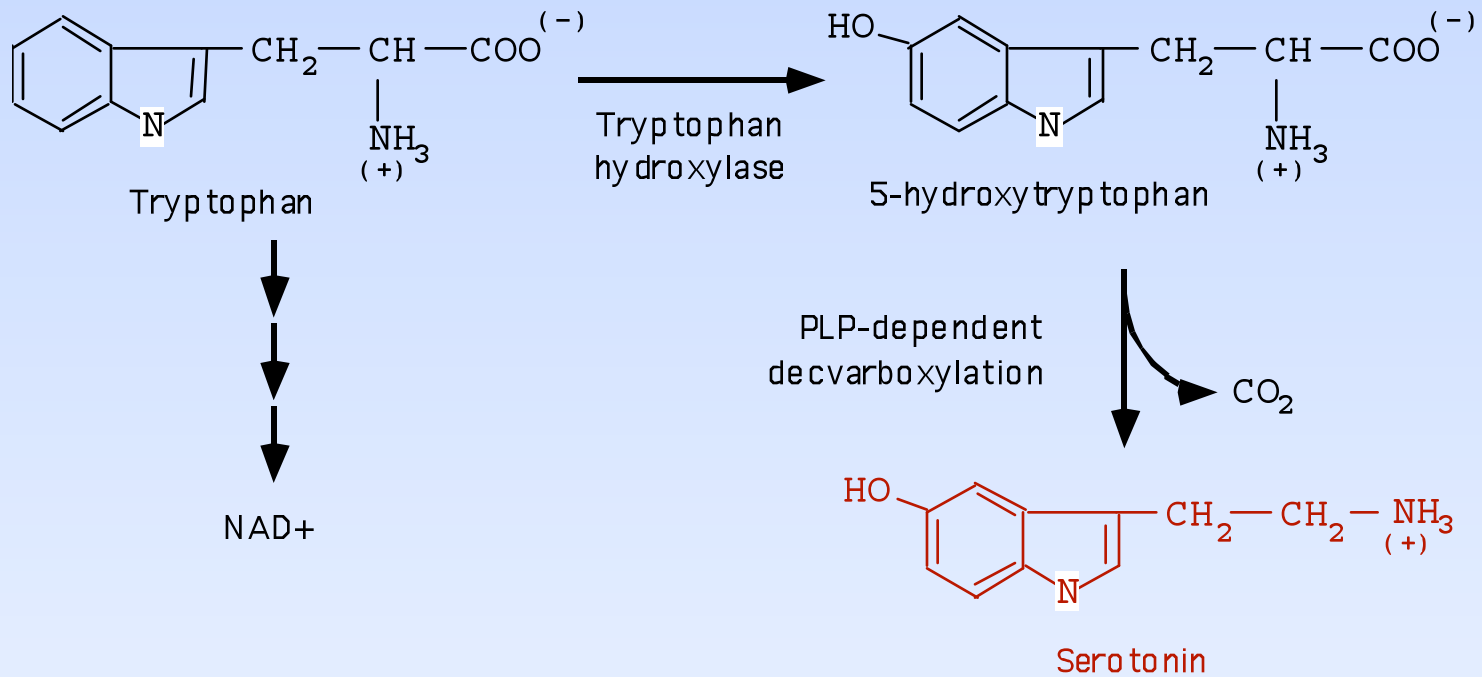
Branched Chain Amino Acids



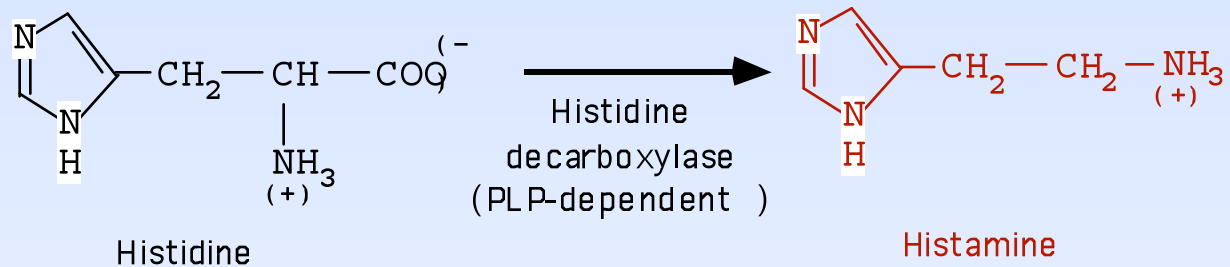
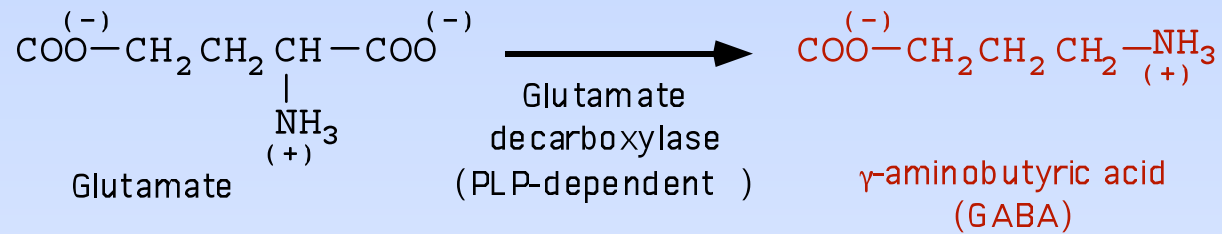
Synthesis of Bioactive Amines



Synthesis of Bioactive Amines



Synthesis of Bioactive Amines



NON-Essential Amino Acids:

Glutamate, aspartate, alanine, glutamine, asparagine,
(proline), glycine, serine (cysteine, tyrosine)

Essential Amino Acids:

Arginine (!), phenylalanine, methionine, histidine,
Isoleucine, leucine, valine, threonine, tryptophan, lysine