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Author: Robert Lyons, Ph.D., 2008

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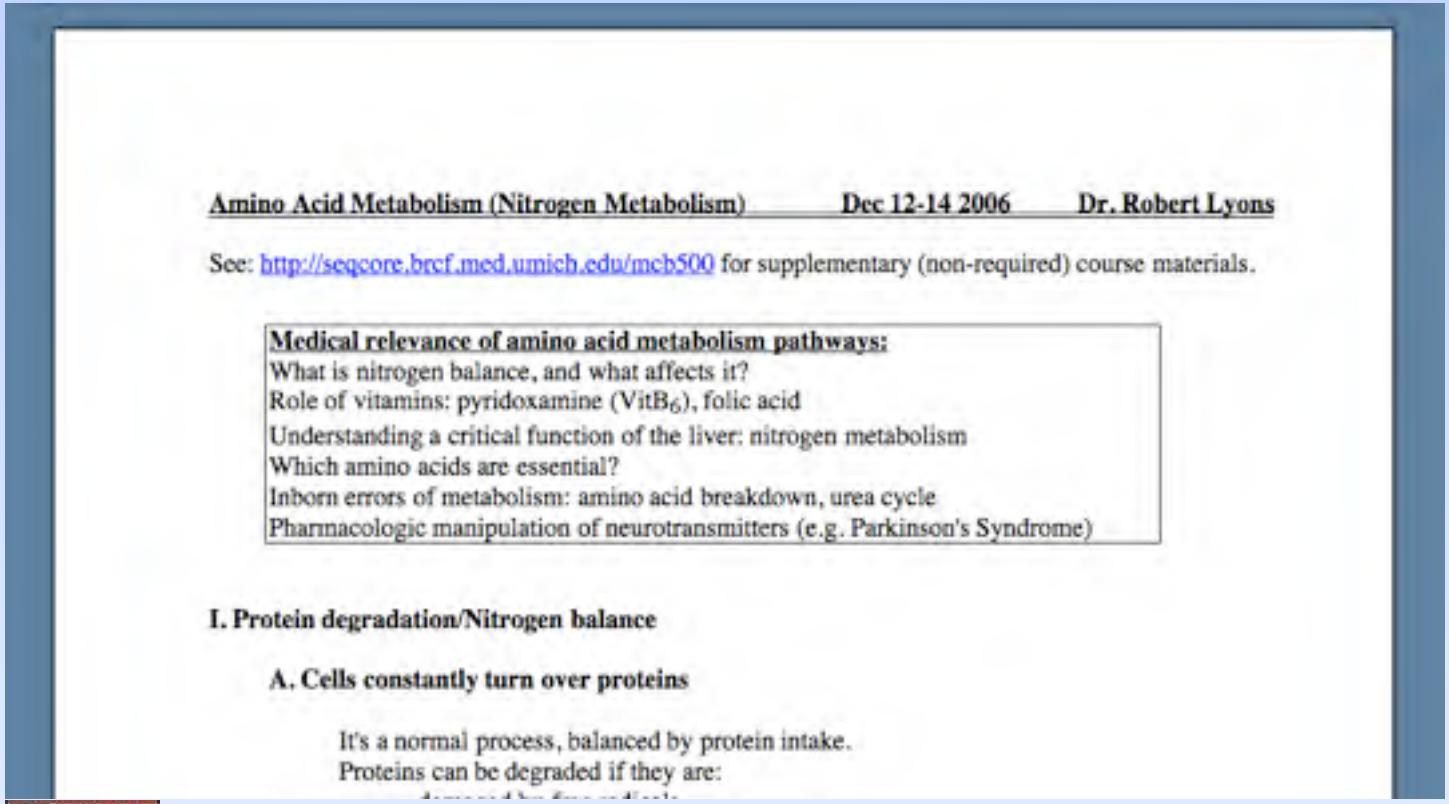
M1 Renal:
Nitrogen Metabolism (and Related Topics)

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

Dr. Robert Lyons
Assistant Professor, Biological Chemistry
Director, DNA Sequencing Core
Web: http://seqcore.brcf.med.umich.edu/mcb500

Fall 2008

University of Michigan
Medical School



Amino Acid Metabolism (Nitrogen Metabolism) **Dec 12-14 2006** **Dr. Robert Lyons**

See: http://seqcore.brcf.med.umich.edu/mcb500 for supplementary (non-required) course materials.

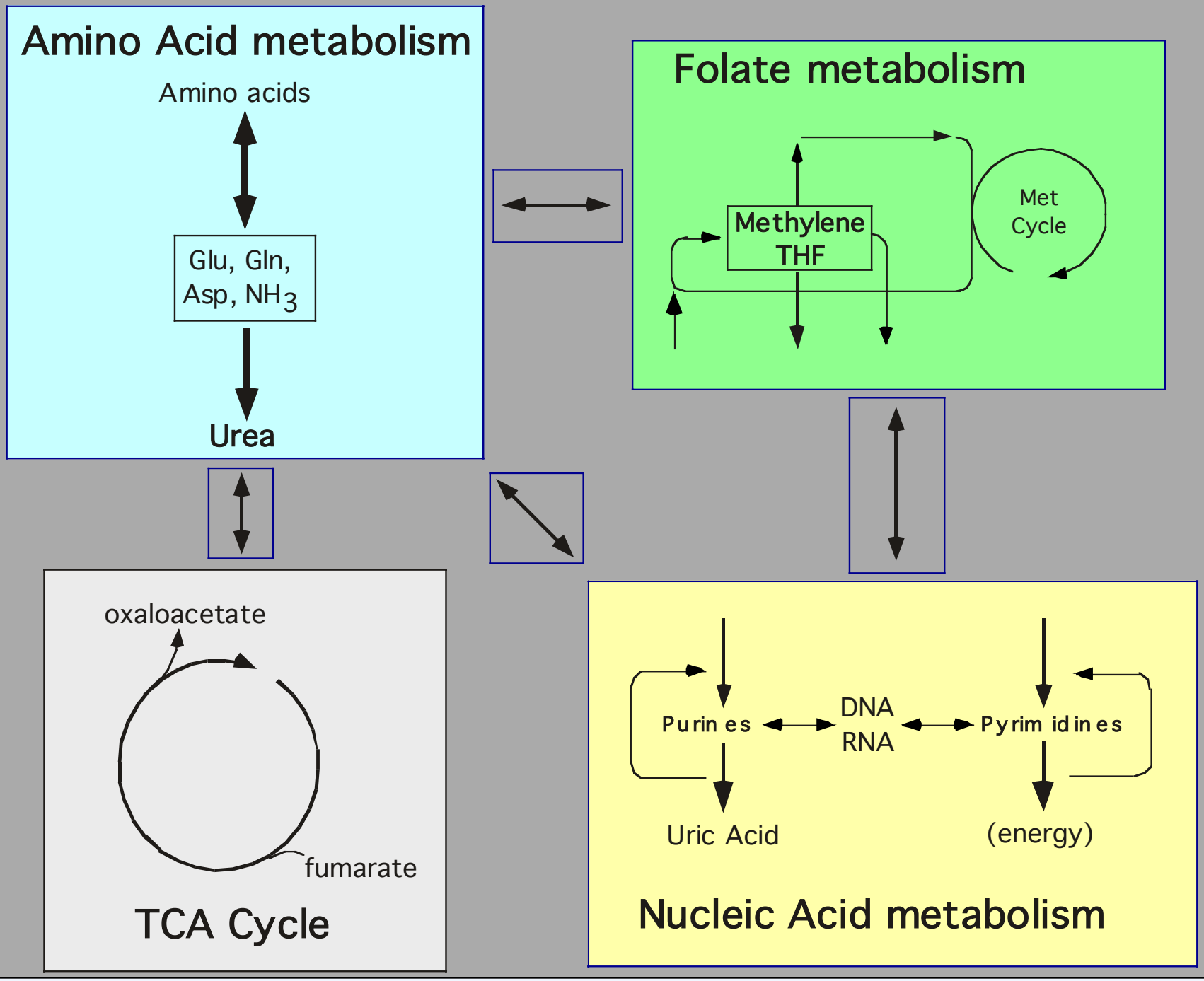
Medical relevance of amino acid metabolism pathways:
What is nitrogen balance, and what affects it?
Role of vitamins: pyridoxamine ($VitB_6$), folic acid
Understanding a critical function of the liver: nitrogen metabolism
Which amino acids are essential?
Inborn errors of metabolism: amino acid breakdown, 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:

Supplementary study material on the Web:
http://seqcore.brcf.med.umich.edu/mcb500


Amino Acid metabolism
Amino acids
Glu, Gln,
Asp, NH3
Urea
Folate metabolism
Methylene
THF
Met
Cycle
oxaloacetate
fumarate
TCA Cycle
Purin es
DNA
RNA
Pyrim id in es
Uric Acid
(energy)
Nucleic Acid metabolism

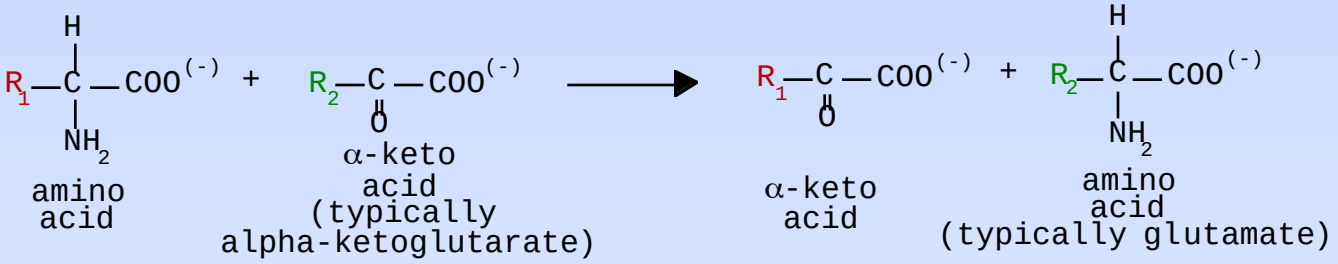
Protein Degradation:

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

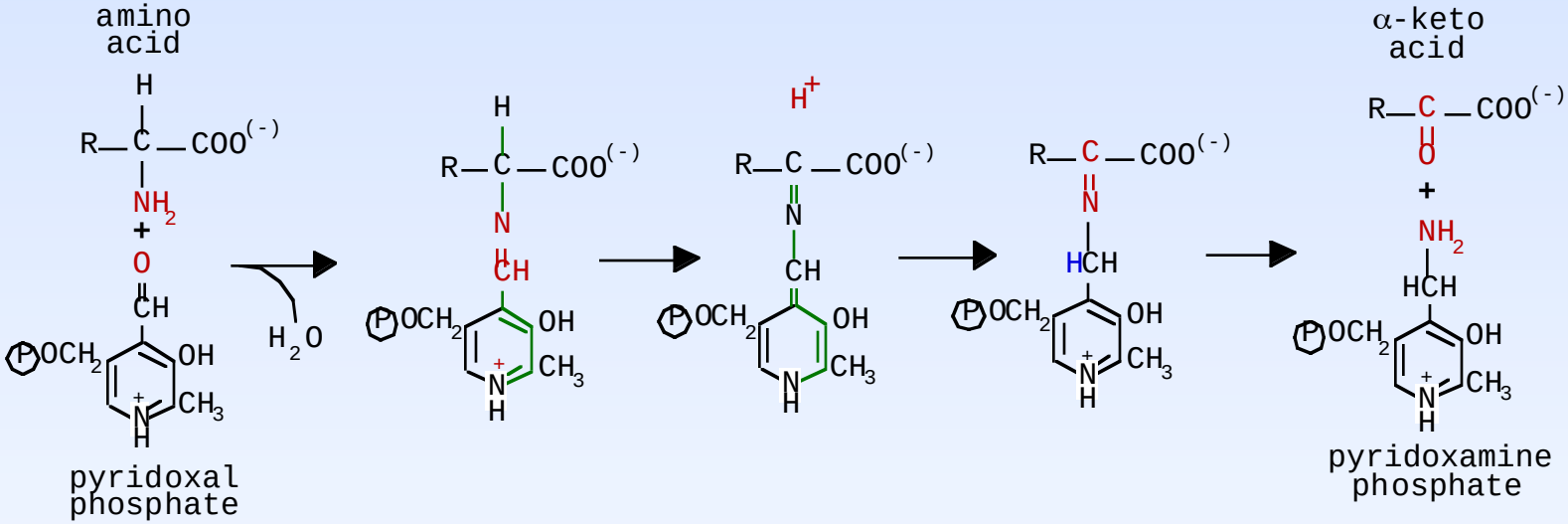
Nitrogen Balance - expresses the patient's current status - are they *gaining* or *losing* net Nitrogen?

Transaminases Collect Amines

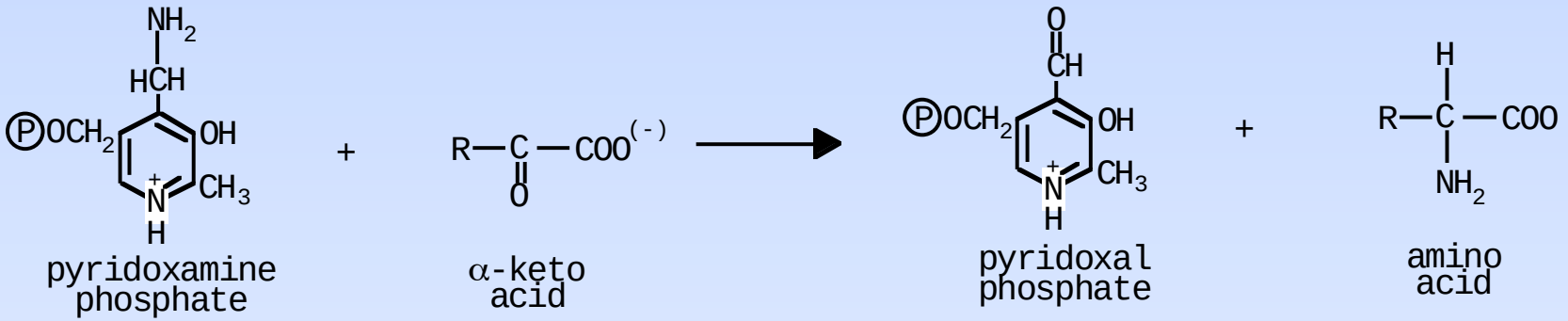
General reaction overview:



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 → some alpha keto acid + Glutamate

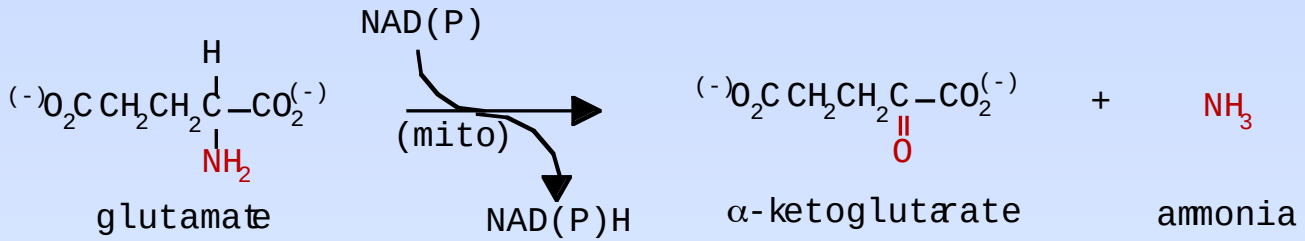
Glutamate can donate its amines to form other amino acids as needed

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

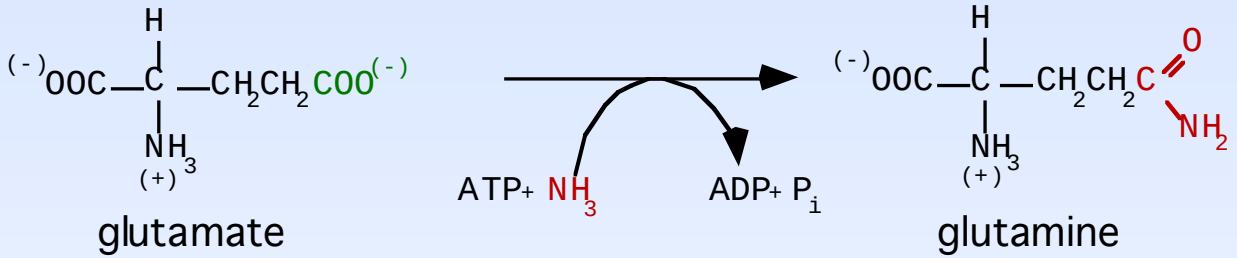
Glutamate + oxaloacetate → α-ketoglutarate + aspartate

Getting Amines Into the Liver

Glutamate Dehydrogenase:

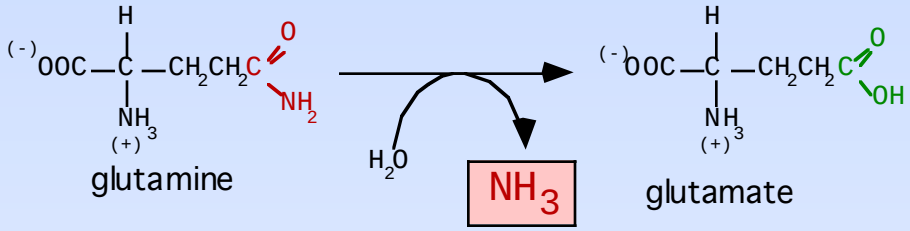


Glutamine Synthetase:



In the Liver: Precursers for Urea Cycle

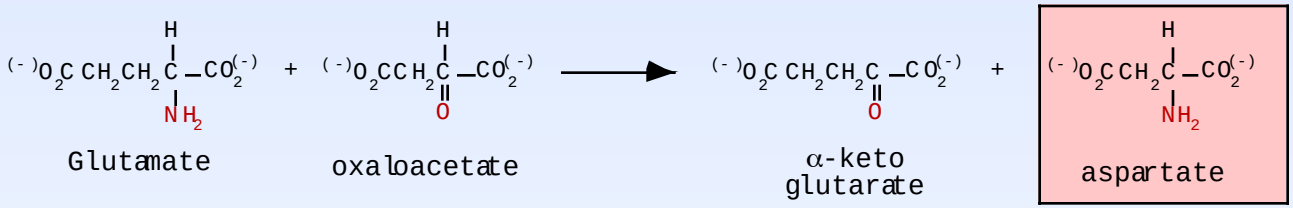
Glutamine is hydrolyzed to glutamate and ammonia:

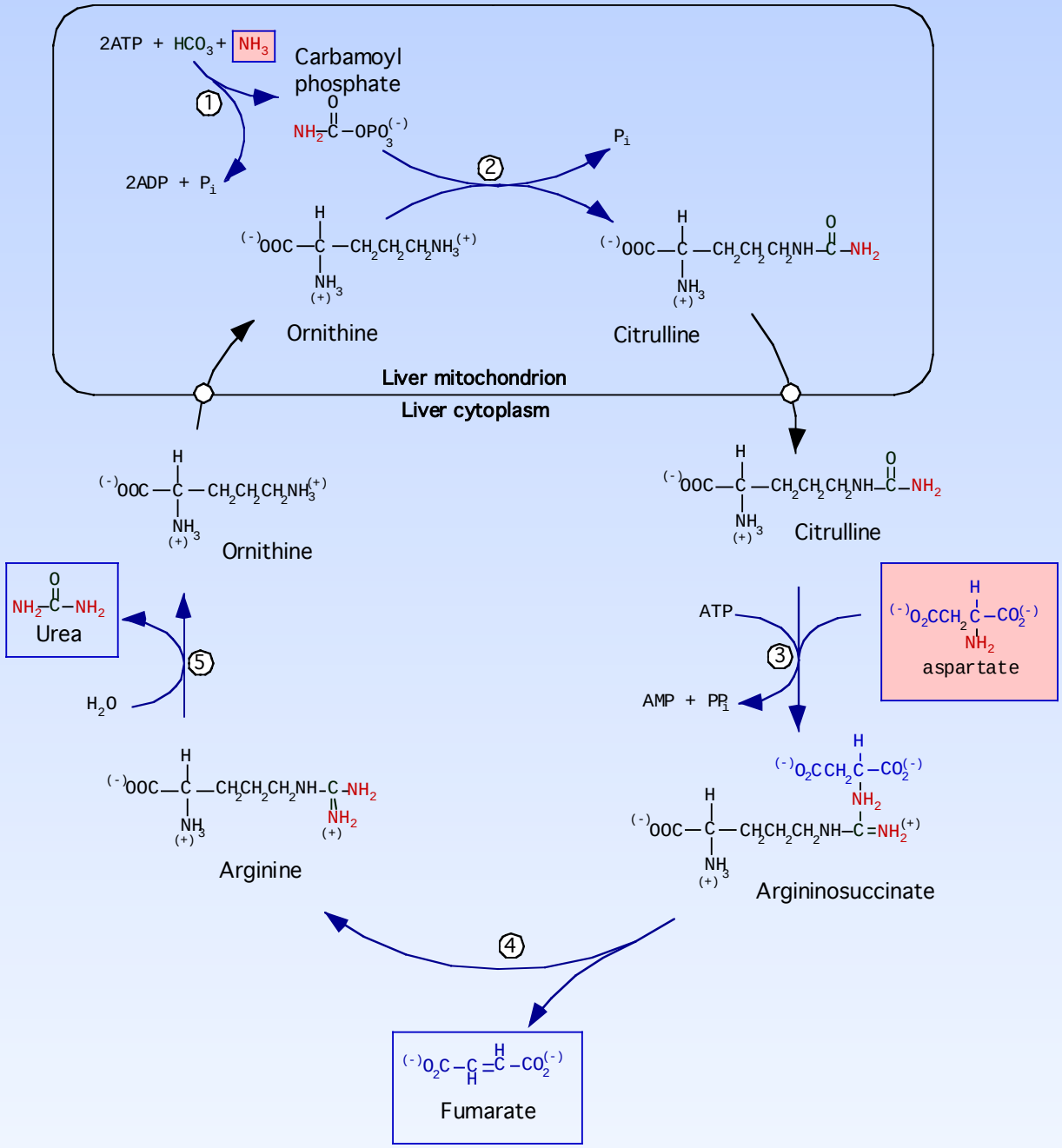


Ammonia can also be formed by the glutamate dehydrogenase reaction and several other reactions as well.

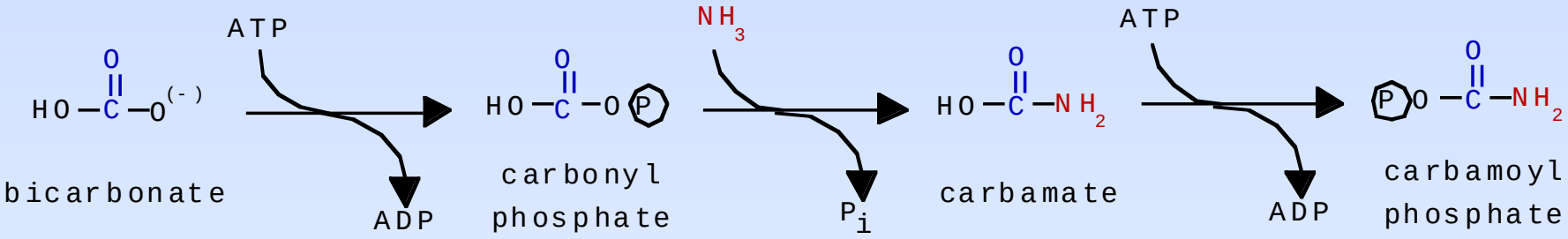
Glutamate donates its amino group to form aspartate:

Glutamate-aspartate aminotransferase:

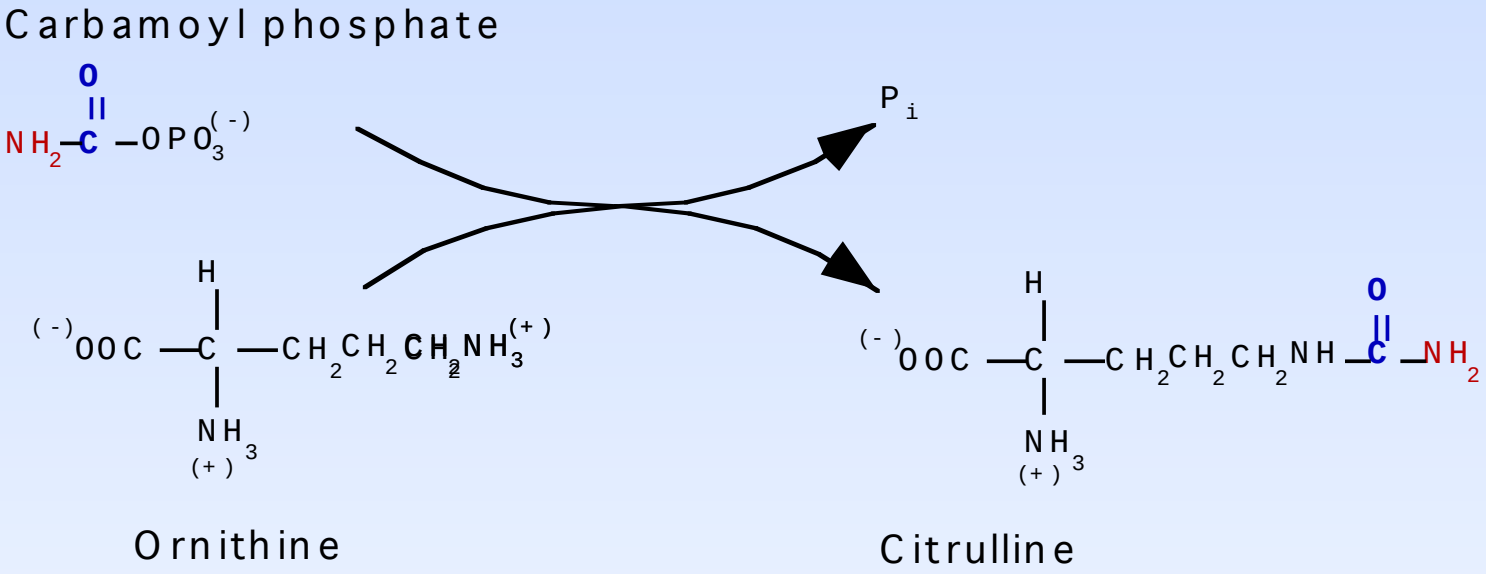




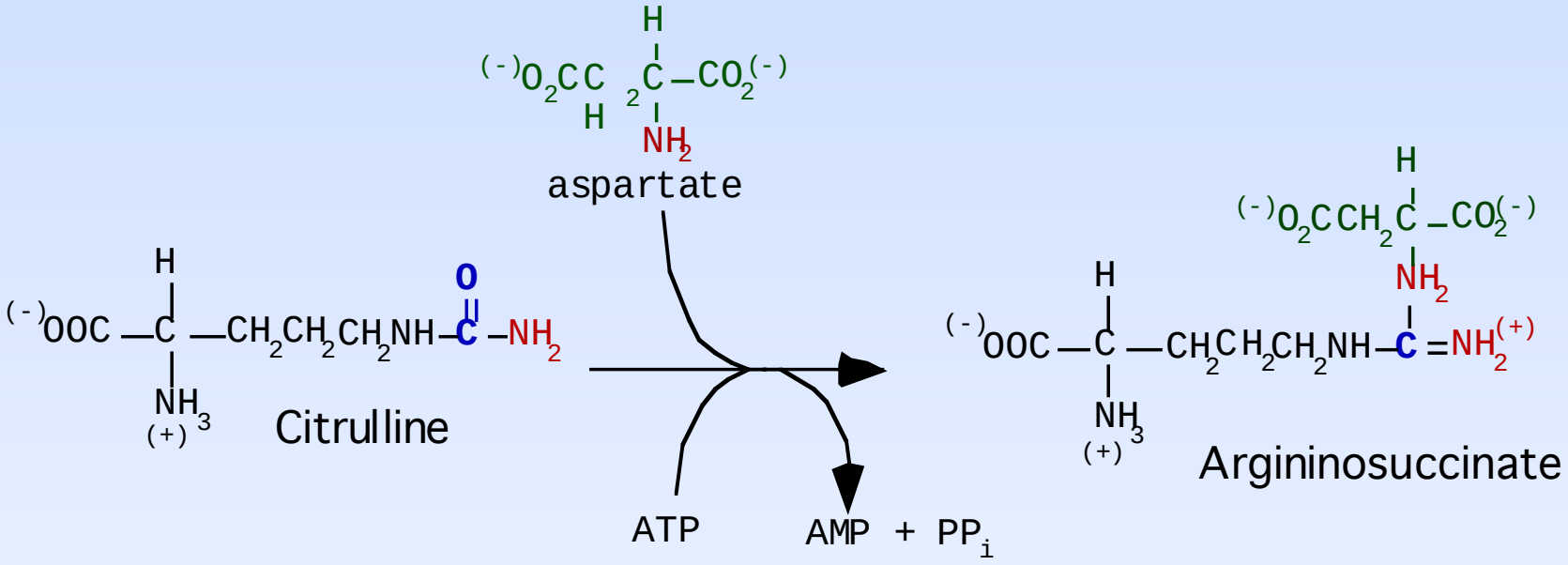
Carbamoyl phosphate synthetase I



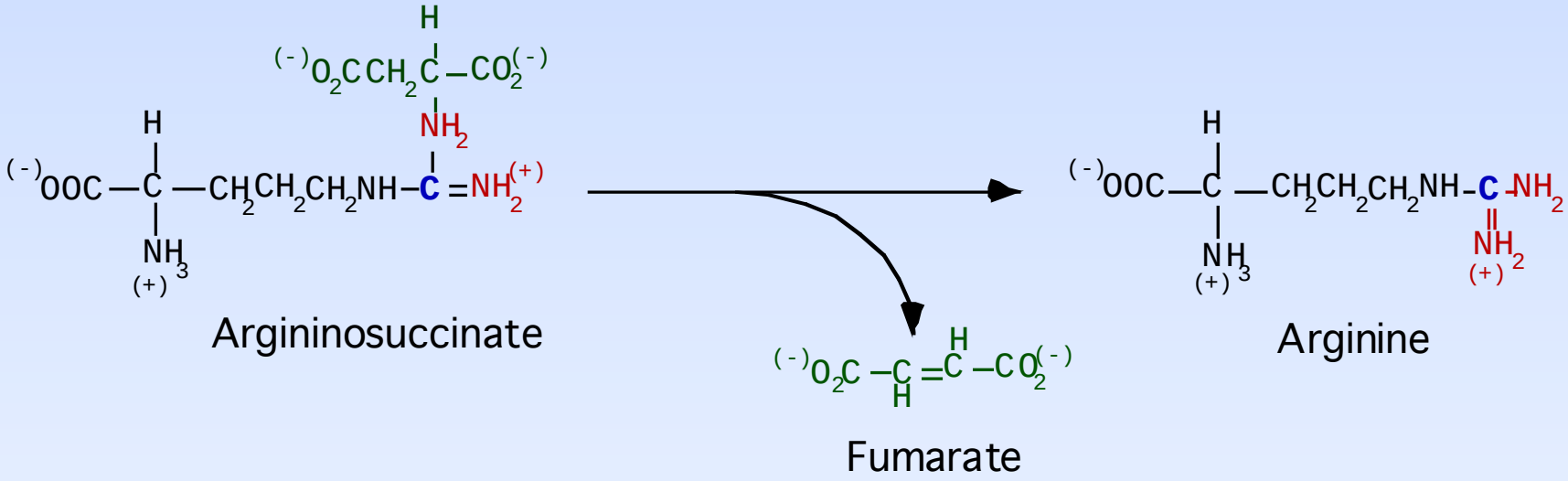
Ornithine Transcarbamoylase



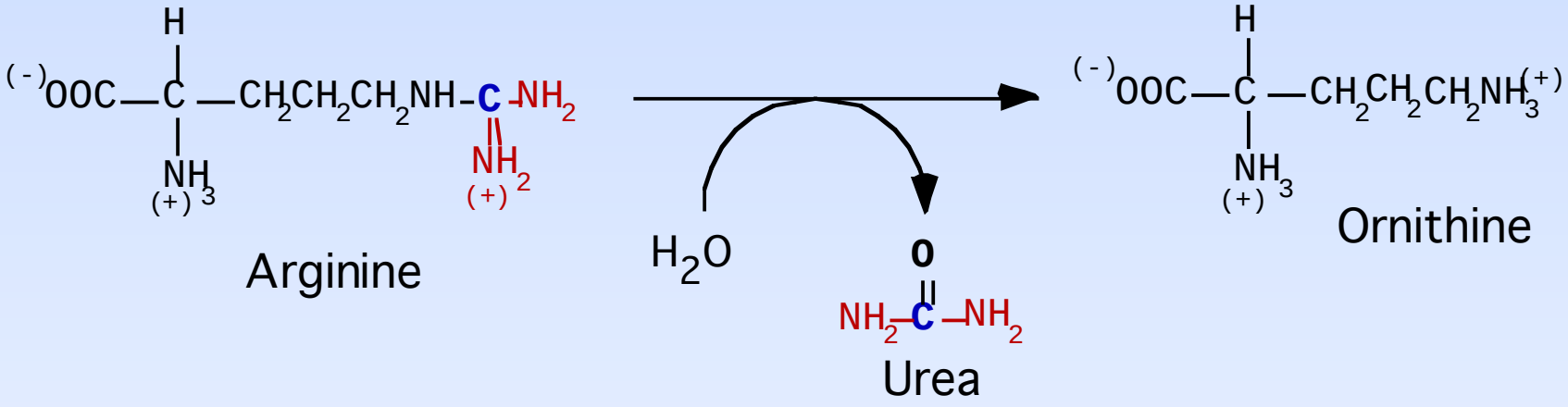
Argininosuccinate synthetase

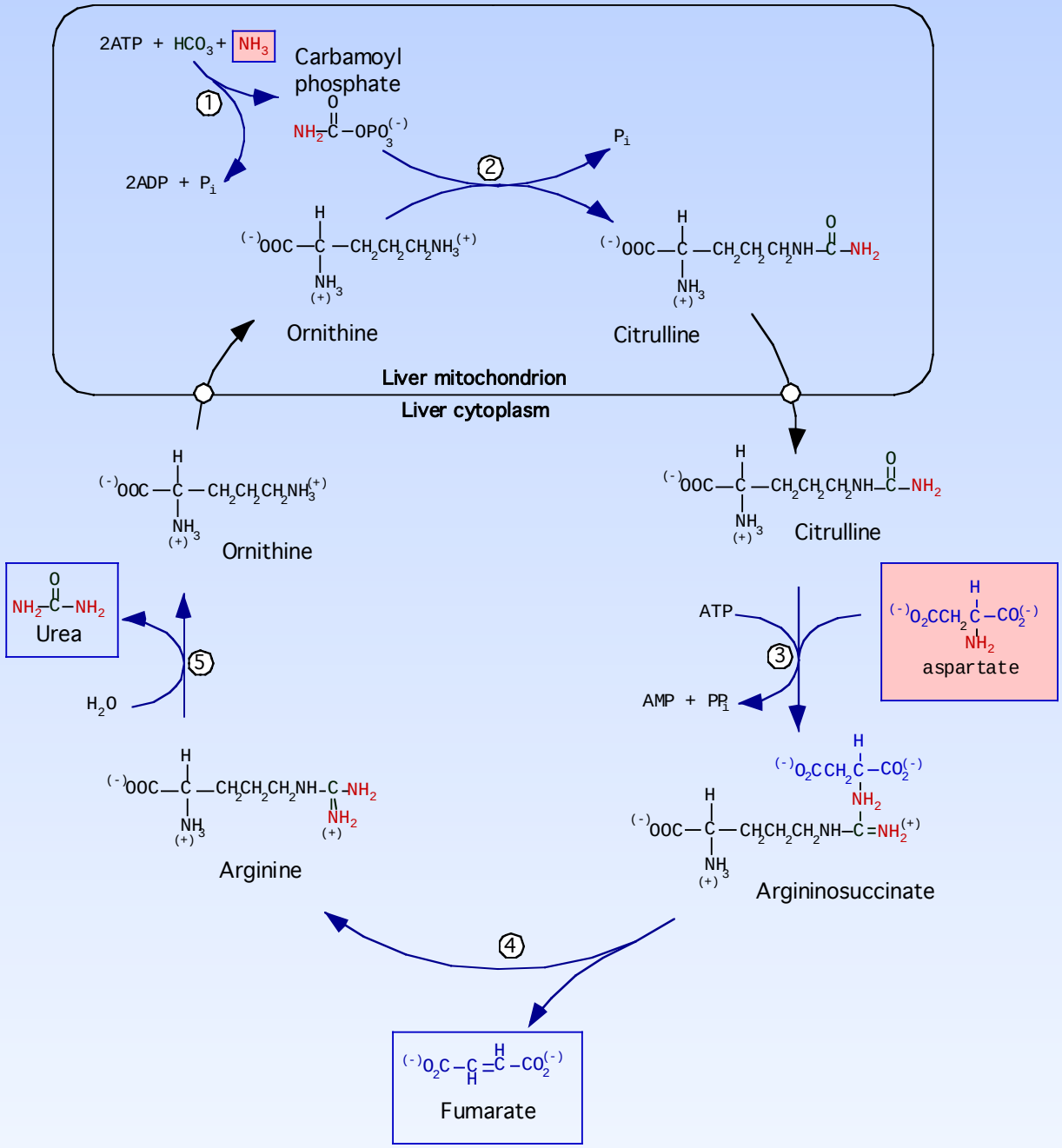


Argininosuccinate lyase

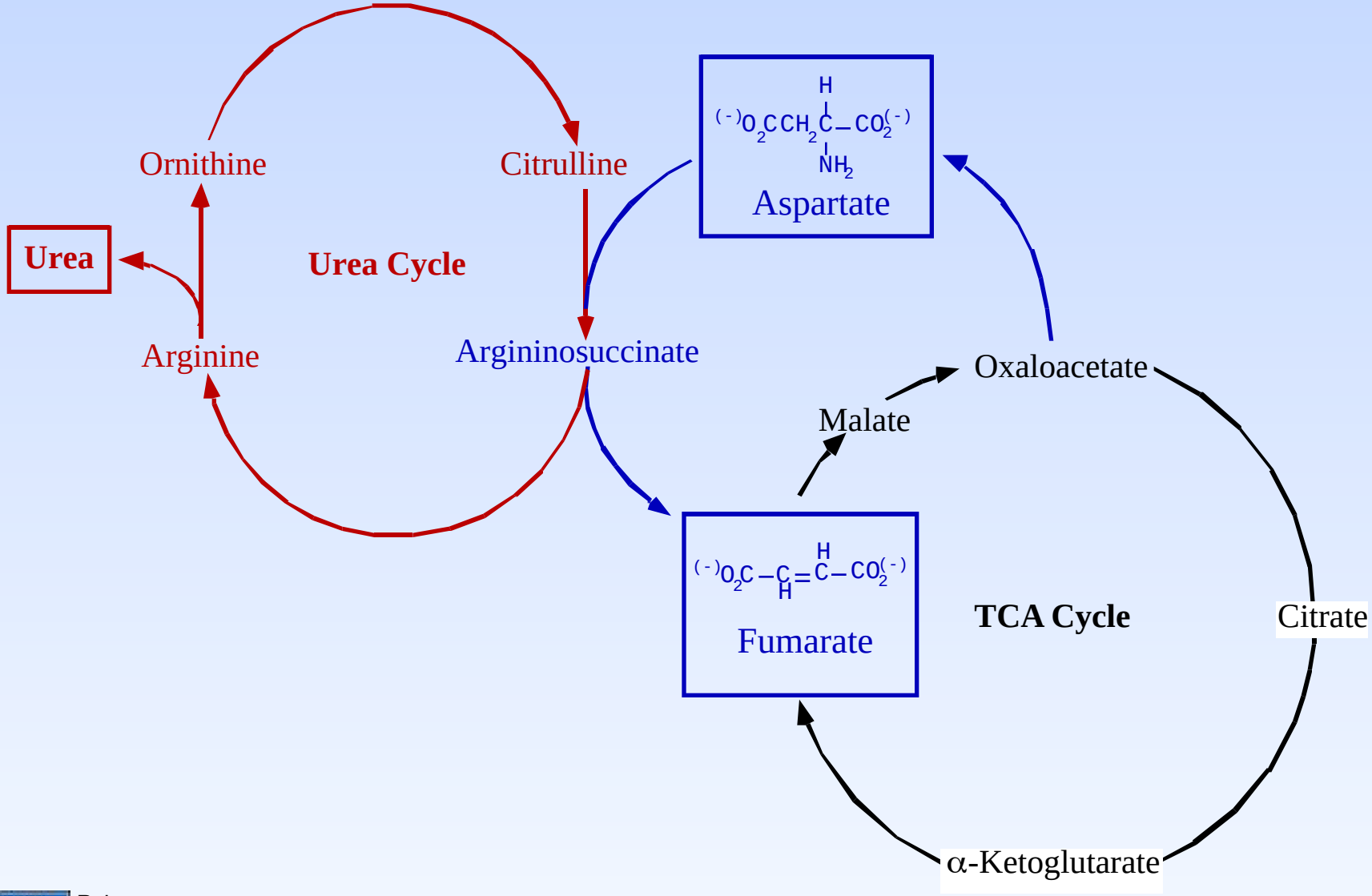


Arginase



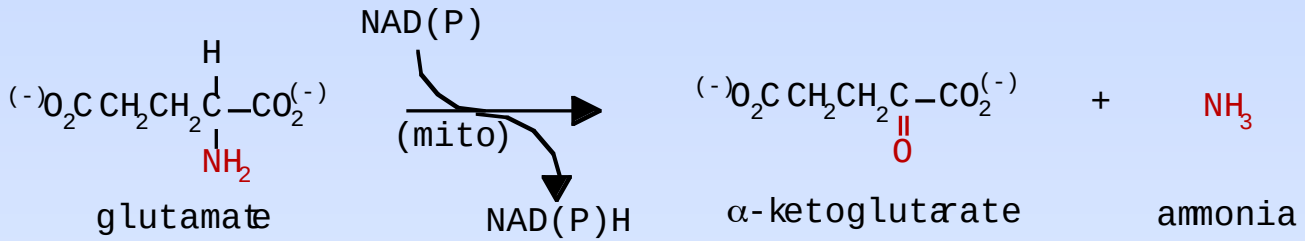


Urea Cycle Connects to TCA Cycle

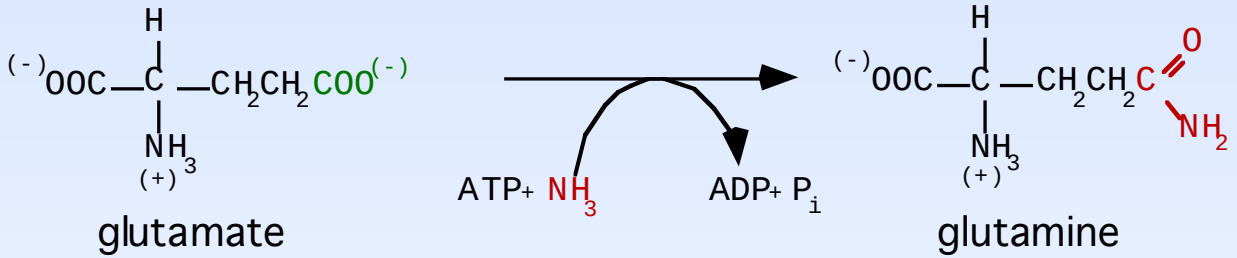


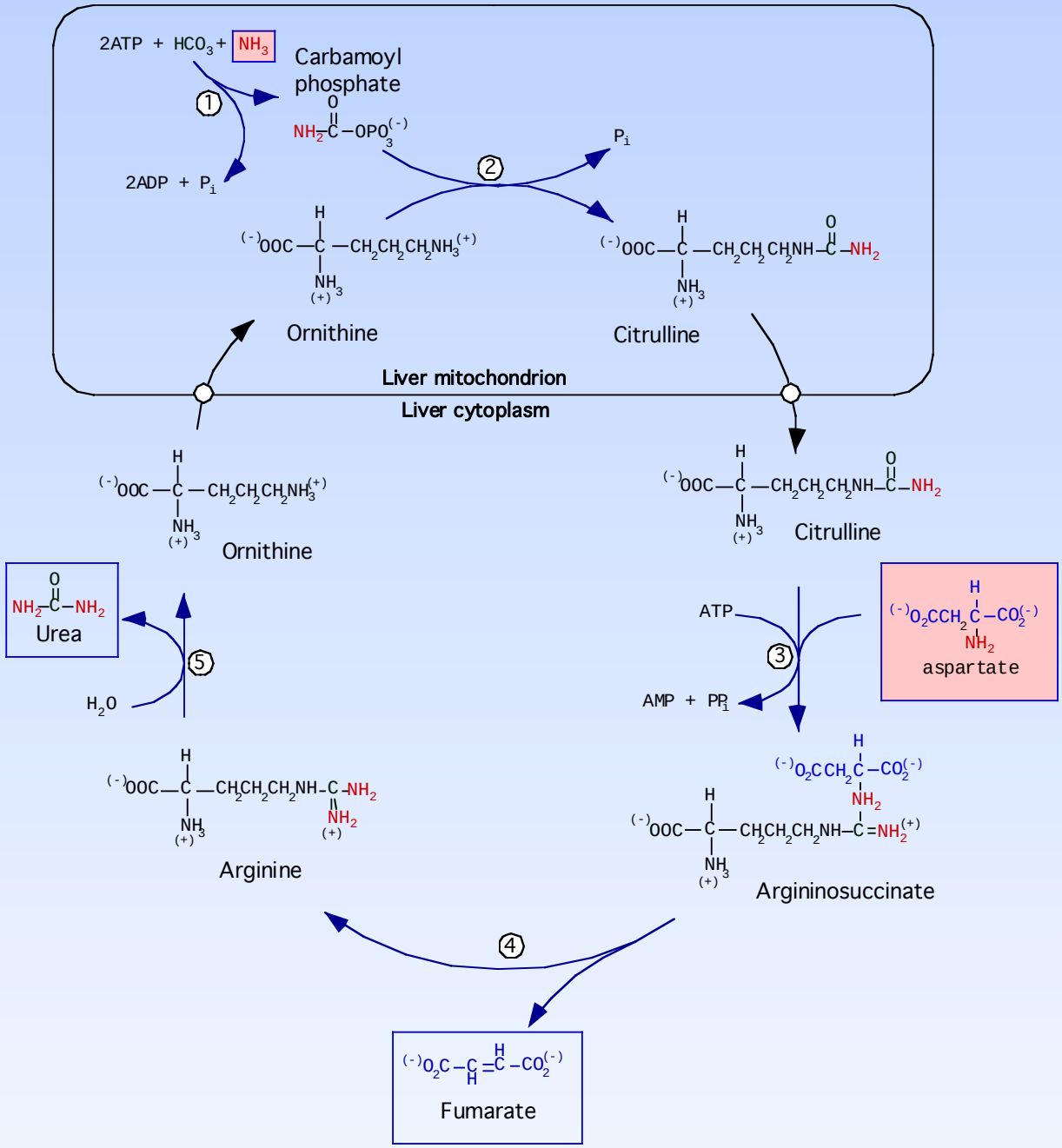
Getting Amines Into the Liver

Glutamate Dehydrogenase:

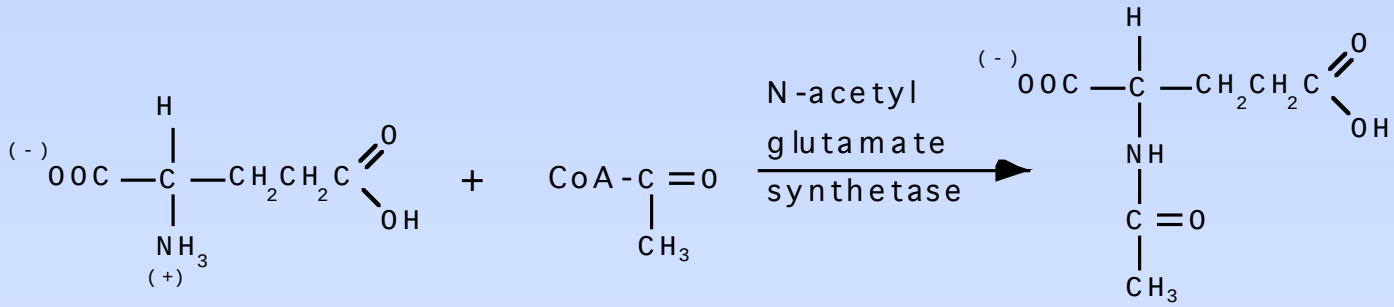


Glutamine Synthetase:

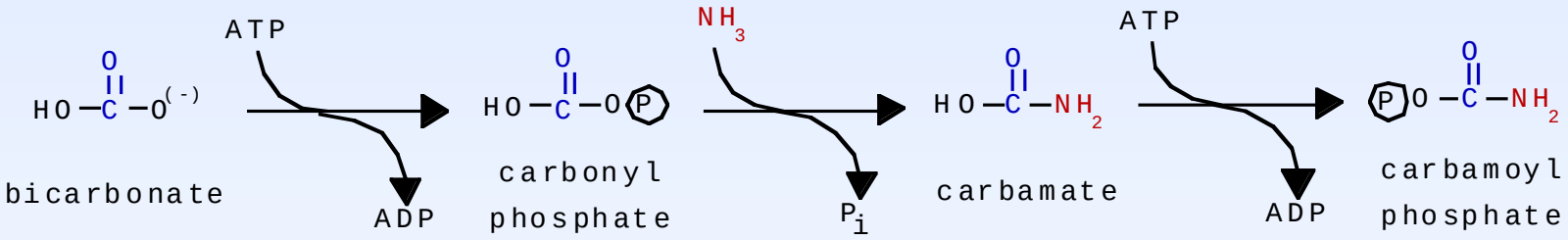




CPS I is Stimulated by NAG



(repeating the figure from page 3 of your handout)



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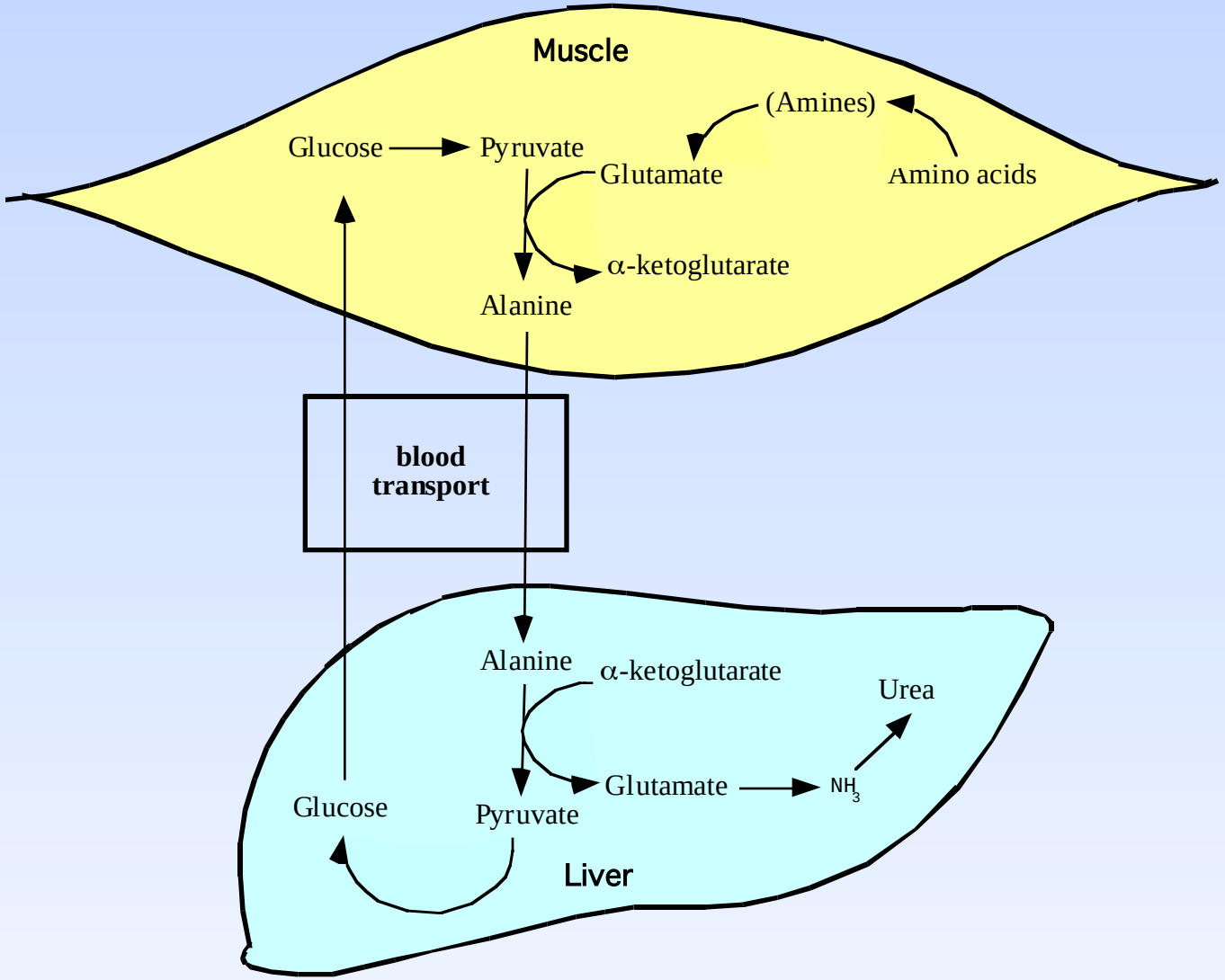
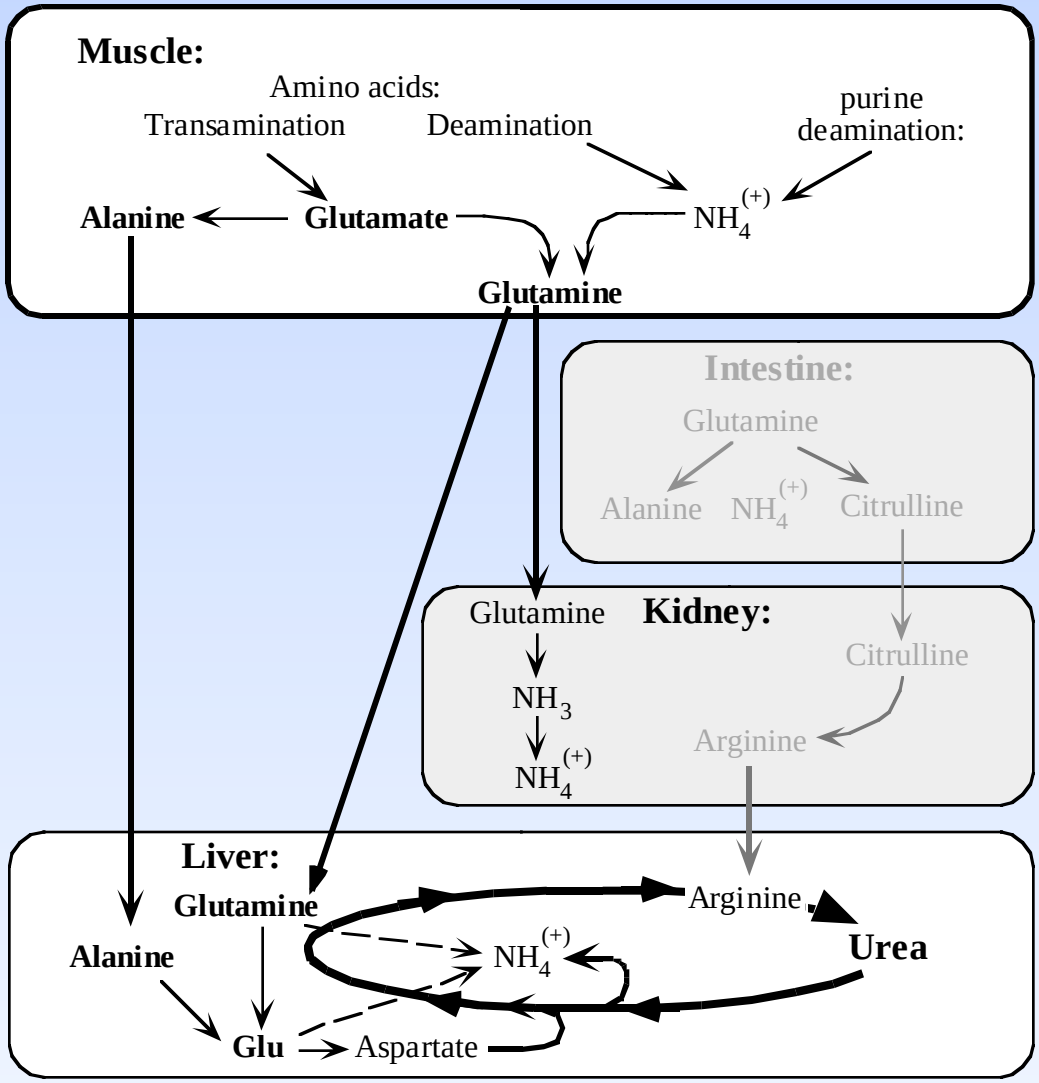

Muscle
(Amines)
Glucose
Pyruvate
Glutamate
Amino acids
α-ketoglutarate
Alanine
blood transport
Alanine
α-ketoglutarate
Urea
Glutamate
NH3
Glucose
Pyruvate
Liver

Complicating the picture: Other tissues may be involved



Why is Ammonia Toxic?

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- Possible neurotoxic effects on glutamate levels (and also GABA)

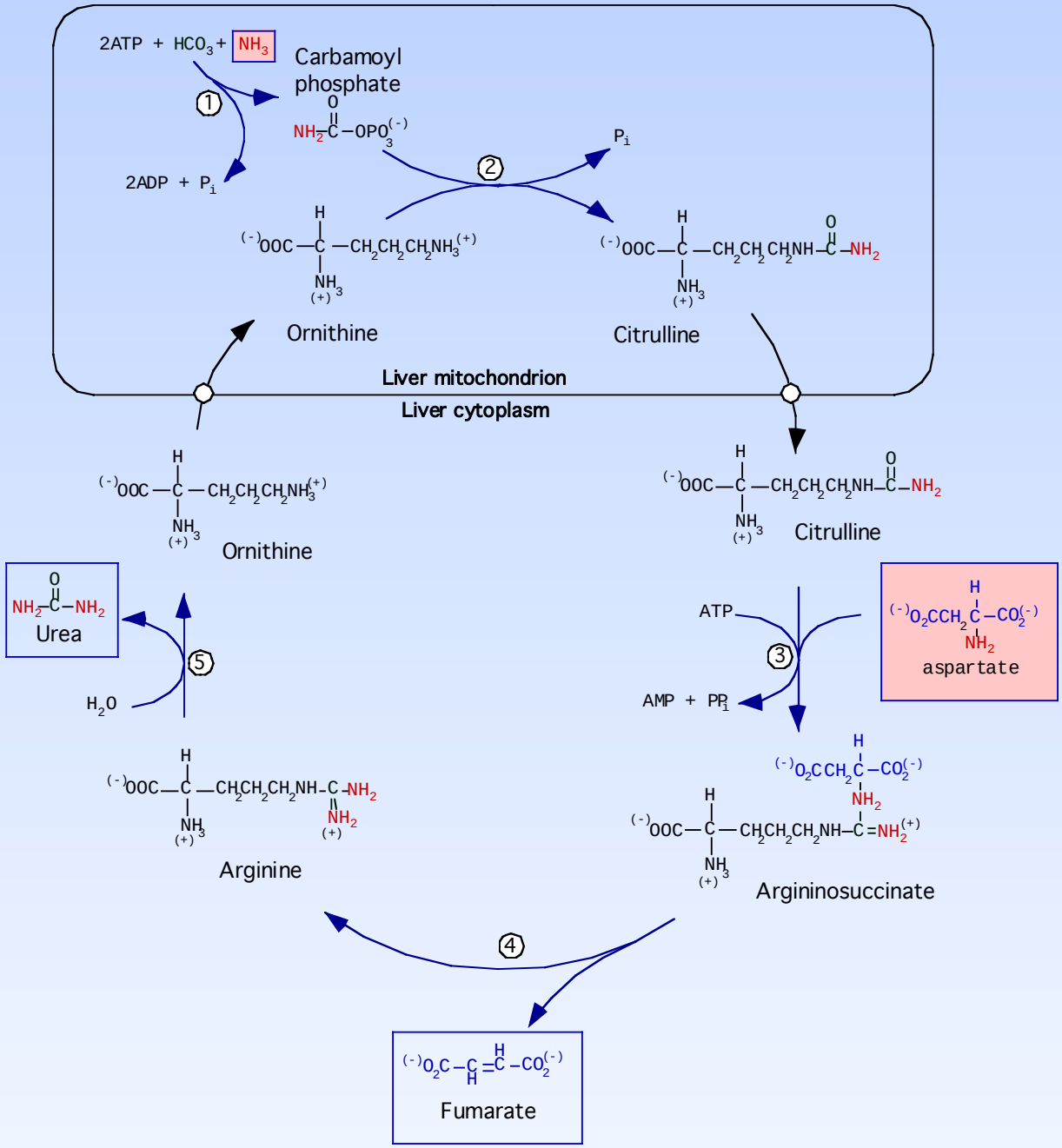
(due to shifting equilibria of reactions involving these compounds)

Why is Ammonia Toxic?

- Possible neurotoxic effects on glutamate levels (and also GABA)

(due to shifting equilibria of reactions involving these compounds)

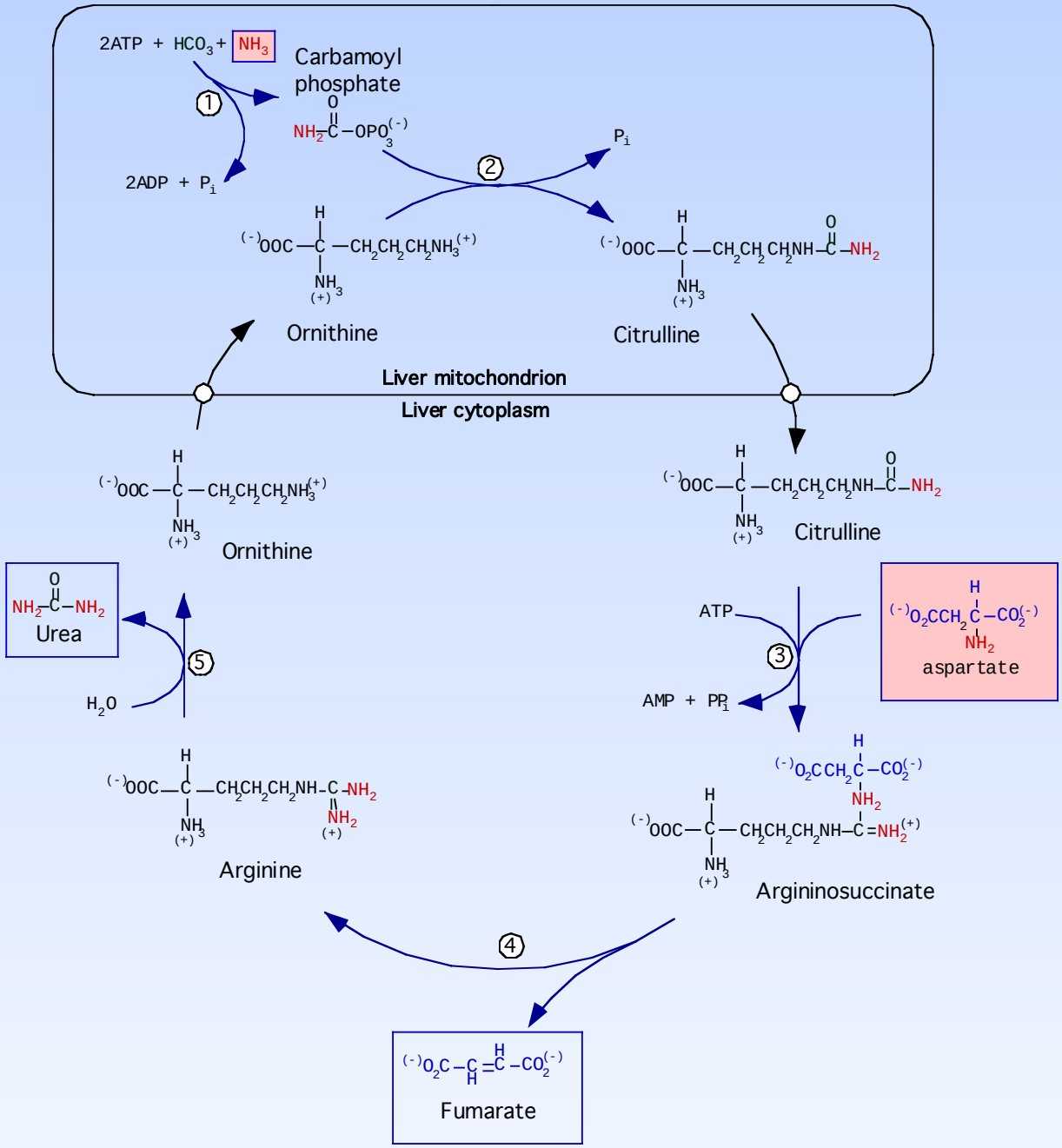
- Possible metabolic/energetics effects:
  - alpha-ketoglutarate levels
  - glutamate levels
  - glutamine



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



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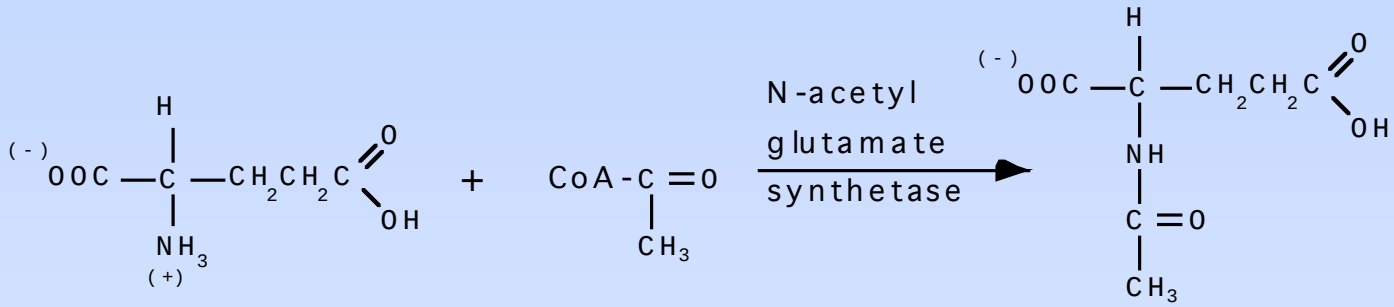
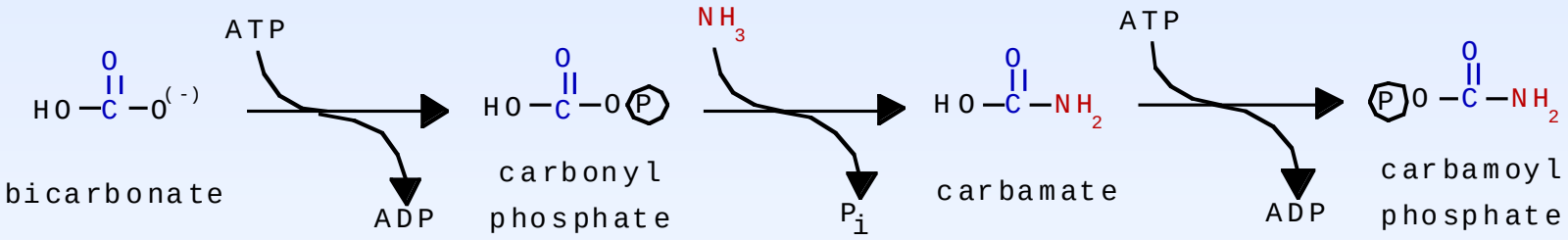
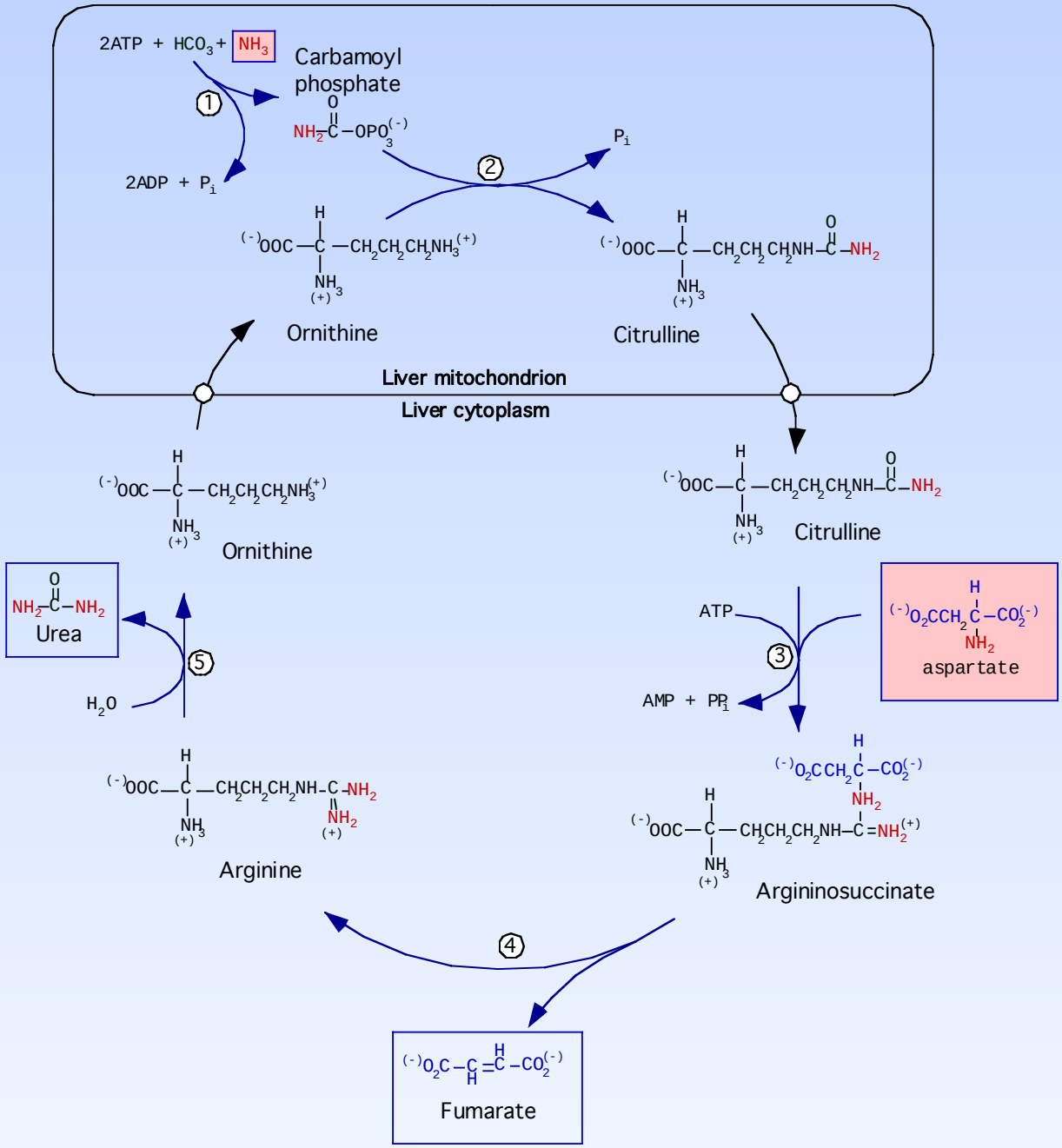


(repeating the figure from page 3 of your handout)

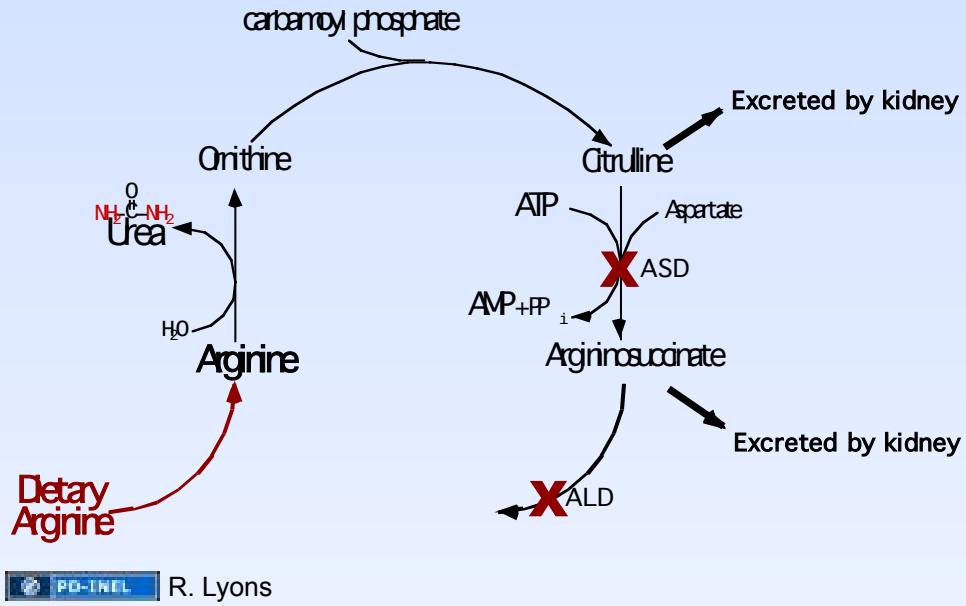




Clinical Management of Urea Cycle Defects

- Dialysis to remove ammonia
- Provide the patient with alternative ways to excrete nitrogenous compounds:

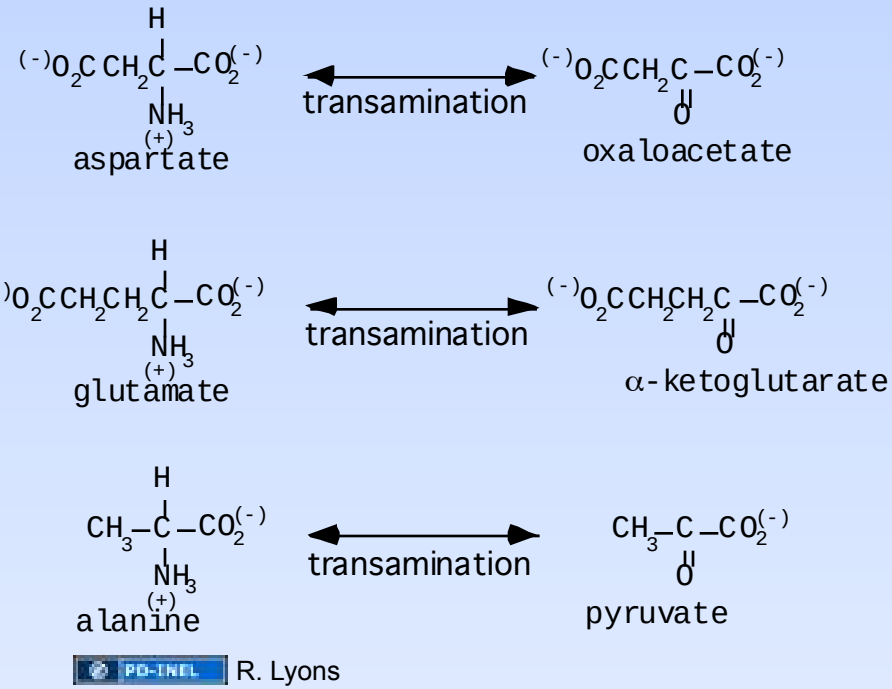
  * Intravenous sodium benzoate or phenylacetate
  * Supplemental arginine



- 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:

Glutamine $\xrightarrow{\text{glutaminase}}$ **glutamate + ammonia**

…and by analogy, how to degrade Asparagine:

Asparagine $\xrightarrow{\text{asparaginase}}$ **aspartate + ammonia**

Amino Acids are categorized as ‘Glucogenic’ or ‘ketogenic’ or both.

Many amino acids are purely glucogenic:

Glutamate, aspartate, alanine, glutamine, asparagine,…

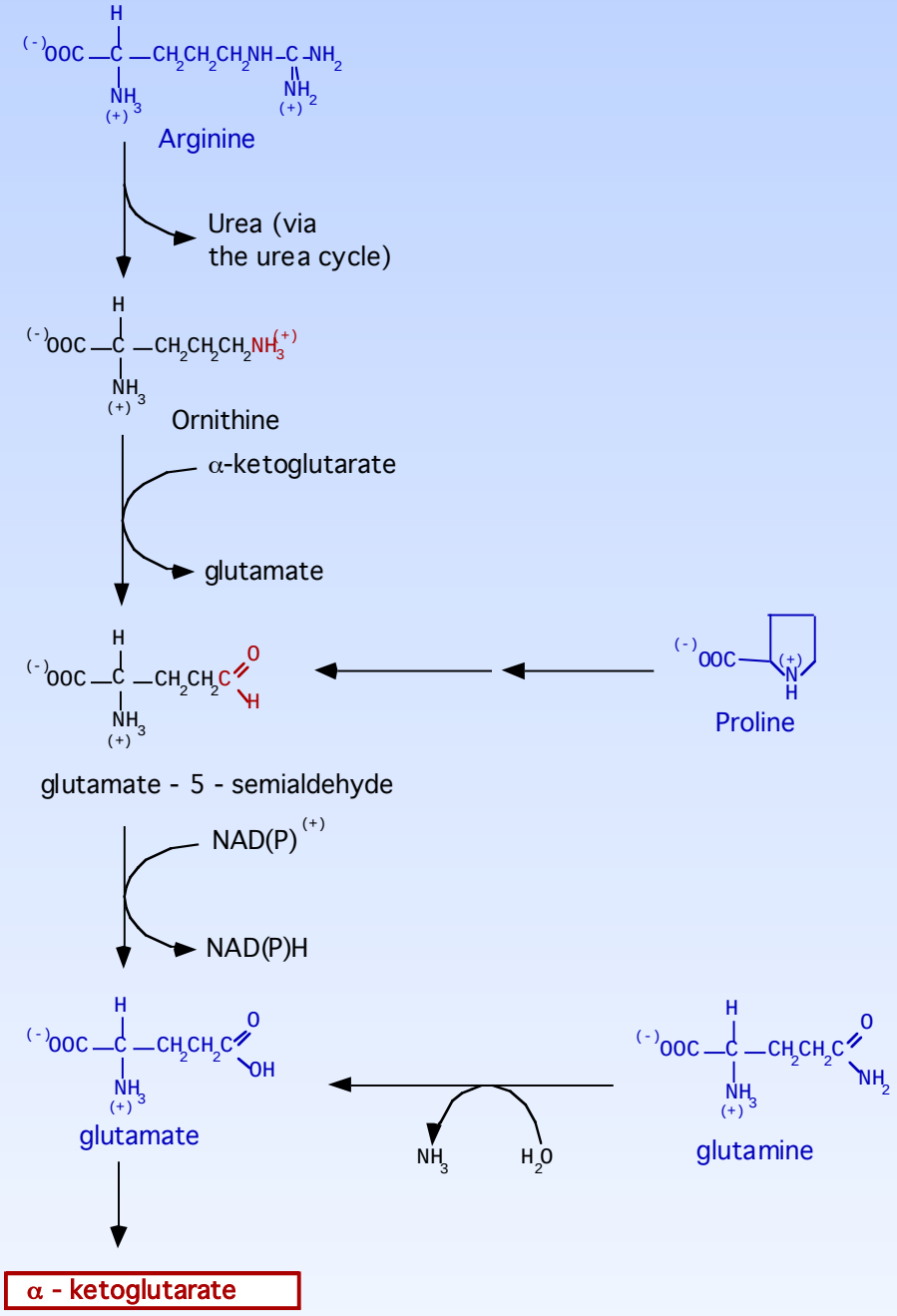
Some amino acids are *both* gluco- and ketogenic:

Threonine, isoleucine, phenylalanine, tyrosine, tryptophan

The only PURELY ketogenic Amino Acids:

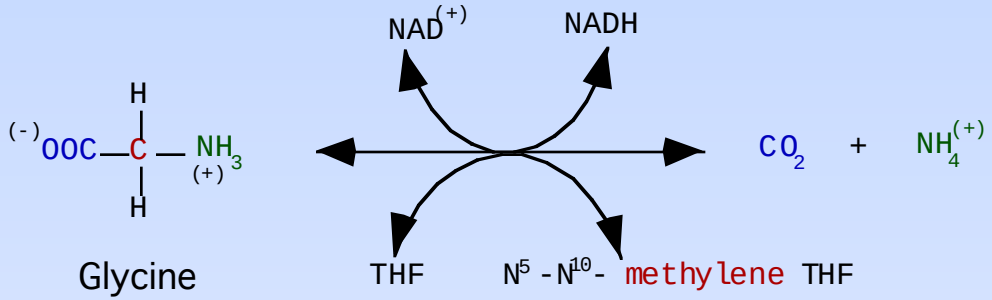
leucine, lysine

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

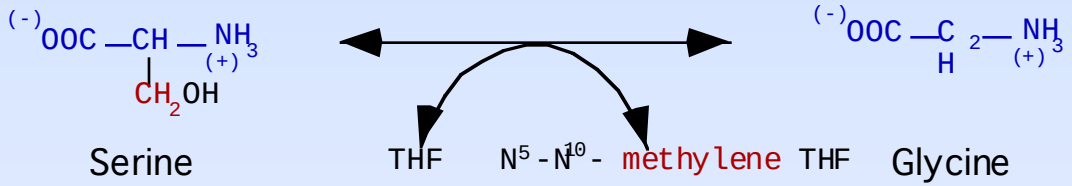


Degradation and Biosynthesis of Serine and Glycine

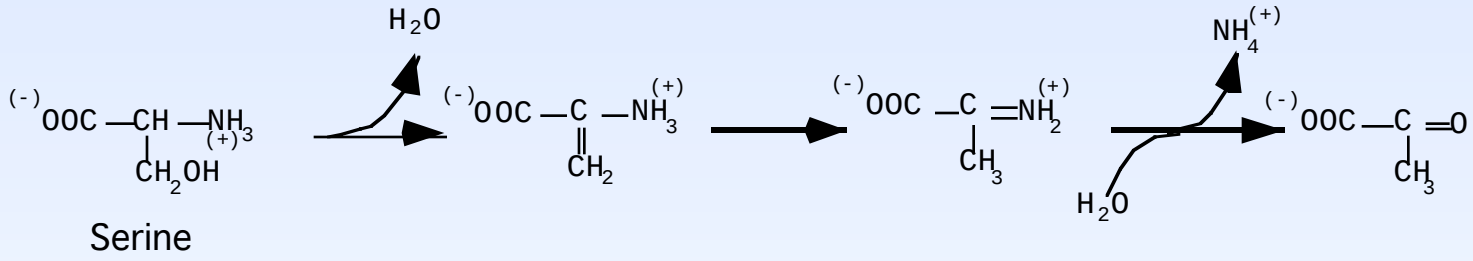
Glycine Synthase:



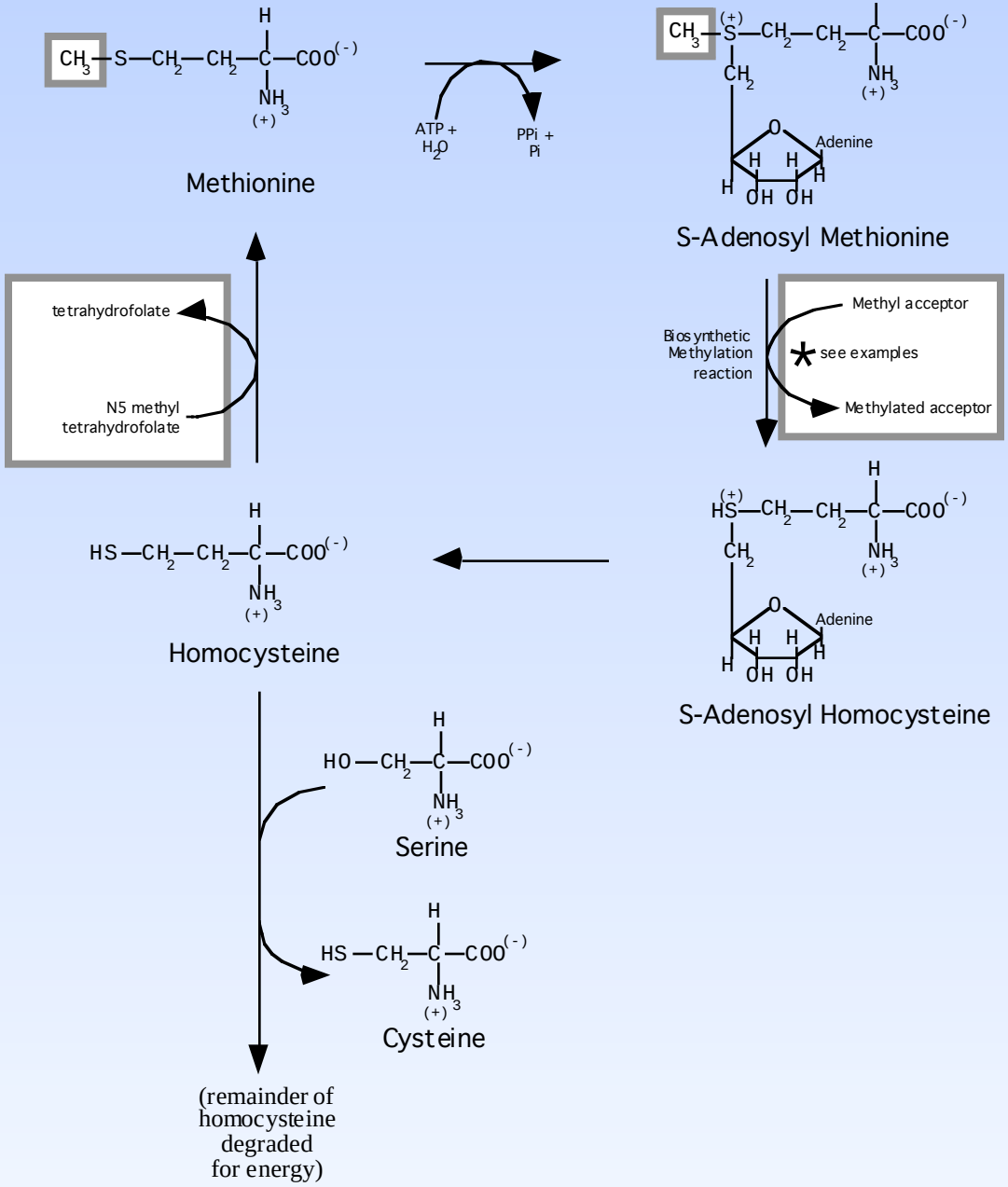
Serine Hydroxymethyl-transferase:



Serine Dehydratase:

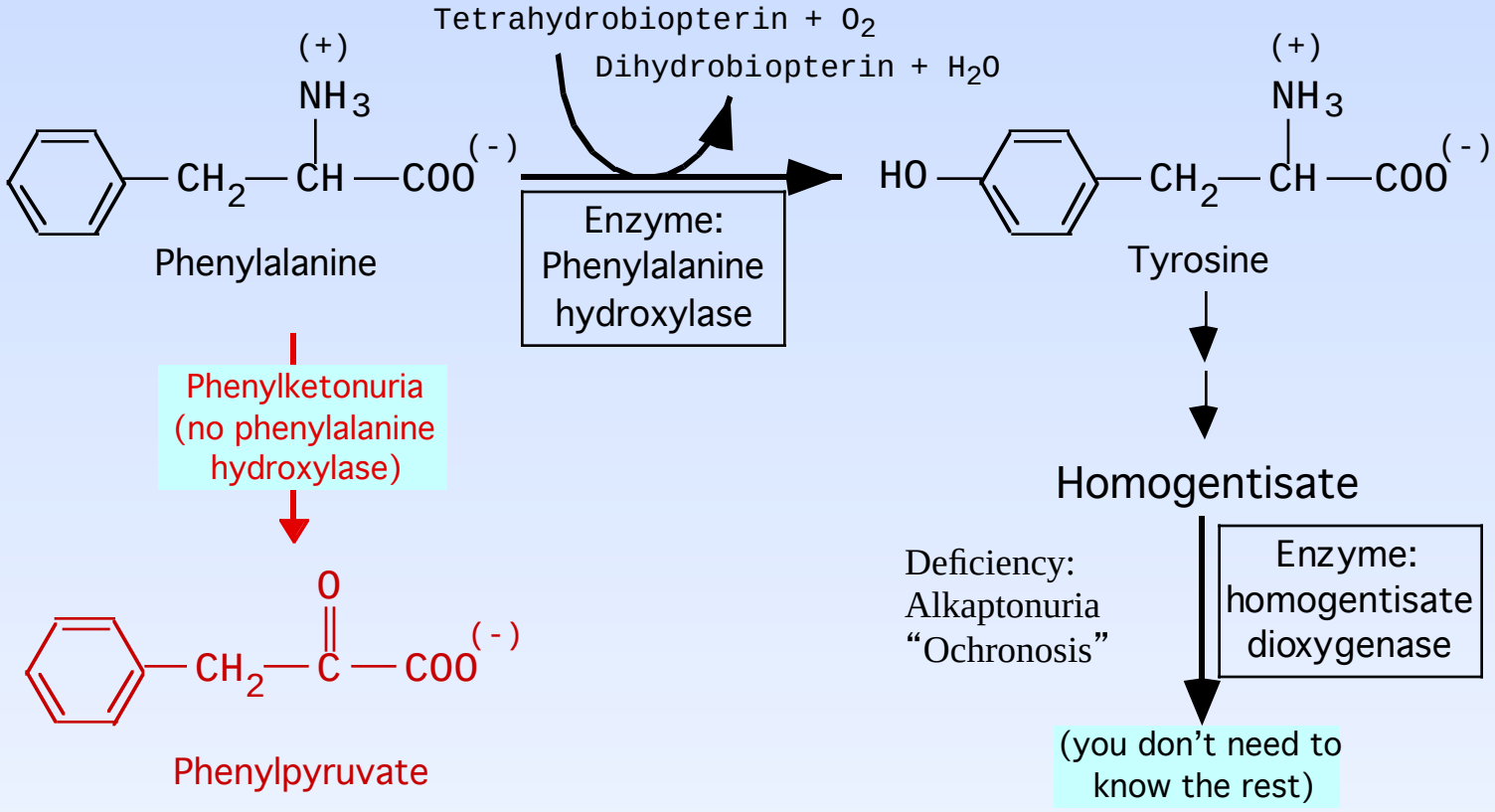


Methionine Cycle And Biological Methyl Groups

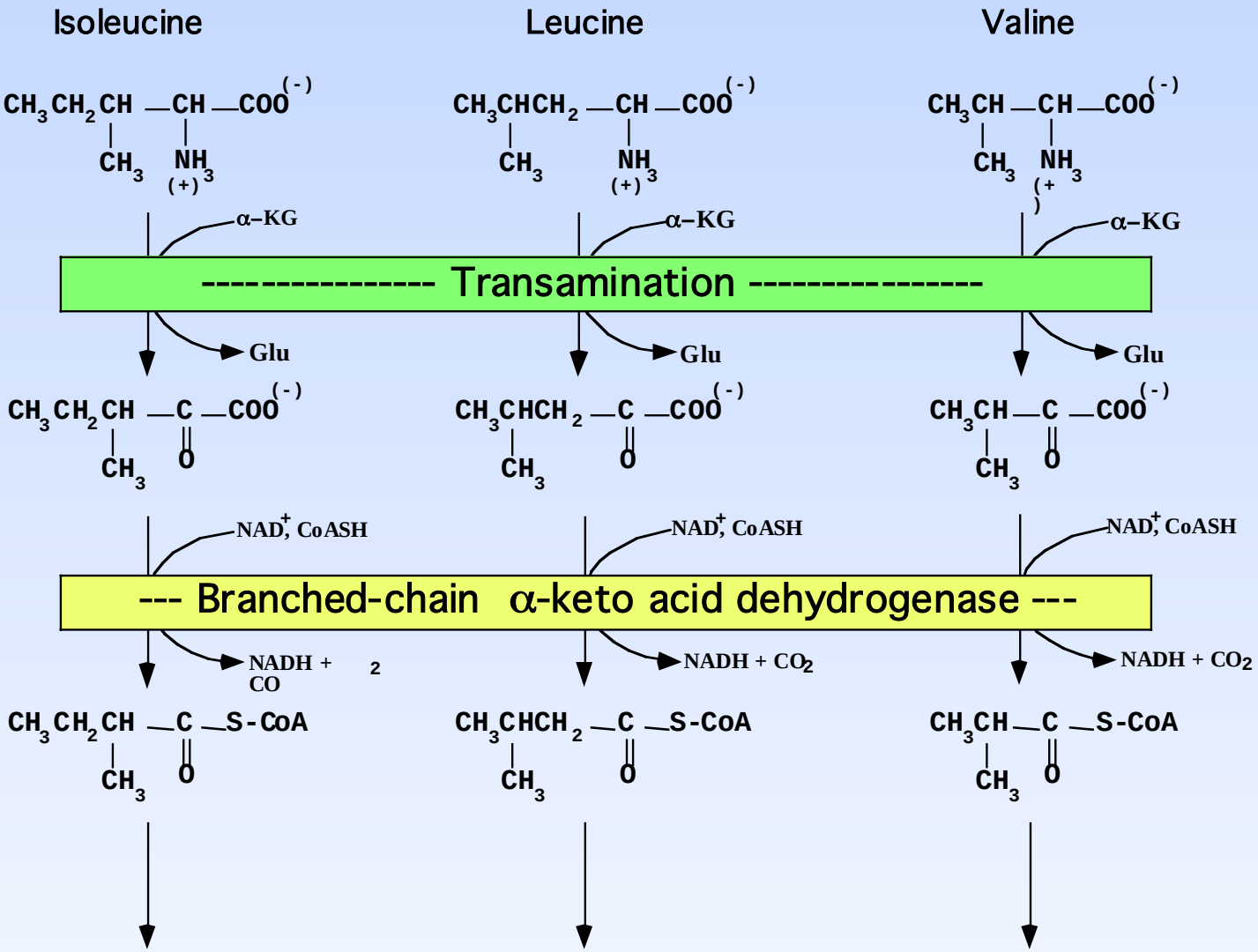


Phenylalanine and Tyrosine

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

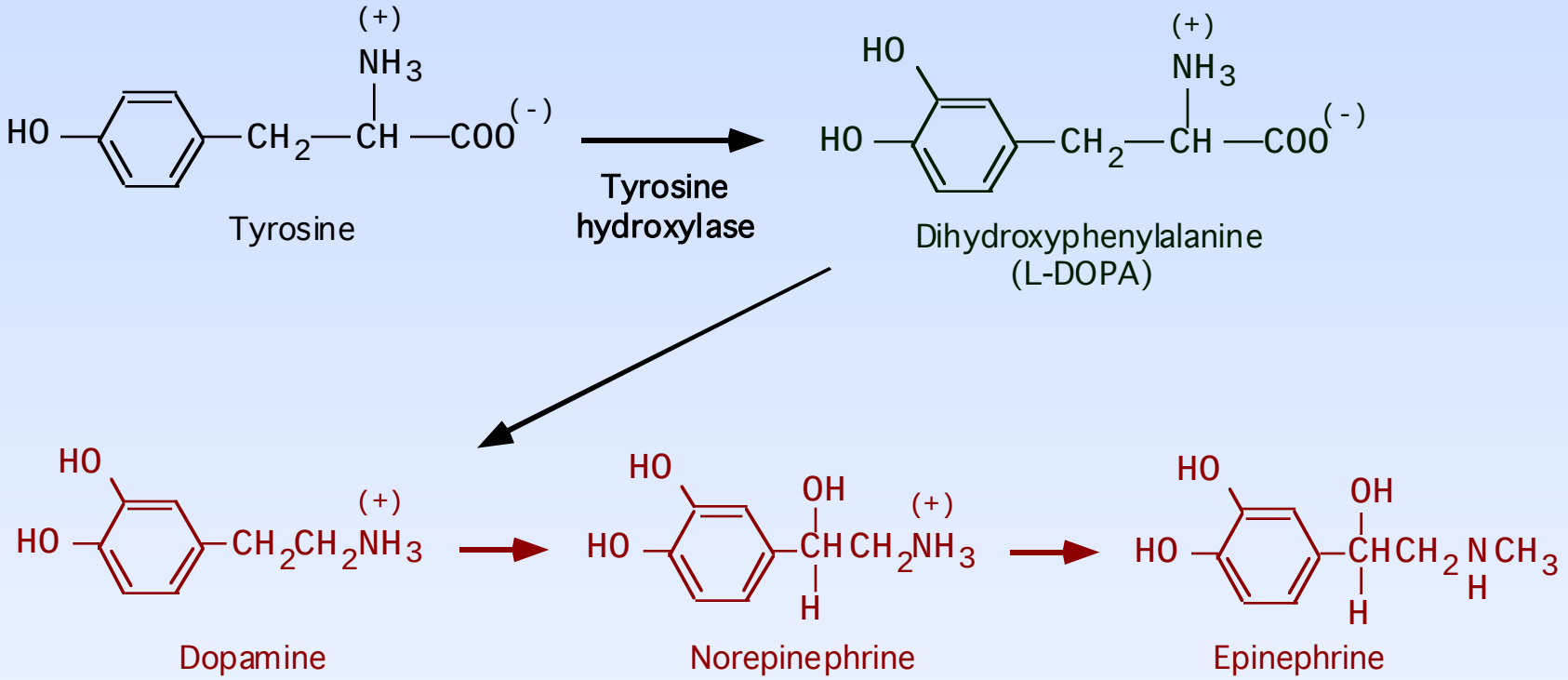


Branched Chain Amino Acids



(continues on to degradation path similar to β-oxidation of fatty acids)

Synthesis of Bioactive Amines



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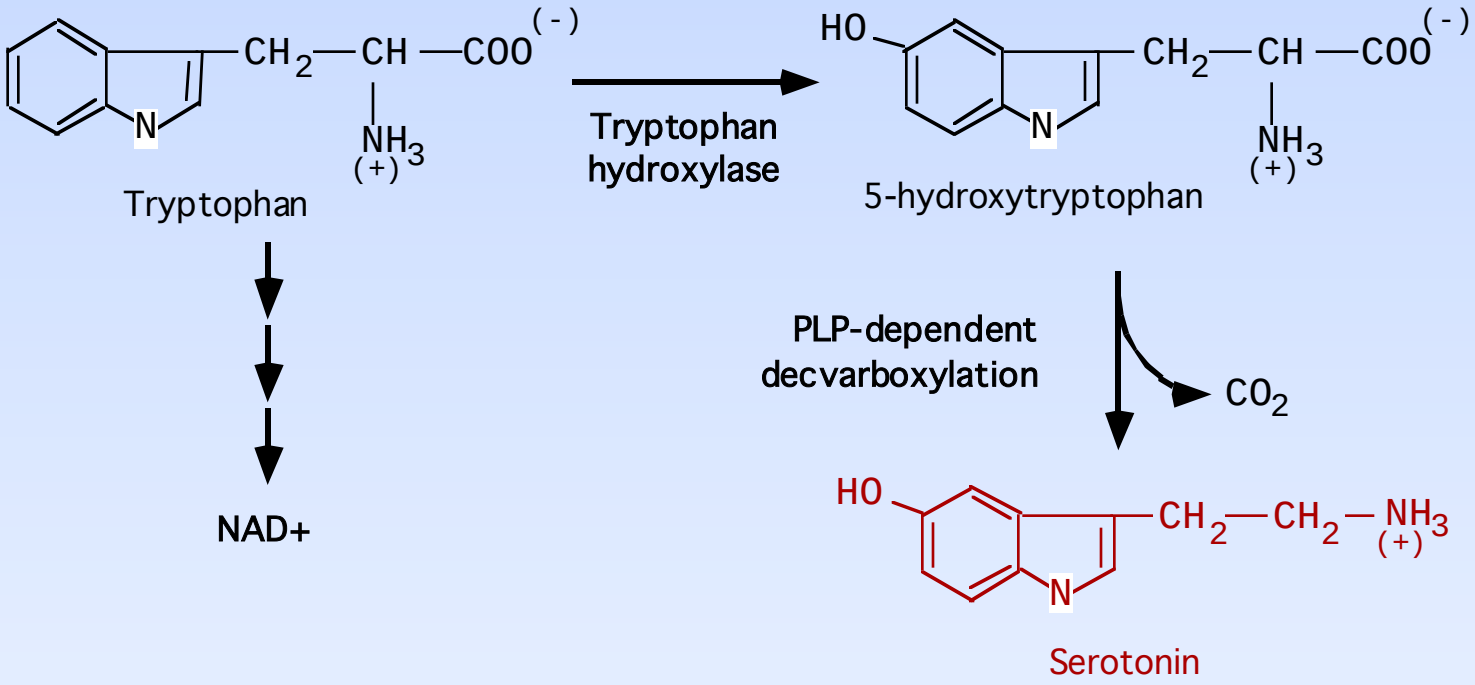

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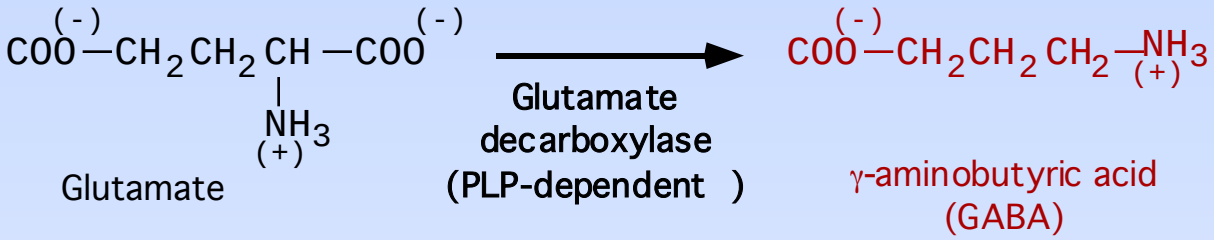

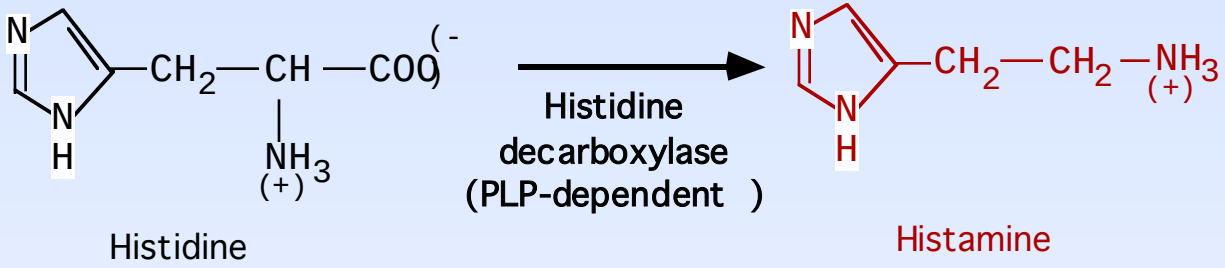

NON-Essential Amino Acids:

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

Essential Amino Acids:

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

Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

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Slide 18: Robert Lyons
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