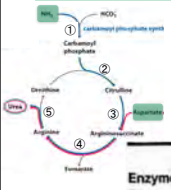
Amino Acid Catabolism: Urea Cycle

Enzymes of the Urea Cycle



See Sapling animated Figure on CPS mechanism ①

See Sapling animated Figure on ASS mechanism ③

	Enzyme	Compartment	Activity	M_r	pH opt	K_m, mM	Equilibrium Constant	Tissue Distribution
	N-acetyl glutamate synthetase, EC 2.3.11	Mitochondrial matrix	0.30–1.49	200,000	8.5	Glu, 3.0 Ac CoA 0.7 Arg, 0.01	Irreversible	Liver, intestine, kidney (trace), spleen
①	Carbamyl phosphate Synthetase EC 6.3.4.16	Mitochondrial matrix	279†	310,000 dimer	6.8–7.6	NH_4, 0.8 HCO_3, 6.7 Mg ATP, 1.1 NAG, 0.1	Irreversible	Liver, intestine, kidney (trace)
②	Ornithine transcarbamylase, EC 2.1.3.3	Mitochondrial matrix	6600	108,000 trimer	7.7	CP, 0.16 Orn, 0.40	$\frac{(Cit)(p)}{(Orn)(CP)} = 10^5$	Liver, intestine, kidney (trace)
③	Argininosuccinic acid synthetase, EC 6.3.4.5	Cytosol	90	185,000 tetramer	8.7	Asp, .03 Cit, .03	$\frac{(ASA)(AMP)(Mg\,PP)(2H)}{(Cit)(Asp)(Mg\,ATP)} = 0.89$‡	Liver, kidney, fibroblasts, brain (trace)
④	Argininosuccinase, EC4.3.2.1	Cytosol	220	173,200 tetramer	7.5	Asp, 0.017 Cit, 0.016 ATP, 0.041	$\frac{(Arg)(fumarate)}{(ASA)} = 11.4 \times 10^{-3}$	Liver, kidney, brain, fibroblasts
⑤	Arginase, EC 3.5.3.1	Cytosol	86,600	107,000 tetramer	9.5	Arg, 10.5	Irreversible	Liver, erythrocytes, kidney, lens, brain (trace)

*Enzyme activity is expressed as micromoles per hour per gram wet weight. Apart from the equilibrium constants, the values described are those of human liver.
†The monomers may have substantial catalytic activity.[11]
‡At pH = 7.0.
Source: Table assembled from Ratner,[4] Snodgrass,[9] Meijer and Hensgens,[10] Jackson, et al.,[11] Beaudet et al.,[12] Lusty,[13] and Bachman et al.[14]

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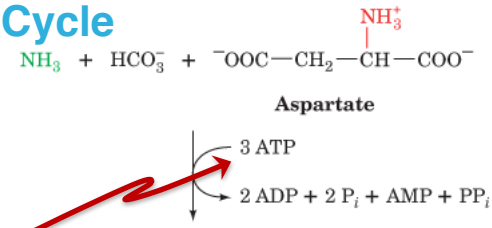
Energetics of Urea Cycle

Per 2 nitrogen atoms to make **one** urea molecule:



2 each to make CP and arginosuccinate

Net is 4 ATP equivalents

[Its not actual ATPs used, its how many it takes to re-cycle the products (2 ADP + 1 AMP)]

- But what about this fumarate?
- What is its fate?
- How do you regenerate Asp to keep the cycle going?

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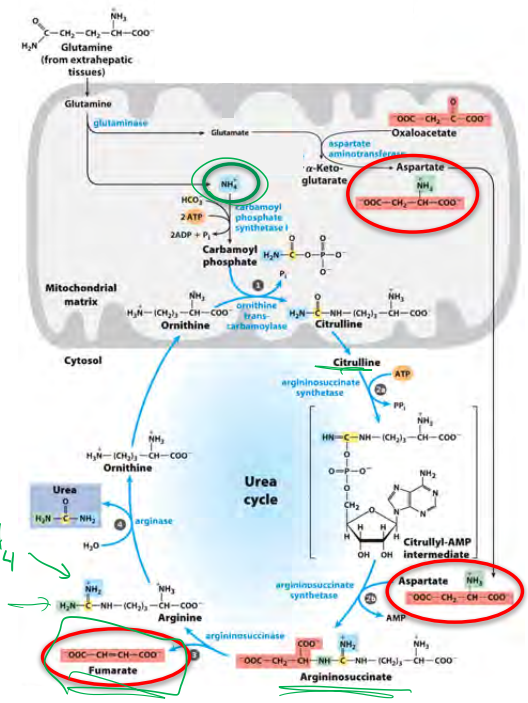


Two issues:

1) What to do with the fumarate?

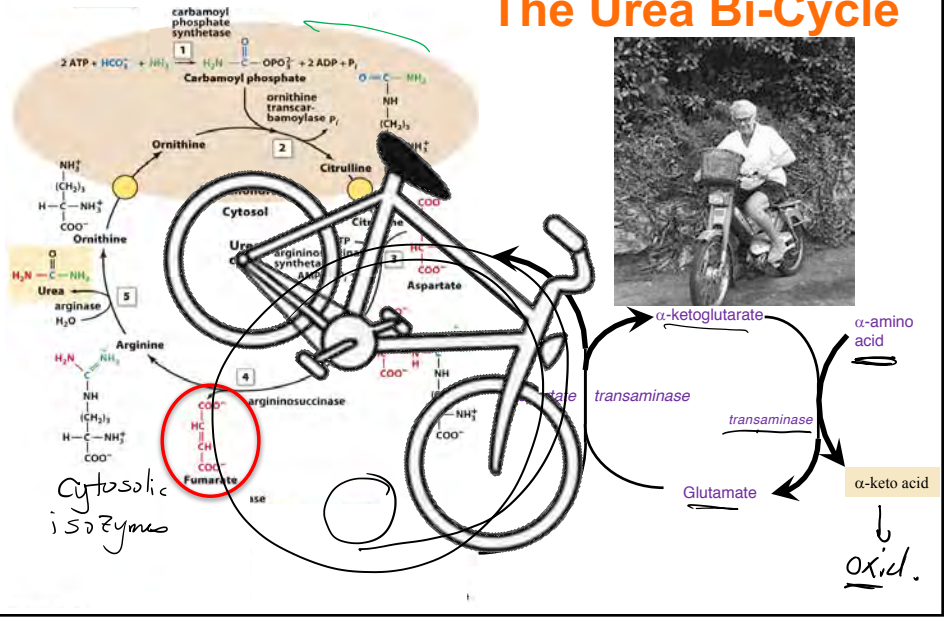
2) What are the sources of the free ammonia?

NH_4^+

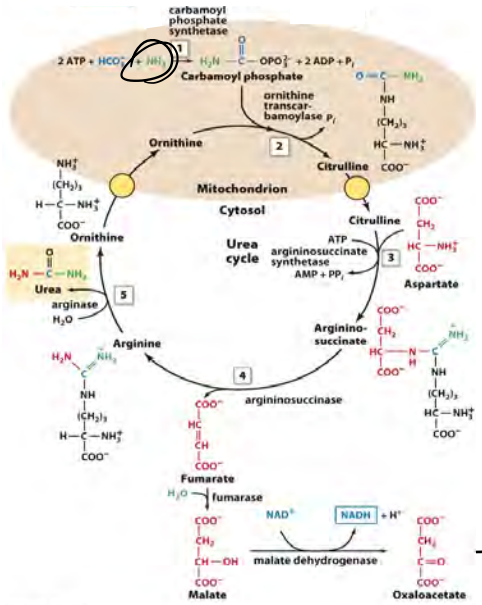
Asp

Amino Acid Catabolism: Urea Cycle

The Urea Bi-Cycle



Amino Acid Catabolism: Urea Cycle



The Urea Bi-Cycle

Two issues:

1) **What to do with the fumarate?**

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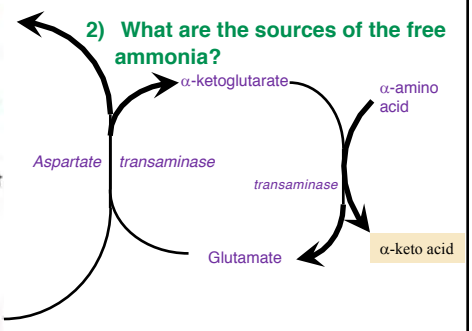

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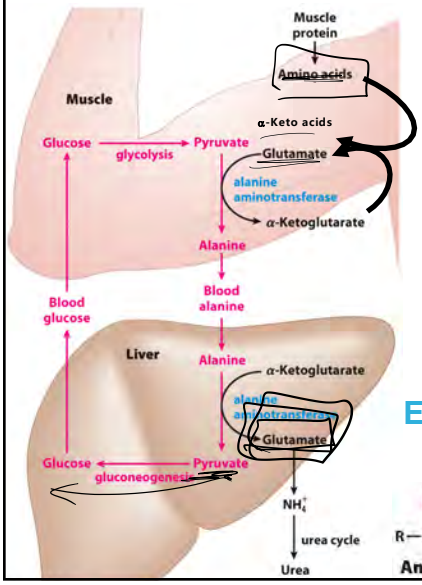
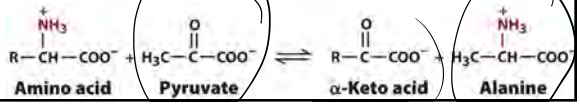
The Glucose-Alanine Cycle



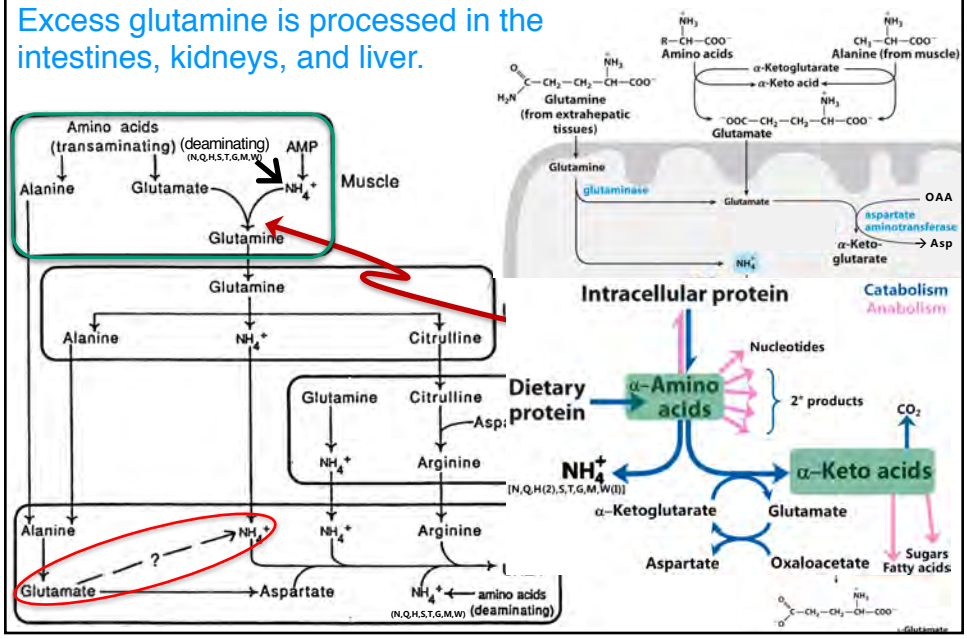
- Vigorously working muscles operate nearly anaerobically and rely on glycolysis for energy.
- Glycolysis yields pyruvate.
  - If not eliminated, lactic acid will build up.
- This pyruvate can be converted to alanine for transport into the liver.

Excess Glutamate is Metabolized in the Mitochondria of Hepatocytes



Amino Acid Catabolism: Urea Cycle

Excess glutamine is processed in the intestines, kidneys, and liver.



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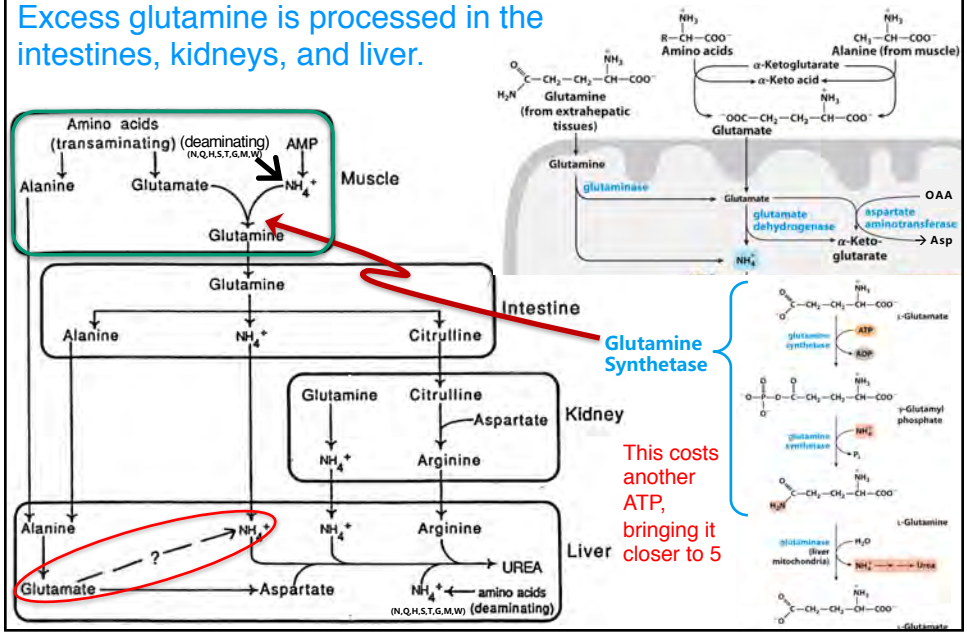
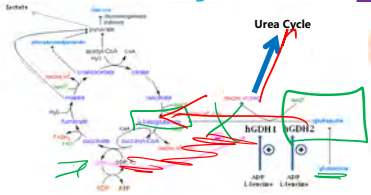


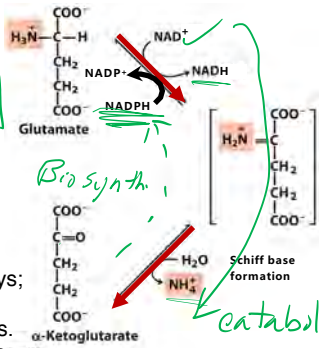
Amino Acid Catabolism: Urea Cycle

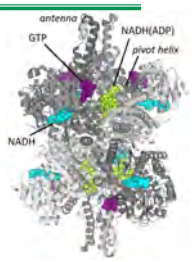
Regulation of the Urea Cycle



- The pool of **Glu** is a critical junction between biosynthesis and catabolism
- The enzyme represents a key link between catabolic and anabolic pathways; when biosynthesis is needed, its off and Glu provides for amino-acid biosynthesis. When energy is needed, the ammonia is pulled off to provide for the urea cycle and oxidation of carbon skeletons.
- Can use either NAD^+ in the catabolic direction (oxidative deamination), or NADPH in the biosynthetic direction.

Glutamate Dehydrogenase





Allosteric inhibitors:
GTP, ATP, Palmitoyl-CoA

Allosteric Activators:
ADP, Leucine, Isoleucine, Valine

- GluDH has a high K_m value (>1 mM) for ammonia, so it mostly functions to provide the initial material for the urea cycle; ammonia, using NAD^+, which is high when energy charge is low.
- Ammonia is processed into urea for excretion. Carbon skeletons are oxidized for ATP.

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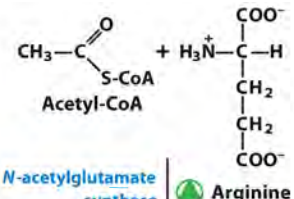
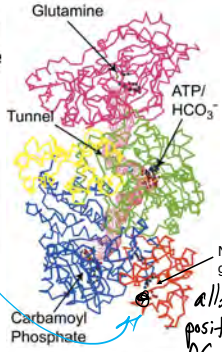
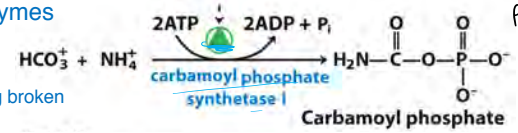
Regulation of the Urea Cycle



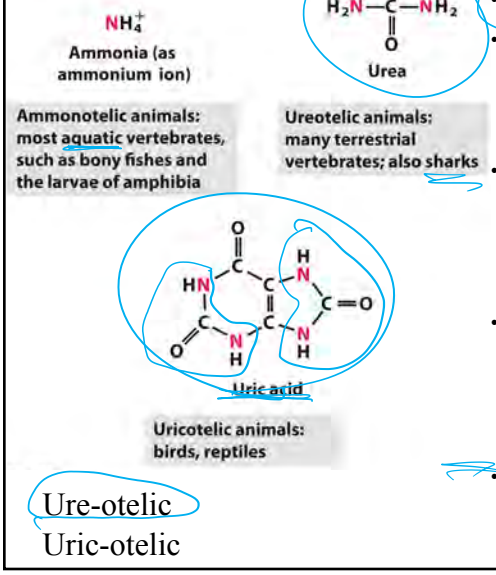


- Urea production is controlled by carbamoyl phosphate synthetase.
- *N*-acetylglutamate is an allosteric activator.
- Carbamoyl phosphate synthase I is activated by *N*-acetylglutamate.
- Formed by *N*-acetylglutamate synthase
  - –when glutatmate and acetyl-CoA concentrations are high
  - –K_m values are 1 and 0.7 mM, respectively
  - –activated by arginine (K_i value of 10 μM!)
- Expression of urea cycle enzymes increases when needed.
  - –high-protein diet
  - –starvation, when protein is being broken down for energy



Amino Acid Catabolism: Urea Cycle

Excretory Forms of Nitrogen: Fates of Nitrogen in Organisms



- Plants conserve almost all the nitrogen.
- Many aquatic vertebrates release ammonia to their environment.
  - –passive diffusion from epithelial cells
  - –active transport via gills
- Many terrestrial vertebrates and sharks excrete nitrogen in the form of urea.
  - –Urea is far less toxic that ammonia.
  - –Urea has very high solubility.
  - –Requires lots of water
- Some animals such as birds and reptiles excrete nitrogen as uric acid.
  - –Uric acid is rather insoluble.
  - –Excretion as paste allows the animals to conserve water.
- Humans and great apes excrete both urea (from amino acids) and uric acid (from purines).

Ure-otelic
Uric-otelic

Amino Acid Degradation

The SEVEN (7) Families

A. Concepts
   1. Convergent
   2. ketogenic/glucogenic
   3. Reactions seen before
B. Transaminase (A,D,E) / Deaminase (Q,N) Family
C. Related to biosynthesis (R,P,H; C,G,S; T,M)
   1. Glu Family
      a. Introduce oxidases/oxygenases
      b. Introduce one-carbon metabolism (1C)
   2. Pyruvate Family
      a. PLP reactions
   3. α–ketobutyric Family
      a. 1-C metabolism
D. Dedicated (F,Y; K,W; V,I,L)
   1. Aromatic Family
      a. oxidases/oxygenases
   2. α–ketoadipic Family
   3. Branched-chain Family