The Urea Cycle

UREA FORMATION REACTION

• HCO_3^- + 1 NH_3 + Aspartate + 3ATP + H_2O ?

• Urea + Fumarate + 2ADP + AMP + 2 Phosphate and 1 Pyrophosphate.

FULL-LENGTH TEXT

• Here we will learn about nitrogen transport and the urea cycle.

• To begin, start a table.

• Denote that urea is the end-product of the catabolism of nitrogen, which enters the urea cycle as ammonium.

• Denote that it occurs in liver cells (aka hepatocytes).

• Denote that the urea cycle is particularly active after a high protein meal and during states of starvation.

Now, let's learn the reactions of the cycle.

• Draw a portion of a mitochondrion in the cytosol and label the matrix.

- The first two reactions of the cycle occur in the mitochondrial matrix and the remaining occur in the cytosol.

• Indicate that carbamoyl phosphate synthase I (CPS I) catalyzes the first reaction the first reaction: carbamoyl phosphate synthesis.

• Indicate that it is the rate-limiting step, thus CPS I is, in essence the pacemaker enzyme of the urea cycle.

• Show that the substrates are bicarbonate, free ammonia (which derives primarily from glutamine and asparagine) and ATP (which makes it essentially an irreversible reaction).

- Note that often it's stated that the condensation is between carbon dioxide and ammonium, probably because nitrogen is transported throughout the body as ammonium (not ammonia) but here we show the condensation as occurring between bicarbonate and ammonia because carbamoyl synthetase actually uses ammonia (not ammonium) as its substrate – this is a small but important distinction to be aware of to avoid confusion.

• Show that these substrates combine to produce the first intermediate: Carbamoyl phosphate, which is:

- Carbamoyl – Carbon bonded to an amide and double bonded to an oxygen.

- Phosphate – phosphorous with 4 oxygen.

• We highlight that the carbon and nitrogen that were derived from bicarbonate and ammonia.

• Show that in the process, ADP, hydrogen, and phosphate are released.

• Next, show that the cofactor N-acetyl glutamate is necessary for CPS I to proceed (it's sufficiently present after a protein meal, especially).

• Indicate that the enzyme N-acetyl glutamate synthase (NAGS) synthesizes it from glutamate and acetyl CoA.

• Next, show that arginine positively regulates this reaction.

- Arginine is a marker of high protein conditions, and thus positively regulates the urea cycle.

Now, for the second reaction in the cycle: citrulline formation.

• An anhydride bond connects the carbamoyl and phosphate groups – which makes the carbamoyl primed for transfer.

• So show that it easily moves to ornithine to form citrulline (still within the mitochondrial matrix) via ornithine transcarbamoylase and the phosphate is lost.

• Next, show that citrulline exits the matrix and enters the cytosol.

• Introduce an aspartate and specify its amino group, which we'll track through the urea cycle.

- Show that argininosuccinate synthetase catalyzes the reaction to combine aspartate with citrulline to form argininosuccinate.

• Indicate that one ATP is converted to AMP and pyrophosphate to drive forward the reaction (pyrophosphate is later hydrolyzed, as well).

• Now, draw the terminal carbon of argininosuccinate so we can see that its two nitrogens form from both the free ammonia from the beginning of the cycle and the aspartate.

• Next, show that argininosuccinase cleaves this large molecule into arginine and fumarate.

- We choose to show fumarate in block lettering because we've seen elsewhere it's importance as a carbon skeleton intermediate in the TCA cycle and its role in the integration of metabolism.

• Now, show that arginase hydrolyzes arginine to ornithine and urea.

• Specify that urea carries that two nitrogen picked up during the urea cycle: one from ammonia and one from aspartate.

Finally, let's write down the reaction for urea formation:

• HCO_3^- + 1NH_3 + aspartate + 3ATP + H_2O yields urea + fumarate + 2ADP + AMP + 2 phosphates and 1 pyrophosphate.

• Thus, as arginine accumulates it promotes the rate-limiting step in the urea cycle by activating N-acetyl glutamate synthase!

- Again, draw the terminal carbon of arginine bound to two highlighted amine groups (from free ammonia and from aspartate).

• Urea is simply our two highlighted amine groups joined by a carbonyl carbon (originally from bicarbonate).

- Urea can safely diffuse into circulation and travel to the kidneys, where it is excreted as urine.

• To emphasize this point, write that urea gains one nitrogen from free ammonia and one nitrogen from aspartate.

• Use a final arrow to indicate that ornithine reenters the cycle at citrulline formation.

• As a clinical correlation, write that defects in CPS-I or in N-acetylglutamate synthase produce hyperammonemia, in which excess ammonia accumulates due to genetic defects in urea cycle enzymes or liver disease.

- Ammonia is extremely toxic when it accumulates and produces CNS-related defects such as impaired cognitive development.

• Consider that CPS II exists in the cytosol and catalyzes pyrimidine synthesis.

- CPS-I mitochondria / CPS-II is located in the cytoplasm

- CPS-I uses ammonia as the source of nitrogen / CPS-II is uses glutamine

- CPS-I requires N-acetylglutamate as an allosteric activator / CPS-II does NOT.

- CPS-I is found in Liver (and kidney) / CPS-II is ubiquitous.