Biosynthesis of Urea

Urea is the main nitrogen containing urinary metabolite in mammals. Besides Urea, other nitrogenous urinary metabolites are ammonia, Creatinine, Creatine and Uric Acid. Except Uric Acid, all other metabolites are degradation products of amino acid metabolism. Uric Acid is a degradation product of purine metabolism and is the excretory form in birds. Ammonia, being a primary degradation product of amino acid metabolism, is excreted out as NH_4^+ ion with water through gill of fishes. In mammals, including human, though some amount of NH_3 is eliminated with urine water as $+NH_4$ ion required in acid-base balance during metabolic acidosis. Major amount of ammonia is utilized in Liver for urea synthesis and removed with urine. Mammals are hence called Ureotelic.

Synthesis of Urea utilizes two toxic gases, NH_3 and CO_2. Carbon dioxide is generated by oxidative decarboxylation in mitochondria by dehydrogenases. such as Pyruvate dehydrogenase complex, α-Ketoglutarate dehydrogenase complex and Isocitrate dehydrogenase.

Most of the CO_2 is transported as HCO_3^- ions from tissues to lungs and expelled to air with expiration. Because of highly neurotoxic nature, blood level of NH_3 is not allowed to exceed normal level (10-20 mg/dl) and is continuously removed from blood through urine. NH_4^+ ions are converted to urea, a mildly toxic metabolite. It takes place in liver cells called hepatocytes.

Urea Cycle

Synthesis of urea involves arrangement of metabolites in cyclic sequence, hence the process is named urea cycle. Urea possesses two amino groups linked to a central Ketonic Carbon. During the process of urea synthesis, one amino group comes from glutamate and other from aspartate. and the Ketonic carbon comes from CO_2. Synthesis of urea requires two mitochondrial and three cytosolic enzymes. The mitochondrial enzymes are Carbamoyl phosphate synthase and ornithine transcarbamylase, whereas cytosolic enzymes are argininosuccinate synthase, arginino succinase and arginase.

Steps of Urea Cycle in Mitochondria –

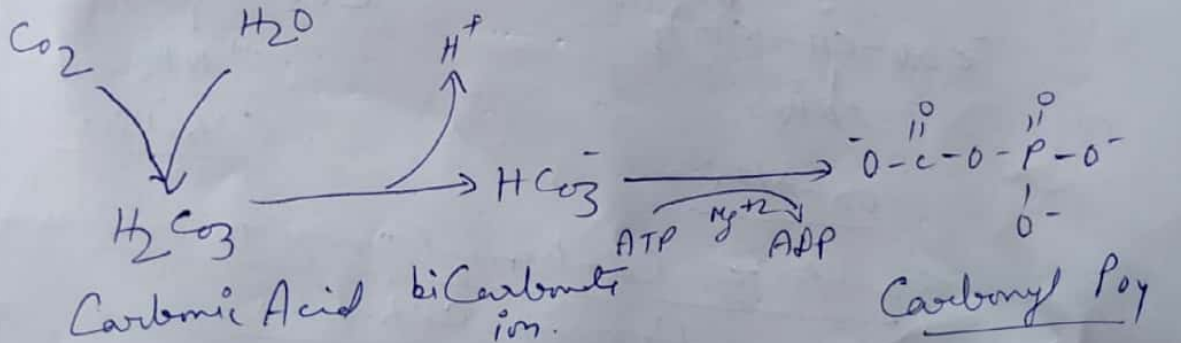
In mitochondria, first step is the [illegible] of Carbamoyl phosphate

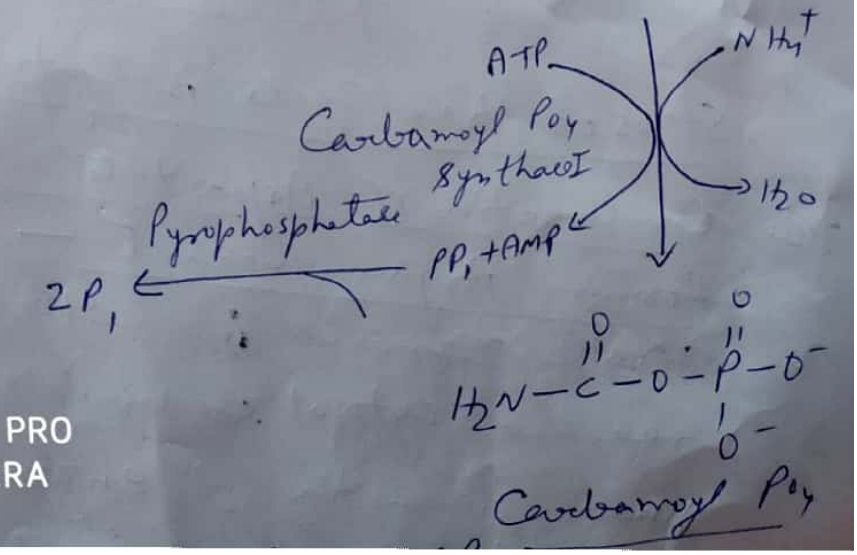
from NH_3 and CO_2, followed by transfer of carbamoyl group to ornithine forming citrulline.

I. Formation of Carbamoyl Phosphate from NH_3 and CO_2 —

one molecule of CO_2, one molecule of NH_3 along with two molecules of ATP, forms Carbamoyl phosphate under the action of enzyme carbamoyl phosphate Synthase I

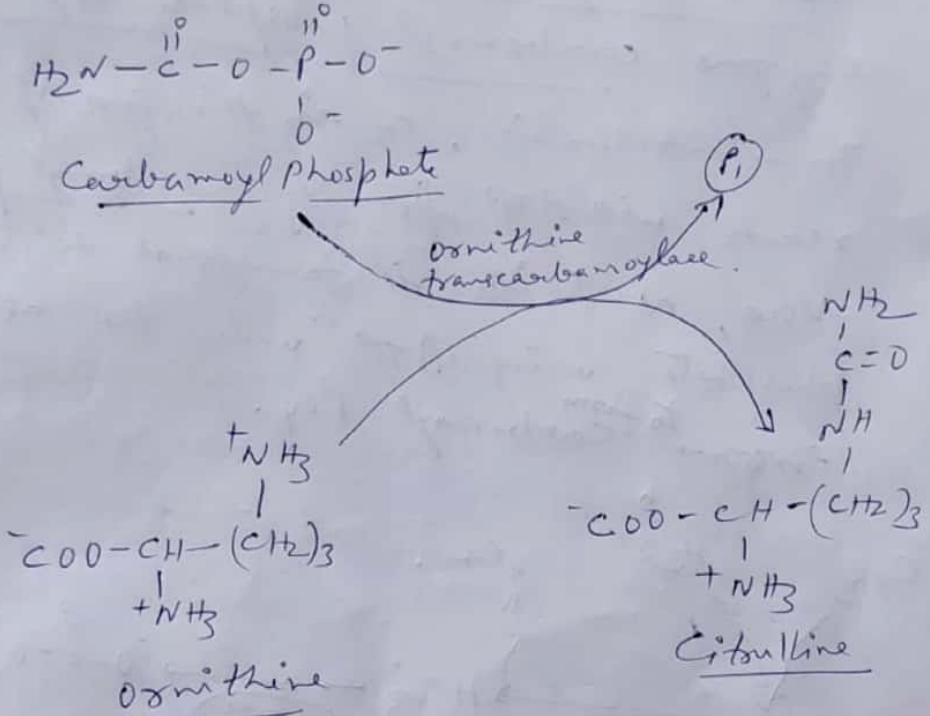
In mitochondria, CO_2 is in the form of HCO_3^- reacts with ATP forming carbonyl phosphate. Now, NH_4^+ ion is transferred to Carbonyl phosphate using ATP under the action of enzyme to form Carbamoyl PO_4.





II Transfer of Carbamoyl Group to Ornithine forming Citrulline — This is the second step, in which enzyme ornithine transcarbamoylase brings transfer of carbamoyl group from Carbamoyl P'y to ornithine forming Citrulline. This is then transported to cytosol of the hepatocyte.

Steps of Urea Cycle in Cytosol —



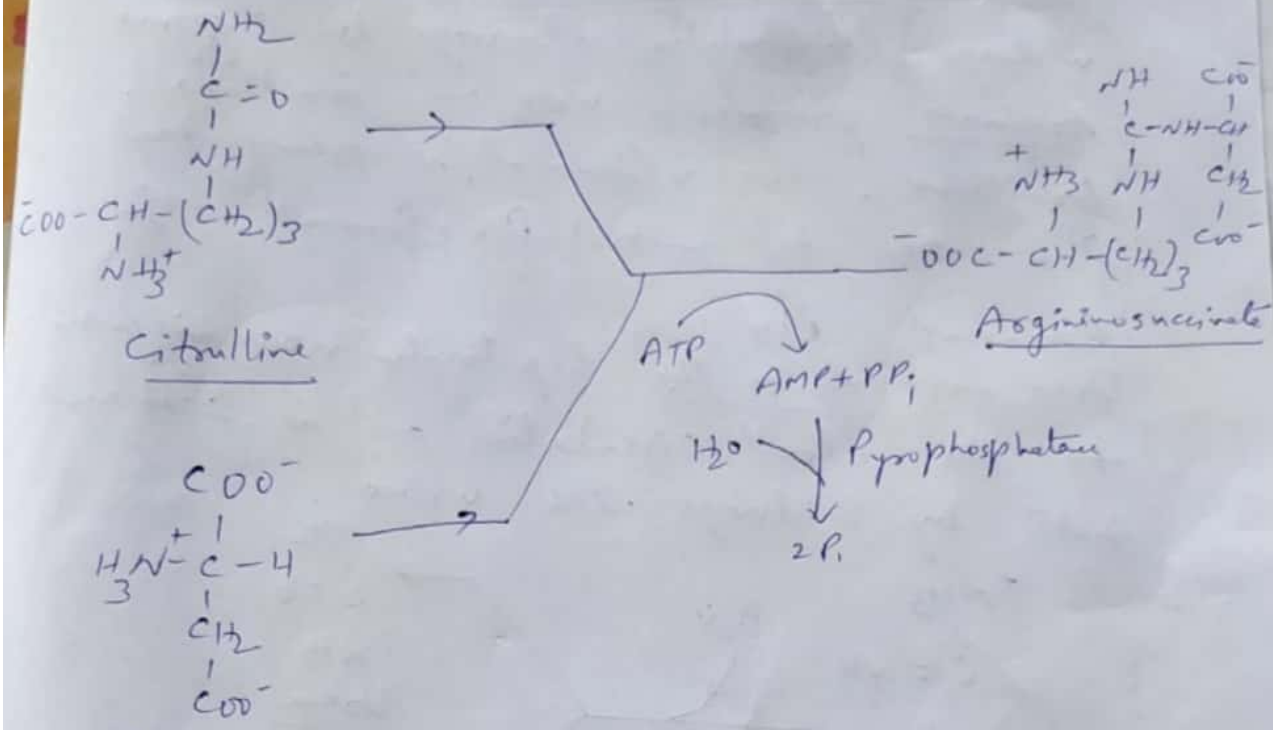
Transfer of Carbamoyl group to ornithine forming Citrulline

Steps of Urea Cycle in Cytosol →

III Condensation of Aspartate with Citrulline forming Argininosuccinate —

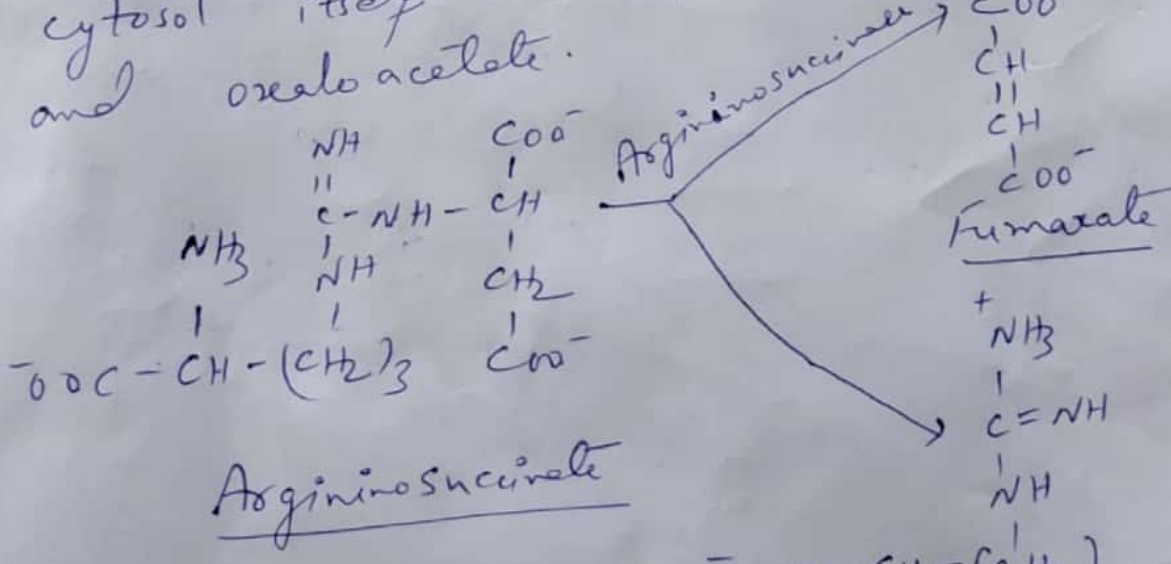
Citrulline formed in mitochondria now reaches cytosol combines with aspartate. under the action of enzyme argininosuccinate synthase forming a covalent bond

The energy required comes from ATP

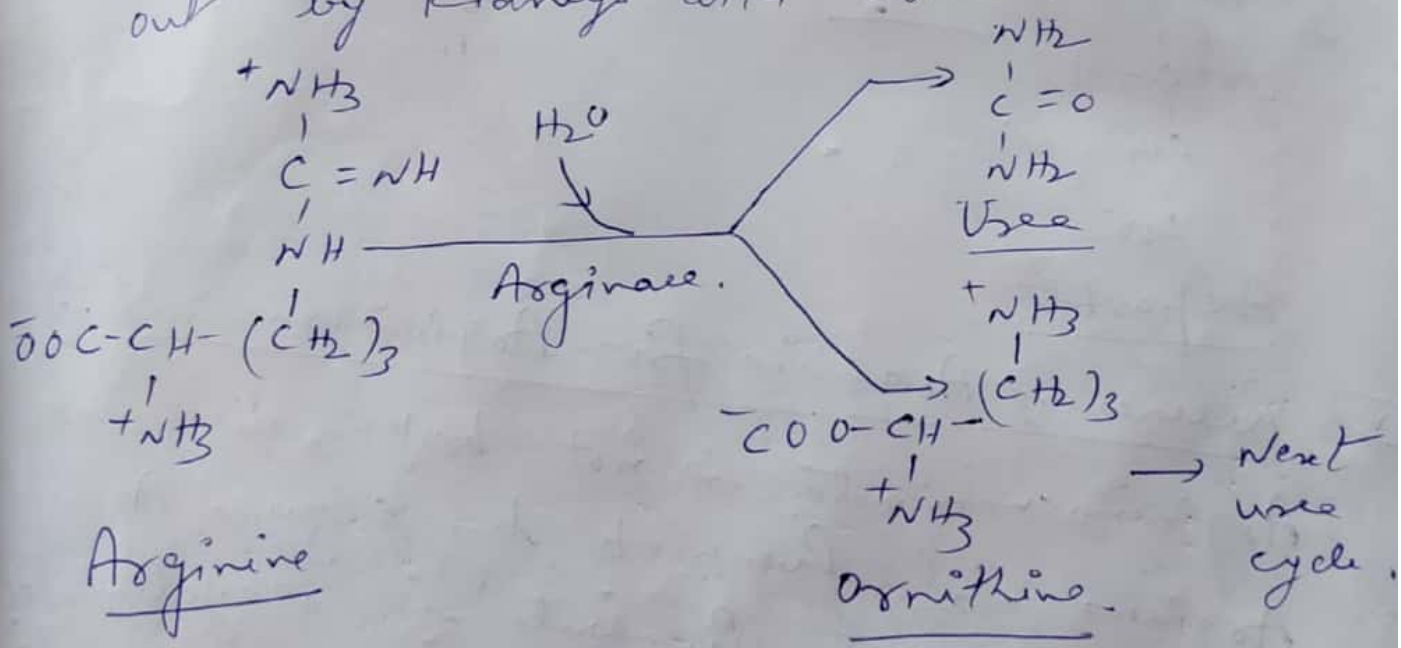


v) Release of Arginine from Argininosuccinate →

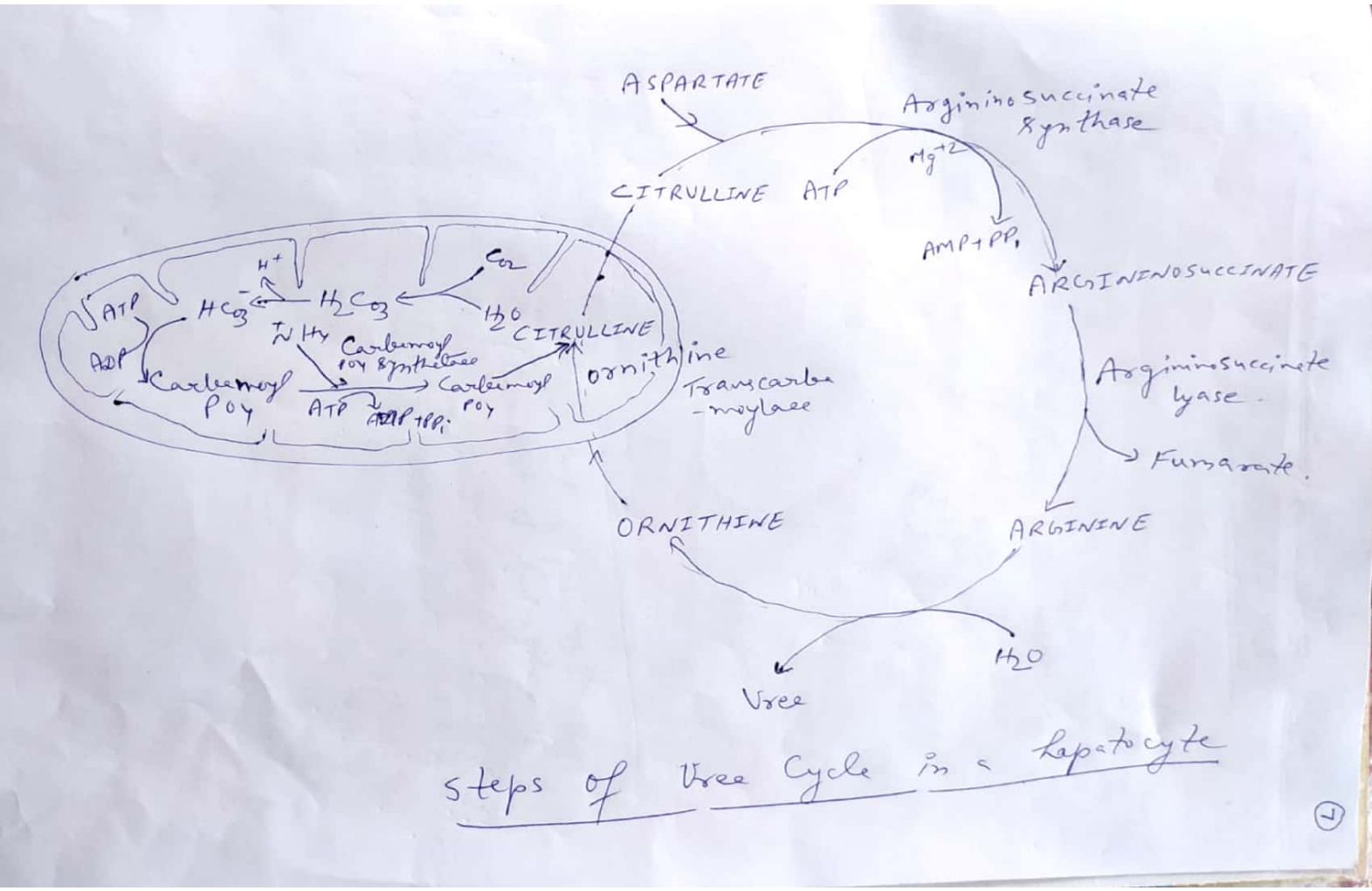
Argininosuccinate is not broken down into Arginine and fumarate by enzyme Argininosuccinase. The fumarate is recycled in cytosol itself to aspartate via malate and oxaloacetate.



V. Production of Urea from Arginine - Arginine formed undergoes hydrolytic cleavage by enzyme Arginase producing urea and ornithine. Ornithine, thus reformed, is transported from cytosol to mitosol for reformation of Carbamoyl PO_4. Urea formed in the hepatocytes now diffuses to the blood circulation and is filtered out by kidneys with urine.



Arginine



steps of Urea Cycle in a hepatocyte