5^{TH} SEM MAJOR

ORNITHINE CYCLE

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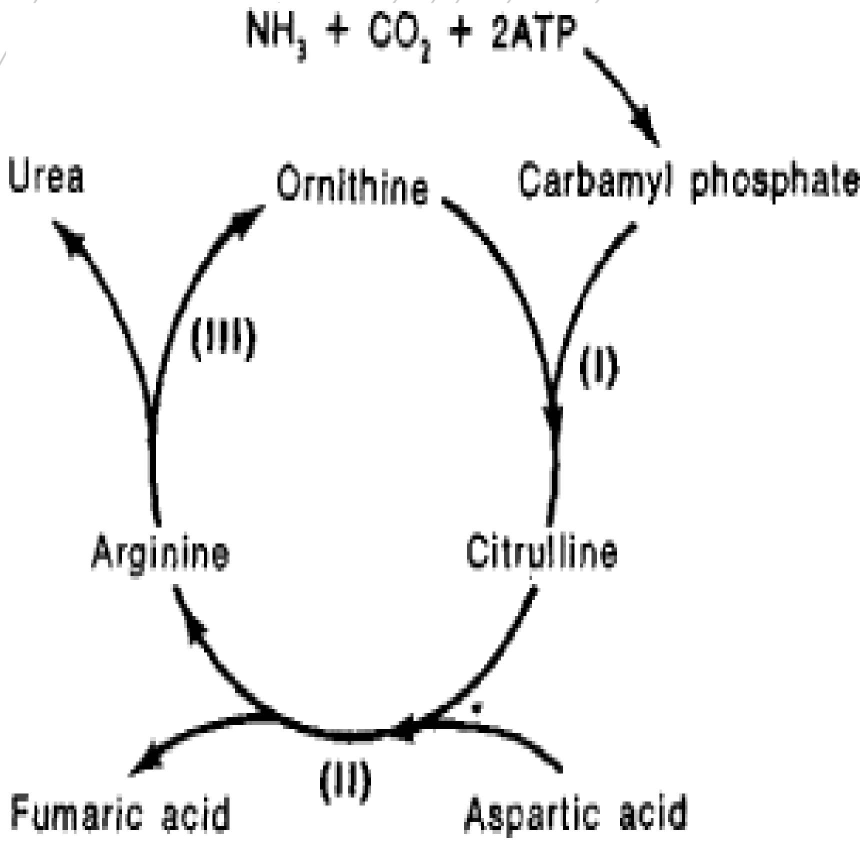
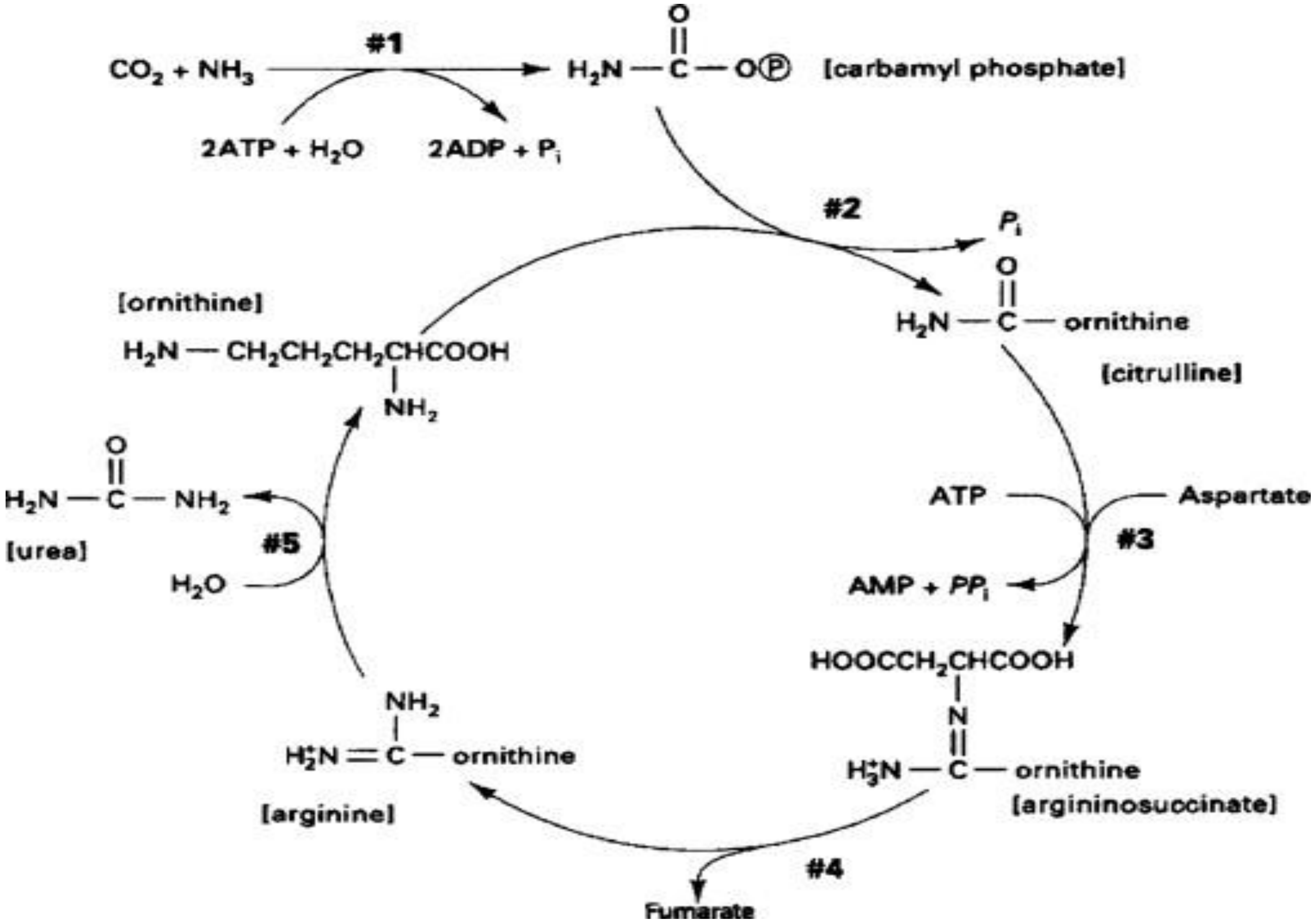


- **The urea cycle is a cycle of biochemical reactions that produces urea $(NH_2)_2CO$ from ammonia. This cycle occurs in ureotelic organisms. The urea cycle converts highly toxic ammonia to urea for excretion. This cycle was the first metabolic cycle to be discovered, five years before the discovery of the TCA cycle**



#1
$CO_2 + NH_3$
2ATP + H_2O
2ADP + P_i
[carbamyl phosphate]
#2
P_i
[ornithine]
$H_2N - CH_2CH_2CH_2CHCOOH$
NH_2
ornithine
[citrulline]
[urea]
#5
H_2O
ATP
Aspartate
#3
AMP + PP_i
HOOCCH$_2$CHCOOH
ornithine
[arginine]
[argininosuccinate]
#4
Fumarate

The urea cycle (also known as the ornithine cycle) is a cycle of biochemical reactions that produces urea (NH2)2CO from ammonia (NH3). This cycle occurs in ureotelic organisms. The urea cycle converts highly toxic ammonia to urea for excretion.[1] This cycle was the first metabolic cycle to be discovered (Hans Krebs and Kurt Henseleit, 1932), five years before the discovery of the TCA cycle. This cycle was described in more detail later on by Ratner and Cohen. The urea cycle takes place primarily in the liver and, to a lesser extent, in the kidneys.

Function

Amino acid catabolism results in waste ammonia. All animals need a way to excrete this product. Most aquatic organisms, or ammonotelic organisms, excrete ammonia without converting it.[1] Organisms that cannot easily and safely remove nitrogen as ammonia convert it to a less toxic substance such as urea via the urea cycle, which occurs mainly in the liver. Urea produced by the liver is then released into the bloodstream where it travels to the kidneys and is ultimately excreted in urine. The urea cycle is essential to these organisms, because if the nitrogen or ammonia are not eliminated from the organism it can be very detrimental.[2] In species including birds and most insects, the ammonia is converted into uric acid or its urate salt, which is excreted in solid form.

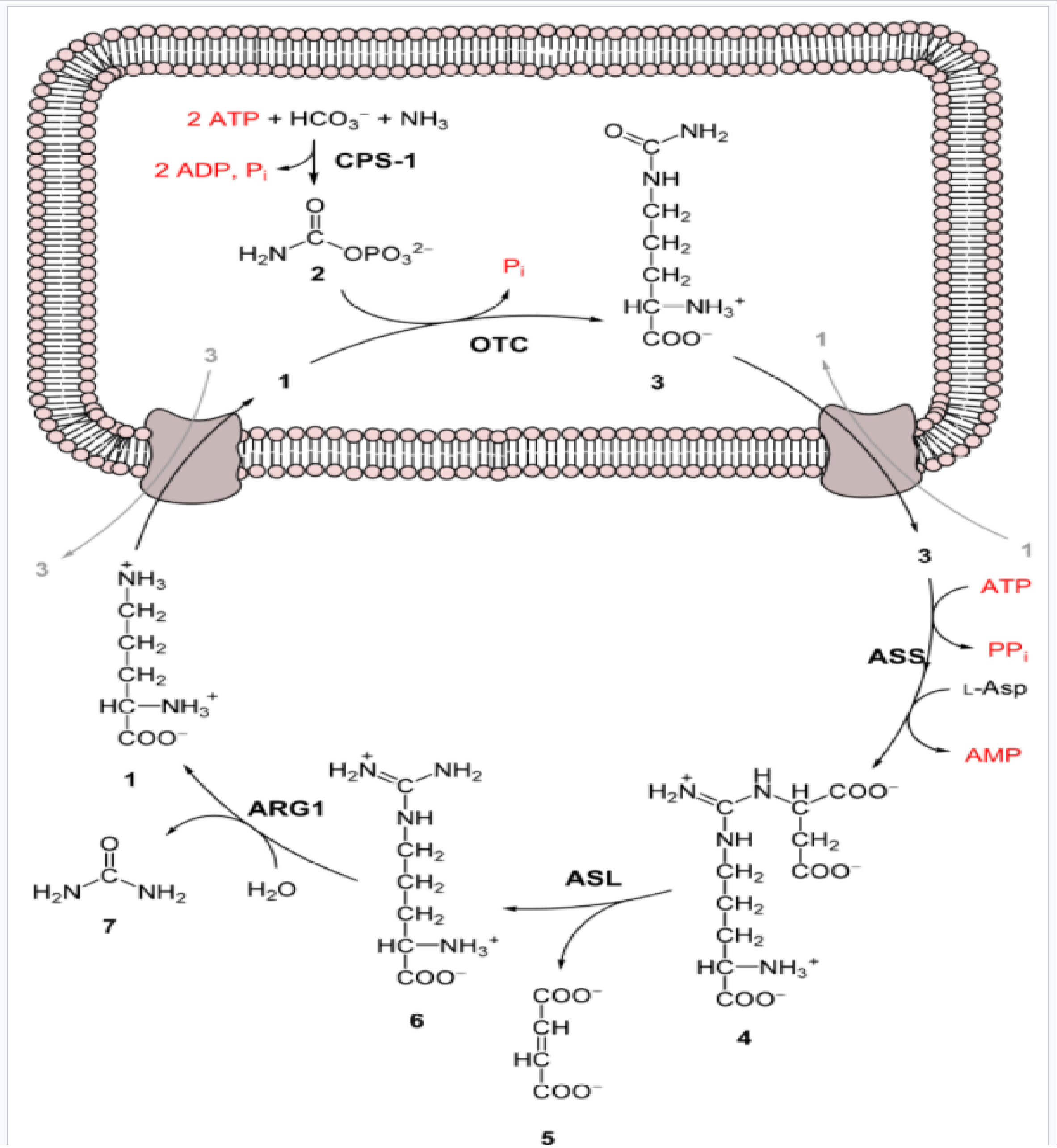
Reactions

The entire process converts two amino groups, one from NH+ 4 and one from Aspartate, and a carbon atom from HCO− 3, to the relatively nontoxic excretion product urea at the cost of four "high-energy" phosphate bonds (3 ATP hydrolyzed to 2 ADP and one AMP). The conversion from ammonia to urea happens in five main steps. The first is needed for ammonia to enter the cycle and the following four are all a part of the cycle itself. To enter the cycle, ammonia is converted to carbamoyl phosphate. The urea cycle consists of four enzymatic reactions: one mitochondrial and three cytosolic.

Reactions of the urea cycle

Step	Reactants	Products	Catalyzed by	Location
1	$NH_3 + HCO_3^- +$ 2ATP	carbamoyl phosphate + 2ADP + P_i	CPS1	mitochondria
2	carbamoyl phosphate + ornithine	citrulline + P_i	OTC, zinc, biotin	mitochondria
3	citrulline + aspartate + ATP	argininosuccinate + AMP + PP_i	ASS	cytosol
4	argininosuccinate	arginine + fumarate	ASL	cytosol
5	arginine + H_2O	ornithine + urea	ARG1, manganese	cytosol

The reactions of the urea cycle



1 L-ornithine
2 carbamoyl phosphate
3 L-citrulline
4 argininosuccinate
5 fumarate
6 L-arginine
7 urea
L-Asp L-aspartate
CPS-1 carbamoyl phosphate synthetase I
OTC Ornithine transcarbamoylase
ASS argininosuccinate synthetase
ASL argininosuccinate lyase
ARG1 arginase 1

First reaction: entering the urea cycle

Before the urea cycle begins ammonia is converted to carbamoyl phosphate. The reaction is catalyzed by carbamoyl phosphate synthetase I and requires the use of two ATP molecules.[1] The carbamoyl phosphate then enters the urea cycle.

Steps of the urea cycle

1. Carbamoyl phosphate is converted to citrulline. With catalysis by ornithine transcarbamoylase, the carbamoyl phosphate group is donated to ornithine and releases a phosphate group.[1]
2. A condensation reaction occurs between the amino group of aspartate and the carbonyl group of citrulline to form argininosuccinate. This reaction is ATP dependent and is catalyzed by argininosuccinate synthetase.[1]
3. Argininosuccinate undergoes cleavage by argininosuccinase to form arginine and fumarate.[1]
4. Arginine is cleaved by arginase to form urea and ornithine. The ornithine is then transported back to the mitochondria to begin the urea cycle again.

Overall reaction equation

In the first reaction,

$NH_4^+ + HCO_3^-$ is equivalent to $NH_3 + CO_2 + H_2O$.

Thus, the overall equation of the urea cycle is:

$NH_3 + CO_2$ + aspartate + 3 ATP + 3 H_2O → urea + fumarate + 2 ADP + 2 P_i + AMP + PP_i + H_2O

Since fumarate is obtained by removing NH_3 from aspartate (by means of reactions 3 and 4), and $PP_i + H_2O \rightarrow 2\ P_i$, the equation can be simplified as follows:

2 NH_3 + CO_2 + 3 ATP + 3 H_2O → urea + 2 ADP + 4 P_i + AMP

Note that reactions related to the urea cycle also cause the production of 2 NADH, so the overall reaction releases slightly more energy than it consumes. The NADH is produced in two ways:

One NADH molecule is produced by the enzyme glutamate dehydrogenase in the conversion of glutamate to ammonium and α-ketoglutarate. Glutamate is the non-toxic carrier of amine groups. This provides the ammonium ion used in the initial synthesis of carbamoyl phosphate.

The fumarate released in the cytosol is hydrated to malate by cytosolic fumarase. This malate is then oxidized to oxaloacetate by cytosolic malate dehydrogenase, generating a reduced NADH in the cytosol. Oxaloacetate is one of the keto acids preferred by transaminases, and so will be recycled to aspartate, maintaining the flow of nitrogen into the urea cycle.

We can summarize this by combining the reactions:

CO_2 + glutamate + aspartate + 3 ATP + 2 NAD^+ + 3 H_2O → urea + α-ketoglutarate + oxaloacetate + 2 ADP + 2 Pi + AMP + PPi + 2 NADH

The two NADH produced can provide energy for the formation of 5 ATP (cytosolic NADH provides 2.5 ATP with the malate-aspartate shuttle in human liver cell), a net production of two high-energy phosphate bond for the urea cycle. However, if gluconeogenesis is underway in the cytosol, the latter reducing equivalent is used to drive the reversal of the GAPDH step instead of generating ATP.

The fate of oxaloacetate is either to produce aspartate via transamination or to be converted to phosphoenolpyruvate, which is a substrate for gluconeogenesis.

THANK YOU