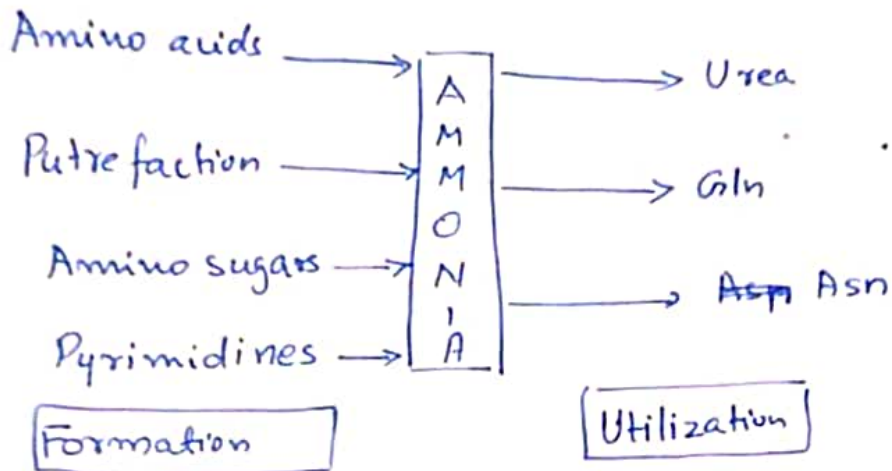


METABOLISM OF AMMONIA

Formation and utilization of ammonia



Detoxification of ammonia involves

- ① Trans. de amination [Transamination followed by de amination]
- ② Urea cycle

TRANS DEAMINATION

This includes

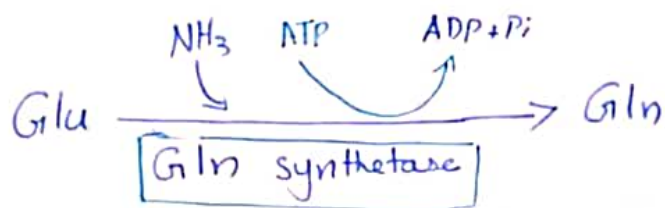
- ① Transamination of amino acids
- ② Transport to liver
- ③ Deamination in liver

Transamination

Definition,
Examples,
Significance

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Most of the amino acids undergo transamination and concentrate ammonia as glutamate.
In many tissues like brain and intestine one more ammonia is added to Glu to form Gln.



Transport to liver

From most of the tissues ammonia ~~reaches~~ is transported to liver as glutamate.

From brain and intestine, it is mainly transported as Glutamine.

From muscles - mainly as Alanine.

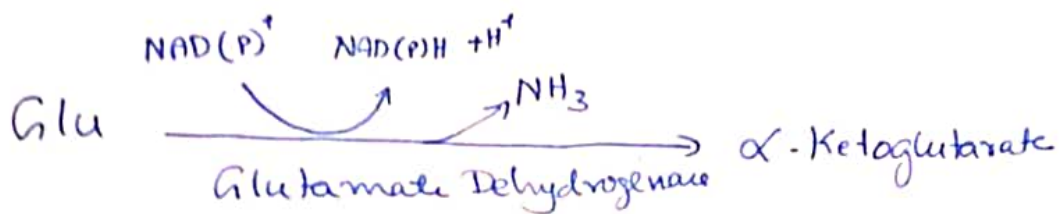
Deamination

Occurs in liver

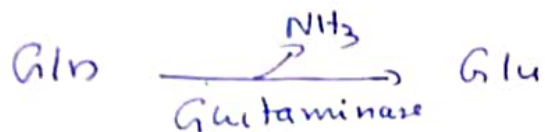
→ Oxidative deamination
→ Non oxidative deamination

Oxidative deamination

Mainly by Glutamate dehydrogenase



Glutamine is deaminated by glutaminase



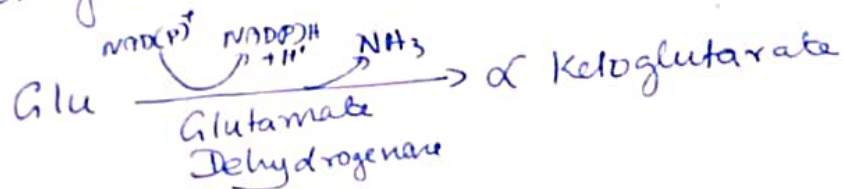
Other enzymes that catalyze oxidative deamination are

- L- amino acid oxidase
- D- amino acid oxidase

S.N

Glutamate dehydrogenase

Catalyzes oxidative deamination of Glu. It can use NAD^+ or NADP^+ as coenzyme. It is present in liver



GDH is inhibited by GTP. If it cannot be inhibited by GTP, it will lead to overactivity of GTP $\rightarrow$ leads to HH syndrome

[Hyperammonemia - Hyperinsulinism syndrome]

Non-oxidative deamination

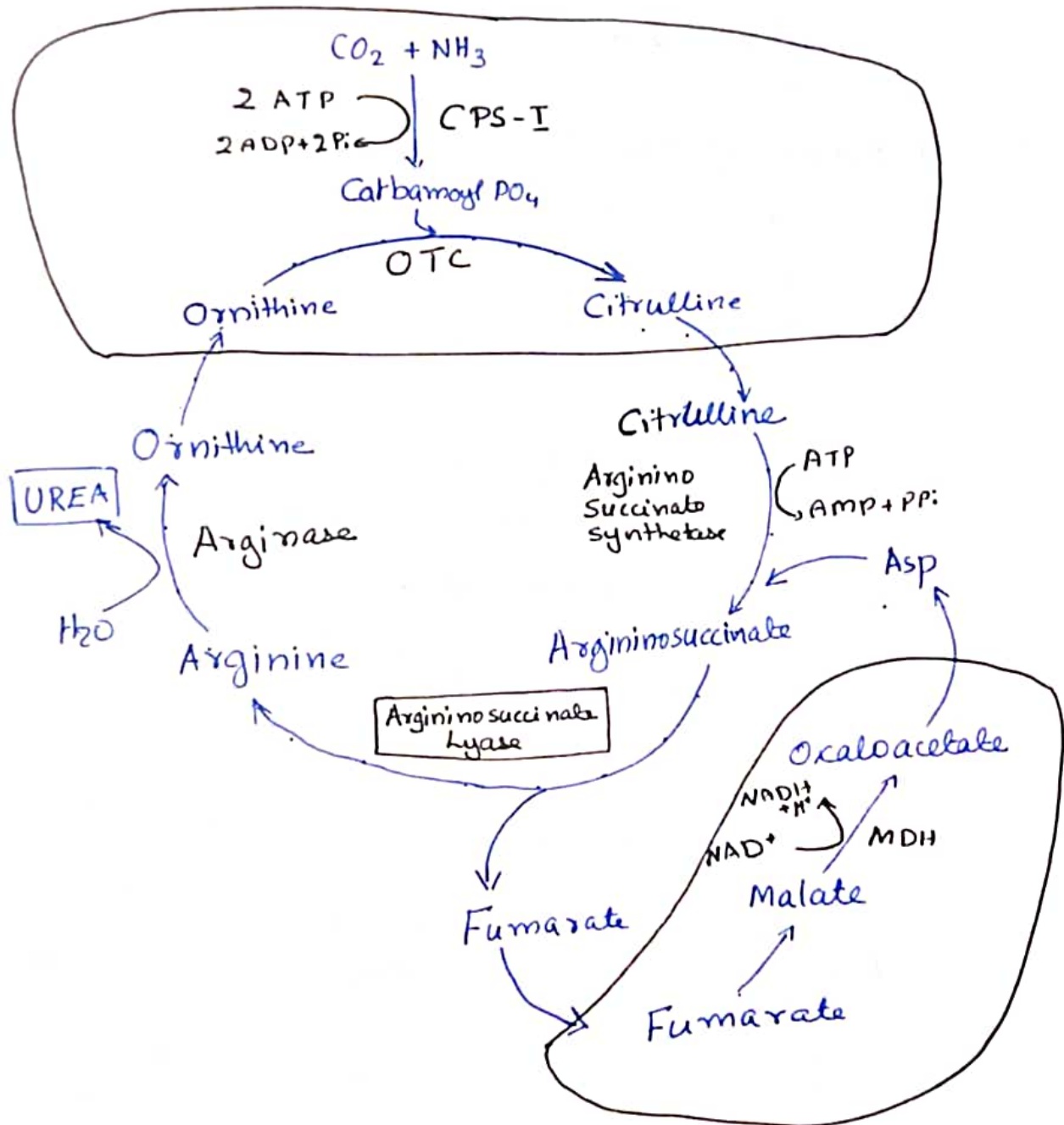
By Histidase, Dehydratase etc

UREA CYCLE

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For detoxification of ammonia

Site: Liver, Partly mitochondrial and cytoplasmic



Steps

① Formation of carbamoyl PO_4 (Mitochondria)

NH_3 and CO_2 combine to form carbamoyl PO_4 . Enzyme is Carbamoyl PO_4 synthetase - I **(CPS-I)**

⑬

This is the rate limiting enzyme.

It needs 2 ATP

N-acetyl glutamate is an allosteric activator of CPS - I

② Carbamoyl PO_4 combines with ornithine to form citrulline with the help of

Ornithine Transcarbamoylase (OTC) [Mitochondria]

Citrulline goes out to cytoplasm.

③ Formation of Argininosuccinate [Cytoplasm]

Citrulline combines with Aspartate to form Argininosuccinate by the enzyme

Argininosuccinate synthetase. This requires ATP

④ Cleavage of Argininosuccinate [Cytoplasm]

Argininosuccinate Lyase cleaves Argininosuccinate to Arginine and fumarate

⑤ Hydrolysis of Arginine to form Urea [Cytoplasm]

Arginine is hydrolysed to Urea and Ornithine by Arginase. Ornithine can re-enter mitochondria.

Link between Urea cycle and TCA cycle

Fumarate formed in urea cycle enters mitochondria and takes part in TCA cycle.

Fumarate $\rightarrow$ Malate $\rightarrow$ Oxaloacetate

Oxaloacetate is transaminated to aspartate which can re-enter Urea cycle

Since these 2 cycles are closely related, it is also called Urea bicycle

Energetics

CPS - 1 - 2 ATP

Arg. suc. synthetase - 2 ATP
 - 4 ATP

4 ATPs are used during urea cycle.

When fumarate passes through TCA cycle.

Malate dehydrogenase produces NADH

($= +2.5$ ATP). So the actual expenditure may be considered 1.5 ATPs.

Regulation

Mainly by 3 mechanisms

- $\rightarrow$ Induction
- $\rightarrow$ Allosteric regulation
- $\rightarrow$ Compartmentalization

Induction:

Urea cycle enzymes are induced during starvation and high protein diet

Allosteric regulation

Rate limiting enzyme is CPS-I

It is allosterically activated by

N-acetyl glutamate

Compartmentalization

- Fumarate formed in cytoplasm may cause feedback inhibition on Arginino-succinate Lyase. This is prevented by transporting fumarate to mitochondria

DISORDERS OF UREA CYCLE

Any defect in urea cycle will lead to increased level of ammonia in blood.

These are collectively called hyperammonemias

These disorders manifest with

Nausea

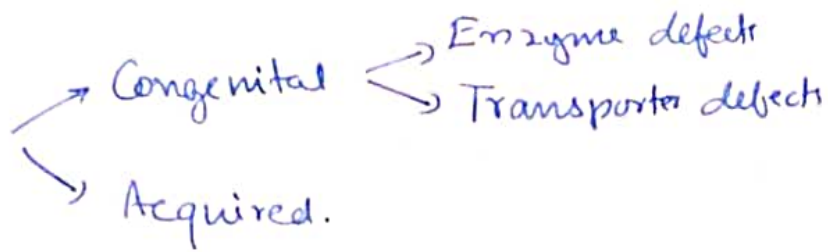
Tiredness

Vomiting

Coma

and may cause death

Hyperammonemias can be



Congenital Hyperammonemias

Enzyme defects

Enzyme	Disease
CPS - I	Hyperammonemia Type I
OTC	Hyperammonemia Type II
Argininosuccinate synthetase	Citrullinemia
Argininosuccinate lyase	Argininosuccinic aciduria
Arginase	Hyperargininemia

Transporter defect

HHH syndrome [Hyperammonemia - Hyperornithinemia - Homocitrullinuria syndrome]

- Due to defect in Ornithine translocase (the transporter that transports ornithine from cytoplasm to mitochondria)

Acquired hyperammonemias

Seen in chronic liver disease, liver cirrhosis, liver failure etc

Treatment of hyperammonemia

- ① Methods to decrease the production of ~~ammonia~~ ammonia.

Low protein diet

Laxatives and Antibiotics to decrease putrefaction in intestine

- ② Enzyme activator

Arginine activates NAGS

(N-Acetyl Glutamate Synthase). This will produce more N-acetyl glutamate (NAG) and activate CPS-I

- ③ Ammonia scavengers

They remove ammonia from cells

Eg: Sodium benzoate

Sodium phenyl butyrate

- ④ In acquired hyperammonemia, treat the cause

Blood urea

Nl level 15 - 40 mg/dl

It is increased in

- ① Physiological ↑
- High protein diet
 - Slight ↑ seen with ↑ in age.

② Pre-renal causes

Any condition which ↓s the blood flow to kidneys

Hypovolemia
Shock
Vomiting
Diarrhea
Burns

③ Renal causes

Diseases affecting kidney which ~~are~~ interfere with glomerular filtration

Glomerulonephritis
Renal failure etc

④ Post-renal causes

Any obstruction to the flow of urine ↓s effective filtration pressure and ↑s blood urea

Enlargement of prostate
Stricture of urethra
Ureteric stones etc

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Decreased blood urea is seen in
liver diseases
