AMINOACID METABOLISM

FATE OF AMINOACIDS & UREA CYCLE
SOURCE & FATE OF AA

The aminoacids obtained from DIETARY SOURCE or BODY PROTEIN TURNOVER are utilized for protein biosynthesis and the production of a wide range of N₂ containing compounds like creatine, amines, porphyrins...

The aminoacids undergo certain common reactions like TRANSAMINATION followed by DEAMINATION for the liberation of Ammonia. The amino group of aa is utilized for the formation of UREA. The carbon skeleton of aa is first converted to ketoacids which meet one or more of the following fates:

1. Utilized to generate energy
2. Used for glucose synthesis
3. Diverted for fat / ketone formation
4. Production of non-essential amino acids
DIETARY PROTEIN \rightarrow AMINOACIDS \rightarrow SYNTHESIS OF 'N' COMPOUNDS

BODY PROTEIN \rightarrow SYNTHESIS OF PROTEIN \rightarrow AMINOACIDS

AMINOACIDS \rightarrow α KETOGLUTATRATE

α KETOGLUTATRATE \rightarrow TRANSMINATION

TRANSMINATION \rightarrow GLUTAMATE \rightarrow NH₃ \rightarrow UREA

UREA \rightarrow KETOACIDS

KETOACIDS \rightarrow ENERGY \rightarrow GLUCOSE \rightarrow FAT \rightarrow NON ESSENTIAL AA
The transfer of an amino(-NH2) group from an aminoacid to a ketoacid is Transamination.

This process involves the inter-conversion of a pair of aminoacids & ketoacids, catalyzed by a group of enzymes – TRANSAMINASES

1. ASPARTATE TRANSAMINASE 2. ALANINE TRANSAMINASE

Important for redistribution of aminoacids and production of non-essential aminoacids as per the requirement of the cell.

REVERSIBLE – Involves both anabolism & catabolism of aa

Diverts excess aa towards energy generation

Serum Transaminases – Diagnostic value

MECHANISM – Transfer of aminogroup to PLP. Transfer of amino group from Pyridoxamine phosphate to keto acid
ALANINE  +  α KETOGLUTARATE

ALANINE TRANSAMINASE  
(PLP)

PYRUVATE  +  GLUTAMATE
The removal of aminogroup from the aminoacids as NH₃ is Deamination. Simultaneously the carbon skeleton of amino acids is converted to Ketoacids.

**glutamate dehydrogenase**

\[
\text{GLUTAMATE} \xrightarrow{\text{GDH}} \alpha \text{KG} + \text{NH}_3
\]

Thus GLUTAMATE serves as ‘COLLECTION CENTRE’ for amino groups in the biological system. GDH can utilise NAD or NADP.

* This reaction is important as it reversibly links glutamate metabolism with TCA CYCLE through α Ketoglutarate.

GDH – regulated allosterically – GTP & ATP inhibits & viceversa
OXIDATIVE DEAMINATION

- It is the liberation of free ammonia from the amino group of amino acids coupled with oxidation.
- Takes place mostly in liver and kidney.

\[
L\text{-Amino acid Oxidase} \\
L\text{-Amino acid} \rightarrow \alpha\text{-Keto acid} + \text{NH}_3
\]

\[
\begin{align*}
\text{FMN} & \quad \text{FMNH}_2 \\
\text{H}_2\text{O}_2 & \quad \frac{1}{2} \text{O}_2
\end{align*}
\]

Catalase

NON-OXIDATIVE DEAMINATION – Some aa can be deaminated to liberate \text{NH}_3 without undergoing oxidation. Eg: Dehydratases, Desulfhydrases & Histidase
Liver contains only glutamate dehydrogenase which deaminates Glutamate. Thus all aminoacids are first Transaminated to Glutamate which is finally deaminated. This coupling of Transamination and de-amination is called TRANSDEAMINATION.

\[
\begin{align*}
\text{ANY AMINOACID} & \quad \alpha \text{ KETOGLUTARATE} \\
\text{TRANSAMINATION} & \quad \text{DEAMINATION} \\
\text{CORRESPONDING KETOACID} & \quad \text{GLUTAMATE} \quad \text{NH}_3 + \alpha \text{ KG} \\
& \quad \text{NAD} \quad \text{NADH H}^+ 
\end{align*}
\]
AMMONIA METABOLISM

- FORMATION OF AMMONIA
- TRANSPORT OF AMMONIA
- FUNCTIONS OF AMMONIA
- DISPOSAL OF AMMONIA
- TOXICITY OF AMMONIA
PRODUCTION OF AMMONIA OCCURS FROM THE AMINOACIDS (TRANS DEAMINATION), BIOGENIC AMINES, AMINO GROUP OF PURINES & PYRIMIDINES & BY THE ACTION OF INTESTINAL FLORA

TRANSPORT – IN THE FORM OF GLUTAMINE OR ALANINE
AMMONIA TOXICITY

- **AMMONIA IS NEEDED** FOR SYNTHESIS OF NON-ESSENTIAL AMINO ACIDS, AMINO SUGARS, PURINES AND PYRIMIDINES.
- **MARGINAL ELEVATION** – HARMFUL TO BRAIN. SLIRRING OF SPEECH, BLURRING OF VISION & CAUSES TREMORS. MAY LEAD TO COMA & FINALLY DEATH IF NOT CORRECTED.

\[ \alpha \text{KG} + \text{NH}_3 \rightarrow \text{GLUTAMATE} \]

**BIOCHEMICAL BASIS OF TOXICITY**

ACCUMULATION OF AMMONIA UTILISES & DEPLETES \( \alpha \text{KG} \) WHICH IS THE KEY INTERMEDIATE IN TCA CYCLE.

NET PRODUCTION OF ATP BY THE BRAIN IS REDUCED LEADING TO TOXIC MANIFESTATIONS.
AMMONIA DISPOSAL

- UREA IS THE END PRODUCT OF PROTEIN METABOLISM (AMINO ACID METABOLISM). THE NITROGEN OF AMINO ACIDS CONVERTED TO AMMONIA IS TOXIC TO THE BODY. IT IS CONVERTED TO UREA AND DETOXIFIED. UREA ACCOUNTS TO 90% OF THE NITROGEN CONTAINING SUBSTANCES EXCRETED IN THE URINE.

- UREA – SYNTHESISED IN LIVER & TRANSPORTED TO KIDNEYS FOR EXCRETION.

- KREBS-HENZELEIT CYCLE – UREA CYCLE

- SOURCES OF UREA ATOMS – AMINO GROUPS ARE CONTRIBUTED BY AMMONIA & ASPARTATE, CARBON ATOMS FROM CARBON DIOXIDE.
UREA CYCLE

5 STAGES
1. SYNTHESIS OF CARBAMOYL PHOSPHATE
2. FORMATION OF CITRULLINE
3. SYNTHESIS OF ARGININOSUCCINATE
4. FORMATION OF ARGinine
5. FORMATION OF UREA

- FIRST 2 ENZYMES ARE PRESENT IN MITOCHONDRIA AND THE REST IN CYTOSOL
**Diagram of Urea Cycle and Arginine Metabolism**

- **Carbamoyl phosphate**
- **Citrulline**
- **Arginosuccinate**
- **Arginine**
- **Ornithine**
- **CO₂ + NH₄**
- **2ATP**
- **2ADP+Pi**
- **Carbamoyl phosphate synthase I**
- **Ornithine trans-carbamoylase**
- **Aspartate**
- **Fumarate**
- **Urea**
- **Arginase**
- **Argininosuccinate synthase**
- **Argininosuccinate**
- **H₂O**
- **ATP**
- **AMP**
- **Arginase**
- **Citrulline**
- **Fumarate**
- **Argininosuccinate synthase**
1. SYNTHESIS OF CARBAMOYL PHOSPHATE

- SITE – MITOCHONDRIAL
- CARBAMOYL PHOSPHATE SYNTHASE I (CPS-I)

\[ \text{CO}_2 + \text{NH}_4 \rightarrow \text{CARBAMOYL PHOSPHATE} \]

- IRREVERSIBLE AND RATE LIMITING
- REQUIRES 2 ATP
- REQUIRES N-ACETYL GLUTATHMATE (NAG) FOR ITS ACTIVITY – ALLOSTERIC ACTIVATOR
- DIFFERS FROM CPS-II
2. FORMATION OF CITRULLINE

- SITE – MITOCHONDRIAL

- L-ORNITHINE TRANSCARBAMOYLASE

  CARBAMOYL PHOSPHATE + ORNITHINE

  CITRULLINE

CITRULLINE LEAVES MITOCHONDRIA TO CYTOPLASM FOR FURTHER REACTIONS TO TAKE PLACE
3. SYNTHESIS OF ARGININOSUCCINATE

SITE – CYTOSOL

ARGININOSUCCINATE SYNTHETASE

CITRULLINE + ASPARTATE $\rightarrow$ ARGININOSUCCINATE

ASPARTIC ACID PROVIDES THE 2$^{\text{ND}}$ ‘N’ OF UREA

ATP HYDROLYSIS TO AMP – 2 HIGH ENERGY ‘P’ BONDS UTILISED
4. FORMATION OF ARGinine

- **SITE** – CYTOSOL

- **ARGININO SUCCINASE**

  \[ \text{ARGININOSUCCINATE} \rightarrow \text{ARGININE} + \text{FUMARATE} \]

- **ARGININE** – IMMEDIATE PRECURSOR OF UREA

- **FUMARATE** – SERVES AS A CONNECTING LINK BETWEEN TCA CYCLE AND GLUCONEOGENESIS
5. FORMATION OF UREA

- SITE – CYTOSOL
- ARGINASE – MOSTLY IN LIVER

\[
\text{ARGININE} \longrightarrow \text{ORNITHINE} + \text{UREA}
\]

- ORNITHINE RE-ENTERS LIVER MITOCHONDRIA TO CONTINUE THE CYCLE
- ACTIVATED BY CO\(^{2+}\) & Mn\(^{2+}\)
- ORNITHINE & LYSINE COMPETES WITH ARGININE
ENERGETICS OF UREA CYCLE

\[ \text{NH}_3 + \text{CO}_2 + \text{ASPARTATE} \rightarrow \text{UREA} + \text{FUMARATE} \]

- 2 ATP UTILISED FOR CPS PRODUCTION
- 1 ATP IS CONVERTED TO AMP + PPI
- TOTAL 4 HIGH ENERGY PHOSPHATE BONDS

- FUMARATE ENTERING TCA CYCLE PRODUCES 1 NADH EQUIVALENT TO 3 ATP
- HENCE ONE HIGH ENERGY PHOSPHATE IS USED
REGULATION OF UREA CYCLE

- COARSE REGULATION
- FINE REGULATION
- COMPARTMENTALISATION

**COARSE REGULATION** – STARVATION INCREASES UREA CYCLE ENZYMES TO MEET INCREASED RATE OF PROTEIN CATABOLISM
FINE REGULATION – NAG STIMULATES THE BINDING OF CPS WITH ATP

GLUTAMATE + ACETYL CoA --> N-ACETYLGlutamate

ARGININE ACTIVATES NAG SYNTHASE

COMPARMENTATLISATION – INHIBITORY EFFECT OF FUMARATE ON ITS OWN FORMATION IS AVOIDED SINCE FUMARASE IS IN MITOCHONDRIA & ARGININOSUCCINASE IS IN CYTOSOL
## DISORDERS OF UREA CYCLE

<table>
<thead>
<tr>
<th>DEFECT</th>
<th>ENZYME INVOLVED</th>
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<tbody>
<tr>
<td>HYPERAMMONEMIA I</td>
<td>CARBAMOYL PHOSPHATE SYNTHASE – I</td>
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<tr>
<td>HYPERAMMONEMIA II</td>
<td>ORNITHINE TRANSCARBAMOYLASE</td>
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<td>CITRULLINEMIA</td>
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<td>ARGININOSuccinic ACIDURIA</td>
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<td>HYPER ARGININEMIA</td>
<td>ARGINASE</td>
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BLOOD UREA

- NORMAL UREA LEVEL IN BLOOD 15 – 40 mg/dl
- INDICATOR OF RENAL FUNCTION
- ELEVATION OF BLOOD UREA IS CLASSIFIED INTO
  1. **PRE-RENAL** – INCREASED PROTEIN BREAKDOWN
     - POST SURGERY, PROLONGED FEVERS, THYROTOXICOSIS, DIABETIC COMA
  2. **RENAL** – RENAL DISORDERS – AGN, CHRONIC NEPHRITIS, NEPHROSCLEROSIS
  3. **POST-RENAL** – UT OBSTRUCTION – TUMORS, STONES, PROSTATE ENLARGEMENT