**ROLE OF NITRIC OXIDE**

***Nitric oxide (NO) is formed in the body from amino acid arginine***

It is a wonder molecule having diverse biological functions. Endothelium derived relaxing factor (EDRF) which produces vasodilatation is now proved to be nitric oxide.

***Formation of NO***

Arginine is acted upon by an enzyme called ***nitrogen oxide synthase***, a cytosolic enzyme and converts arginineto citrulline and nitric oxide (NO). Nitric oxide synthase (NOS) is a very complex cytosolic enzyme which requires five redox cofactors: **NADPH, FAD, FMN, haem and tetrahydrobiopterin** (FH4).

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**Functions of Nitric Oxide**

• It acts as a **vasodilator** and causes relaxation of smooth muscles.

• It has important role in the regulation of blood flow and maintaining blood pressure.

• It is involved in penile erection.

• Acts as a **neurotransmitter** in the brain and peripheral autonomic nervous system.

• May have also role in relaxation of skeletal muscles.

• Inhibits adhesion, activation and aggregation of platelets.

• May constitute part of a primitive immune system and may mediate bactericidal actions of macrophages.

• Low level of nitric oxide may be involved in causation of pylorospasm of infantile hypertrophic pyloric stenosis.

***Inhibitors***

• Nitric oxide (NO) is inhibited by Haemoglobin and other haem proteins which bind it tightly.

• Chemical inhibitors of *NO synthase* are now available that causes marked decrease formation of NO.

• ***Endogenous inhibitor:*** Asymmetric dimethyl arginine (ADMA), an endogenous arginine analogue may function as a competitive inhibitor of NO synthase. ADMA has been found to be increased in preeclampsia.

**CLINICAL ASPECT**

• **Nitroglycerine:** The important coronary artery vasodilator used in Angina Pectoris acts to increase intracellular release of endothelium-derived relaxing factor (EDRF) (now proved to be NO) and cGMP↑.

• **In septic shock:** Bacterial lipopolysaccharide present in blood causes uncontrolled production of NO leading to dilatation of blood vessels and lowering of BP.

• **In eclampsia and pre-eclampsia:** The hypertension is due to decreased production of nitric oxide (NO) due to probably formation of ADMA (asymmetric dimethyl arginine).

• **Iron supplements:** Iron supplements can dramatically reduce dry cough symptoms in heart patients. Cardiac patients using an angiotensin-converting enzyme inhibitor (ACE inhibitors), widely prescribed for hypertension, heart failure and other cardiac conditions often suffer from a dry cough. It is the biggest reason for people stopping taking their medication. Iron supplements act by decreasing the production of Nitric oxide, which is linked to inflammation of the bronchial cells in the lungs.

**Metabolism of Creatine**

Two closely related nitrogenous compounds which are connected with protein metabolism are:

• **Creatine** and

• **Creatinine**.

***Structure and relationship of these two compounds are shown in the following :***

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***Characteristics of the above reaction***

• Reaction is ***irreversible***

• It is ***non-enzymatic***

• Creatinine has ***ring structure*.**

**Occurrence and Distribution:**

***A. Creatine: It is a normal constituent of the body***. It is present in muscle, brain, liver, testes and in blood. Can occur in ***free*** form and also as ***phosphorylated*** form. The phosphorylated form is called as ***creatine- PO4*** or ***phosphocreatine*** or ***Phosphagen***. Total amountin adult human body is approximately 120 gm. 98 percent of total amount is present in muscles, of which 80 percent occurs in phosphorylated form, 1.3 percent in nervous system (brain) and 0.5 to 0.7 percent in tissues.

***Urinary excretion:*** Urinary excretion in normal health is in the form of creatinine and it is only 2 percent of the total. ***In males***, it is 1.5 to 2.0 gm in 24 hrs urine, and ***in*** ***females***, varies from 0.8 to 1.5 gm.

**Note**

• Only vertebrate muscles contain creatine. Creatine concentration is higher in striated muscle as compared to smooth muscle and also in rapidly contracting muscle as compared to pale muscles. Total is 300 to 500 mg/100 gm.

• In invertebrates: Arginine replaces creatine in muscles.

***Blood and plasma level***

• **In whole blood:** Creatine level varies from 2 to 7 mg%.

• **In plasma:** It is less than 1 mg%.

**In male:** It varies from 0.2 to 0.6 mg%.

**In females:** 0.35 to 0.9 mg%.

***B. Creatinine:*** Creatinine is the anhydride of creatine, and ***it is in this form that creatine is excreted in*** ***normal health.*** Removal of one molecule of H2O is *non-enzymatic* and ***irreversible***. Formation of creatinine is a preliminary step and prerequisite for excretion of most of creatine. Total creatinine in muscle is only 0.01 percent (10 mg).

***Blood:*** Whole blood creatinine level varies from 1.0 to 2.0 mg%. Creatinine is evenly distributed in between plasma and RB Cells.

**BIOSYNTHESIS OF CREATINE**

***Three amino acids*** are required in biosynthesis of creatine.

They are:

***(i) Glycine***

***(ii) Arginine*** and

***(iii) Methionine***

**Substrates to start synthesis are Glycine and Arginine.**

**Site of synthesis :**

***• In kidney***

***• In liver***

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**Creatinuria**

Excretion of creatine in urine is called creatinuria. Creatine excretion occurs:

• In children: Reason probably lack of ability to convert creatine to creatinine.

• In adult females in pregnancy and maximum after parturition (2 to 3 weeks).

• ***In febrile conditions***

• ***In thyrotoxicosis***, probably due to associated myopathies.

• In muscular dystrophies, myositis, and myasthenia gravis.

• Lack of carbohydrate in diets and in diabetes mellitus.

• In wasting diseases, e.g. in malignancies.

• In starvation.

**Role of Creatine in Muscles**

**1.** Creatine is the reservoir of energy in muscles. When muscles contract, energy is derived from breakdown of ATP to ADP and Pi. ***ATP must be reformed quickly***,

to supply the energy, which initially comes from creatine ~ (P), subsequently from glycolysis (contracting muscle).



From the above reaction, ATP is formed from creatine~ (P). The high energy phosphate is transferred to ADP and ATP is formed. This reaction is called **Löhmann reaction** and it takes place during activity of the muscles.In the resting condition, creatine ~ (P) is reformed, the enzyme that catalyses the reaction is ***ATP-creatine*** ***transphosphorylase*.**

**2.** A further source of ATP in muscle is by the **Myokinase reaction.** Two ADP molecules react to produce one molecule of ATP and AMP, the reaction is catalysed by the enzyme ***myokinase (Adenylate*** ***kinase).***



In this reaction, one high energy phosphate is transferred from one ADP to another ADP molecule to form one ATP.

***Creatinine Clearance***

Endogenous creatinine clearance is used as renal function test. At normal levels of creatinine in the blood, this metabolite is filtered at the glomerulus but neither secreted nor re-absorbed by the tubules. Hence its clearance measures the glomerular filtrate rate (GFR).

**BRANCHED CHAIN AMINO ACIDS (BCA)**

Valine (Val) (V) is glucogenic; Leucine (Leu) (L) is ketogenic while Isoleucine (Ile) (I) is both ketogenic and glucogenic. All the three are **essential** amino acids. Leucine is the major ketogenic amino acid. These amino acids serve as an alternate source of **fuel for the brain** especially under conditions of starvation.

**Maple Syrup Urine Disease (MSUD)**

●It is also called branched chain ketonuria. The incidence is 1 per 1 lakh births. The name originates from the characteristic smell of urine (similar to burnt sugar or maple sugar) due to excretion of branched chain keto acids.

●The basic biochemical defect is deficient decarboxylation of branched chain keto acids (BKA).

●Clinical findings: Disease starts in the first week of life. It is characterized by convulsions, severe mental retardation, vomiting, acidosis, coma and death within the first year of life.

● Laboratory findings: Urine contains branched chain keto acids, valine, leucine and isoleucine. Rothera’s test is positive, but unlike in cases of ketoacidosis, even boiled and cooled urine will give the test. Diagnosis depends on enzyme analysis in cells. Diagnosis should be done prior to 1 week after birth.

● Treatment: Giving a diet low in branched chain amino acids. Mild variant is called intermittent branched chain ketonuria. This will respond to high doses of thiamine. This is because the decarboxylation of the BKA requires thiamine. Liver transplantation has been successfully tried in some cases of MSUD.

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 Figure: Pathology of maple syrup urine disease

