Ethanol Metabolism

-ethyl alcohol-

Ethanol may replace CHO (carbohydrates) as an energy source when it’s ingested in large amounts.

1) Oxidation to acetate in the liver
   Ethanol is oxidized in the liver by Cytosolic Alcohol dehydrogenase to acetaldehyde.

   \[ \text{CH}_3\text{CH}_2\text{OH} + \text{NAD}^+ \rightarrow \text{CH}_3\text{CHO} + \text{NADH} + \text{H}^+ \]

2) Acetaldehyde is further oxidized to acetate by a mitochondrial Aldehyde dehydrogenase.

   \[ \text{CH}_3\text{CHO} + \text{NAD}^+ + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{COO}^- + \text{NADH} \]

3) Much of the acetate produced from ethanol leaves the liver and is converted to Acetyl CoA and then CO\(_2\) by other tissues.

4) Acetyl CoA may also be formed in the liver and used as a precursor for lipid biosynthesis.

5) Ethanol may also be oxidized by a microsomal Cytochrome P450 oxidase, which is induced by ethanol.

   In the body ethanol is oxidized to Acetaldehyde then acetic acid which is converted to active acetic acid (or acetate), i.e. Acetyl CoA, which enters the CAC and gets converted into ATP, CO\(_2\) and H\(_2\)O.

☆ That 1 gm alcohol gives ≈ 9 calories energy.
How does Disulfiram (a drug used in treatment of chronic alcoholism) work? This drug inhibits the action of Aldehyde dehydrogenase by competing with NAD\(^+\) to the binding site of enzyme and so increases the level of acetaldehyde in blood causing symptoms of vomiting, thirst, sweat and headache.

♫ A person may ingest methyl alcohol (methanol) by mistake, so what happens?

Methanol is oxidized by liver alcohol dehydrogenase to give formaldehyde and this is oxidized to formic acid (formate):

\[
\text{CH}_3\text{OH} \rightarrow \text{HCHO} \rightarrow \text{HCOOH}
\]

-Formaldehyde causes retinal damage and blindness.
-Formic acid causes acidosis (coma and death).

Methanol toxicity is treated by giving ethanol as an antidote. It competes with methanol at the dehydrogenase enzyme causing a delay of methanol metabolism and its excretion in urine is increased.

**Chronic Ethanol Ingestion**: can cause fatty liver. Fatty liver occurs in conditions in which there’s an imbalance between hepatic triacylglycerol synthesis and secretion of VLDL. Other conditions are diseases such hepatitis, and uncontrolled diabetes mellitus.

♫ Is ethanol synthesized in the human body?
A: No, but in microorganisms it’s formed from the conversion of Pyruvate by two reactions.

Example of a microorganism that synthesizes ethanol is Yeast.
☆ Alcohol (Ethanol) induces hypoglycemia. Due to inhibition of gluconeogenesis.
Biochemical lesion of CHO metabolism in RBC

RBCs are synthesized in bone marrow and have a range of life span of 120 days. They function in carrying O$_2$ to tissue and transport CO$_2$ to lungs.

A mature RBC has:

1. Glycolytic pathway to provide energy and 2,3 Diphosphoglyceric acid (2,3 DPG) which play a role in the delivery of O$_2$ to tissues.
2. HMP shunt to yield NADPH which help in maintaining the SH group of a) Glutathione b) sulfhydryl-containing proteins in reduced state. Such proteins function as enzymes, glyceraldehyde 3P dehydrogenase in glycolysis and as part of the membrane system in the RBC.

☆ The normal production and release of RBC is under control of glycoprotein hormone Erythropoietin (EPO).

The mechanism of action is through stimulation of mRNA and protein synthesis system, Erythropoietin is produced in the plasma by the action of the Erythropoietic factor which comes from the liver and the kidneys.

Drugs can cause a decrease in the number of circulating RBC either through (a) Impaired production as in Bone Marrow Aplasia due to treatment with chloramphenicol, or due to (b) destruction of Red cells (hemolysis) caused by a variety of chemical compounds. This occurs in persons with deficiency of one or more of the enzymes associated with CHO metabolism as glucose-6-Phosphate dehydrogenase (G6PD).

There are several factors that may contribute to hemolysis of RBC:-

1) Damage to the cell membrane due to oxidation of SH group in the membrane.
2) Inactivation of Gly3P dehydrogenase due to oxidation of SH group in this enzyme.
3) Degradation of Hb and shifting of equilibrium between HbO$_2$* and Met.Hb** due to the lack of the enzyme Glutathione peroxidase which acts on H$_2$O$_2$ to convert it into H$_2$O and oxidized glutathione.
4) Biochemical lesion in synthesis of G.SH
Reduced G.SH=Glutamic acid-Cysteine-Glycine
\[ \text{Glu-Cys-Gly} \]
\[ \text{SH} \]

Oxidized G.SH=Glu-Cys-Gly
\[ \text{SH} \]

5) Glutathione reductase:
   a) Flavoprotein deficiency as in B\(_2\) deficiency leads to RBC hemolysis.
   b) Other deficiency in the production of NADPH

These factors are all interrelated, e.g:
1) Lack of Glyc 3PDH would cause interruption of glycolysis.
2) A decrease of NADH (Lack of NADH) may result in an increase in Met-Hb due to decrease in the reaction:

\[ \text{Met-Hb} \overset{\text{Met-Hb reductase}}{\longrightarrow} \text{Hb} \]
\[ \text{NADH} \]
\[ \text{NAD}^+ \]

\*HbO\(_2\) : Oxyhemoglobin or oxygenated Hb
\**Met-Hb : hemoglobin in which iron is in the ferric form Fe\(^{+3}\) or oxidized form. It can’t carry oxygen, it’s brown and is normally present in very low plasma concentrations.
Drugs such as Sulphonamides may increase Met-Hb, the Symptoms of Methemoglobinemia are due to hypoxia which causes Cynosis & increased respiratory rate

3) Also a decrease in production of 2,3 DPG which lowers the affinity of Hb to O\(_2\) and releases it. This compound is formed from 1,3 DPG by Gly 3P DH.

Glc 6P DH deficiency is an inherited (as a sex-linked factor) inborn error of
metabolism.

Glc 6P DH deficiency- Some drugs given to some people may cause hemolytic anemia like:
   a) Antimalarial drug-Primaquine.
   b) Sulfonamide & sulfones.
   c) Analgesics-acetanilide.
   d) Antibacterial-nitro furagon.
   e) Ingestion of vicia fava bean, nephthaline, phenyl hydrazine.

G6PD converts G6P to 6-phosphogluconic acid and by NADP⁺ as cofactor which becomes NADPH.

NADPH is used to oxidize GSSG by donating hydrogen so reduced glutathione is formed, i.e. GSH.
GSH gives its hydrogen to H₂O₂ so H₂O is formed and if no enzyme is present then H₂O₂ will accumulate inside the cell causing oxidation of the cell membrane.

Glutathione maintains the integrity of the SH group in enzyme, Hb, protein and cell membrane.

Notes

Erythropoietin: (EPO) a glycoprotein hormone, controls erythropoiesis (RBCs production) also known as hematopoeitin or hemopoietin, used as
a drug, i.e. the exogenous EPO (rHu EPO) therapy, mainly produced in kidney and less in liver. Then acts as RBCs precursor in Bone Marrow.

Stimulus: lowered $O_2$ supply to tissues (Hypoxia) and Anemia. 

rHu EPO: recombinant human EPO used in treatment of patients with Renal Failure on hemodialysis.

**Metabolism of Aminosugars**

**Amino sugars:** (glucosamine, mannosamine, galactosamine, and their derivatives).

☆ Glucosamine 6-Phosphate is the precursor of all hexosamine residues in glycosaminoglycans.

*A summary of interrelationships in metabolism of aminosugars*
1. Amidination

2. Activation

3. Conjugation with Glucuronic acid

NANA = N-acetylneuraminic acid
Glc NAc = Acetyl glucosamine
Glc N = glucosamine
Man NAc = Acetyl mannosamine
Gal NAc = Acetyl galactosamine
UTP = Uridine triphosphate
UDP = Uridine Diphosphate
Gln = Amino Acid Glutamine
Glu = Amino Acid Glutamate

Glycosaminoglycans or mucopolysaccharides are important in the formation of Heparin, Hyaluronic acid, chondroitin sulfate...etc. Aminosugars like Glucosamine, Galactosamine...etc. and their derivatives are constituents of these mucopolysaccharides.

For example: Glucosamine and Glucuronic acid are constituents of chondroitin sulfate which is found in the cartilage.
The cartilage is very important for growth and mineralization to form the bones. So how are glucosamine and its derivatives formed?
These compounds come from Glc 6P which comes from:
   a) Glucose
   b) Amino acid metabolism
   c) Glycogen

Glc 6P is aminated by glutamine (Gln) by transaminase to form Glucosamine 6P (Glc N6P) which is converted by mutase to Glc N1P that reacts with UTP forming UDP-GlcN that may conjugate with glucuronic acid to form Heparin (anticoagulant).
Glc N6P may come from diet. Acetylation of Glc N6P by Acetyl CoA by transacetylase gives N-Acetylglucosamine 6P (N-Glc NAc 6P) that converts into N-Acetylglucosamine 1P (N-Glc NAc 1P).
N-Glc NAc 1P is activated with UTP forming UDP-N-acetyl glucosamine that is conjugated with glucuronic acid to form hyaluronic acid needed in Synovial fluid, eye, placenta...etc.

If chondroitin sulfate is needed, the enzyme epimerase converts Glc to Gal and so UDP-Gal NAc is formed and conjugate with glucuronic acid to produce chondroitin sulfate.

If Sialic acid (N-acetyl neuraminic acid=NANA) is needed, the enzyme epimerase converts Glc to Mannose so Glc NAc 6P converts to Man NAc 6P and this reacts with pyruvic acid to form Sialic acid which enters in the formation of Rh factor and Gangliosides.

**Metabolism of Mannose:**

The body utilize glucose as a major source of energy. Other monosaccharides, Fructose, Galactose and Mannose are not used directly but have to be converted to glucose (Glc) or other intermediates that are part of the Glycolytic pathway.

\[
\text{Mannose} + \text{ATP} \xrightarrow{\text{Hexokinase}} \text{Mannose 6P} \\
\text{Man 6P} \xrightarrow{\text{Isomerase}} \text{Glc 6P}
\]

The second reaction is reversible so that if Mannose is needed then the reaction goes to the left and Mannose is obtained and used for sialic acid synthesis with pyruvic acid coming from Glycolysis.