Alcohol Metabolism

Notes:

- This subject found in Marks(book) **not** in Lippincott , so this sheet (or Marks) would be the main reference of this subject .
- What is written here in this sheet is enough , and we are not required to know more than this ☺ .
- Before the exam , just read the **Bold** , and don't read every single word .

Lets start :

لا تنسوا أدعية ما قبل الدراسة ، و اولَها البسملة . . . . . :)

بسم الله الرحمن الرحيم

Knowing about alcohol metabolism is important , why ??!
Simply , because there are many people who ingest alcohol and use it , so you , as a doctor , may face some patient suffering from some problems caused by alcohol .

As we all know , من القرآن , that alcohol has some benefit as well as too many harmful effect , so , for this reason , it's a separate subject , and also for this reason we study it .

Some alcohol types :
Now , the most common type of alcohol is **ethanol ,** and because its to some extent expensive to poor country , they try to produce their own alcohol , and any mistake while they are doing that , they will produce **methanol** , which is a **lethal** compound (actually methanol itself is **not** a lethal , while its metabolism will produce **formaldehyde** , and this is the lethal one , and the first sign which appear on someone who digest methanol is **blindness** and to treat this person we should give them a **droplet of ethanol** because ethanol is a **competitive inhibitor of methanol** , and this allow the bodey to execrate the methanol) .

Ethanol metabolism :

Now lets go back to ethanol , its metabolize by an enzyme called **ethanoldehydrogenase** , giving **NADH** and **acetaldehyde** , now the acetaldehyde immediately go to the mitochondria and converted by **aldehyde dehydrogenase** (acetaldehyde dehydrogenase) to **acetate .**
Note : {**dehydrogenase** :- enzyme that transfers one or more hydrides (H^-) to an electron acceptor, usually NAD^+/$NADP^+$ or a flavin coenzyme .}

Acetate is a **very safe** compounds with no problems , logically because we have it normally in our bodies and **converted to acetalcoA** , so the compound that we are **afraid from is the acetaldehydenot** acetate , and fortunately **90% of acetaldehyde is directly converted to acetate** . (we will talk about the 10% later)

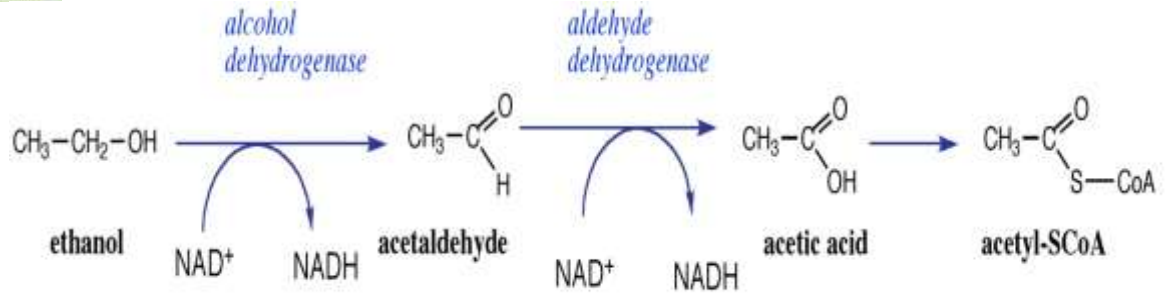
So after the conversion of acetaldehyde to acetate in the mitochondria its **carries by the blood to the muscles** , and then it will enter the muscles cells .

Inside the muscles cells , we have two enzymes :1_ one in the **cytosol** and 2_another in the **mitochondria** , both named **acetyl coA dehydrogenase** , this enzyme use the acetate and convert it to **acetyl coA**

1) If the acetate converted to acetyl coA by the **cytosol copy** of acetyl coA dehydrogenase , this acetyl coA would be used by the **fatty acid synthesis or cholesterol synthesis .**
2) If the acetate converted to acetyl coA by the **mitochondrial copy** of acetyl coAdehydrogenase , this acetyl coA would be used by **TCA cycle (krebs cycle) .**

Net products :

So we can notice that the conversion of **one mole of alcohol** (ethanol) to acetyl coA , will produce 2 NADH >>>>>>>> so **alcohol is high rich energy compound** (because it produce **2*NADH & acetyl coA { which will give me 3*NADH , FADH2 ,GTP }**)



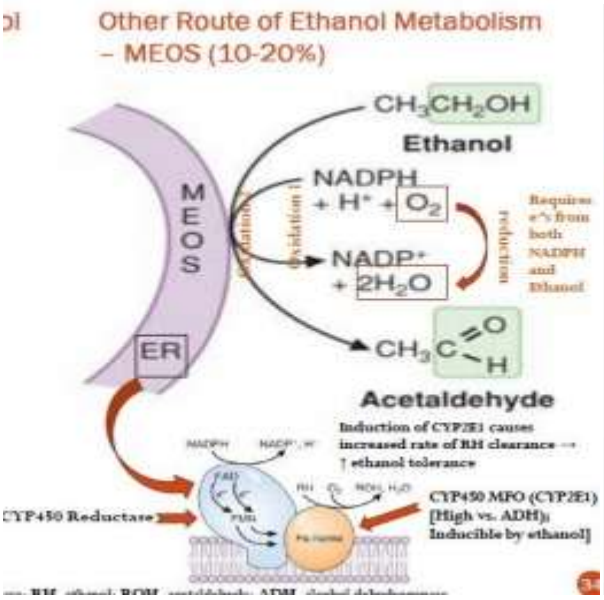
So because of that(the high amount of energy) , most of people who ingest a lot of alcohol **became fat** (زي معظم العايشين في الغرب) .

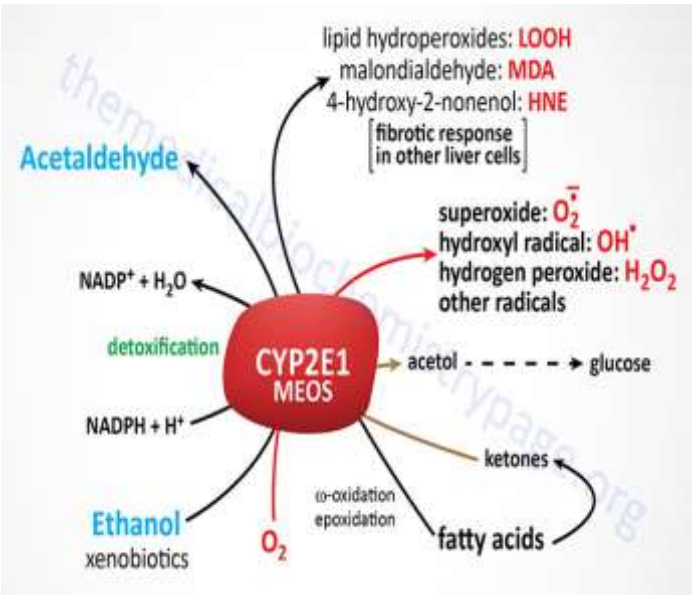
Small portion of the **acetaldehyde (about 10%)** escape to the blood , moving towered the **lungs and the kidneys** , the portion which goes to the lungs would go out by the breath , so you can **smell that** .

Another enzyme that metabolize alcohol :

Now , we have another enzymes can metabolize the alcohol (in addition to alcohol dehydrogenase) ,those enzymes related to **cytochrome P family** ,(the one which metabolize ethanol is**CYP2E1**) :

1) Microsomal enzyme
2) Has **high** Km
3) Metabolize **10_20% of the digested alcohol under moderate intake of alcohol** , but , if the person take a lot of alcohol he/she will induct (يحفز) this enzyme , so this enzyme will work more on alcohol .
4) Need **NADH & O2 (as in the pic. below)**
5) The final product is **acetaldehyde & water (H2O)*2 or free radical (O2`)& NAD+**
6) The protein portion of the CYP has **heme& FAD+** , this **FAD+ ganna to take the electrons** from the NADH one by one , and then these electrons travel to transportaer (could be **FMN or iron_sulfer center (Fe_S**) , then to the O2 to give the 2 H2O .





As we mentioned , CYP activity could produce free radical instead of H2O , as producing **ROS (reaction oxygen species)** , also produce **adducts protein**(defined below) ,,,,,,,,,,,,, these reasons are responsible for the liver damage .

> Note :adducts protein :
> A chemical bond between any substance and DNA, which may upregulate a gene;eg. DNA-carcinogen adducts candrive a cell's molecular machinery towards malignancy.

Variation between individual :

There is a variation between individual in relation to the response to alcohol (alcohol metabolism) , this variation is due to the **polymorphism** , this polymorphism would result in variation **in number & kind of enzymes** (alcohol dehydrogenase & CYP …. etc) between individual >>>> different response .

To sum up :

Ethanol

↓ ethanoldehydrogenase

Acetaldehyde(&NADH) —10%→ to kidneys & lungs ↓

90% ↓ acetaldehyde dehydrogenase

Acetate alcohol smell

↓

To the muscles (by the blood)

↓

To mitochondria | To cytosol

↓ Acetyl coA dehydrogenase ↓

acetylcoA acetyl coA

↓ ↓ ↓

To krebs cycle | to F.A.&cholesterol syn.

↓

- Net: Two NADH & acetyl coA

Finally :

"do what you think that is right , what is common that is right , what is proved that is right ,and then,don't ask or even care about the results"

-9385-

This paragraph is from our book , and our doctor said we have to read it :

Ethanol *is a* ***dietary fuel*** *that is metabolized to acetate principally in the liver with the generation of NADH. The principal route for metabolism of ethanol is through hepatic* ***alcohol dehydrogenases*** *(ADHs), which oxidize ethanol to* ***acetaldehyde*** *in the cytosol (Fig. 25.1). Acetaldehyde is further oxidized by* ***acetaldehyde dehydrogenases*** *to* ***acetate****, principally in* ***mitochondria****. Acetaldehyde, which is toxic, also may enter the blood.* ***NADH*** *produced by these reactions is used for adenosine triphosphate (ATP) generation through oxidative phosphorylation. Most of the acetate enters the blood and is taken up by skeletal muscles and other tissues, where it is activated to* ***acetyl coenzyme A*** *(****acetyl-CoA****) and is oxidized in the tricarboxylic acid (TCA) cycle.*

*Approximately 10% to 20% of ingested ethanol is oxidized through a microsomal ethanol oxidizing system (****MEOS****), comprising* ***cytochrome P450*** *enzymes in the endoplasmic reticulum (especially* ***CYP2E1****). CYP2E1 has a high* K_m *for ethanol and is inducible by ethanol. Therefore, the proportion of ethanol metabolized through this route is greater at high ethanol concentrations and greater after chronic consumption of ethanol.*

Acute effects *of alcohol ingestion arise principally from the generation of NADH, which greatly increases the* ***NADH/NAD_*** *ratio of the liver. As a consequence,* ***fatty acid oxidation is inhibited****, and* ***ketogenesis*** *may occur. The elevated* ***NADH/NAD_*** *ratio may also cause* ***lactic acidosis*** *and inhibit* ***gluconeogenesis****.*

Ethanol metabolism may result in ***alchohol-induced liver disease****, including* ***hepatic steatosis*** *(fatty liver),* ***alcohol-induced hepatitis****, and* ***cirrhosis****. The principal toxic products of ethanol metabolism include* ***acetaldehyde*** *and* ***free radicals****. Acetaldehyde forms* ***adducts*** *with proteins and other compounds. The* ***hydroxyethyl radical*** *produced by the MEOS and other radicals produced during inflammation cause irreversible damage to the liver. Many other tissues are adversely affected by ethanol, acetaldehyde, or by the consequences of* ***hepatic dysmetabolism*** *and injury.* ***Genetic polymorphisms*** *in the enzymes of ethanol metabolism may be responsible for individual variations in the development of alcoholism or the development of liver cirrhosis*

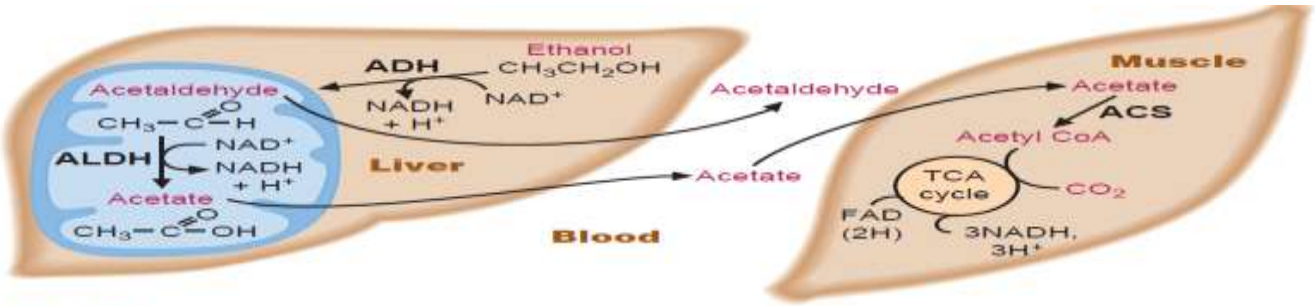


FIG. 25.1. The major route for metabolism of ethanol and use of acetate by the muscle. *ADH,* alcohol dehydrogenase; *ALDH,* acetaldehyde dehydrogenase; *ACS,* acetyl-CoA synthetase.