

# EXPLAIN THE MOLECULAR MECHANISMS THAT RESULT IN THE FORMATION OF A FATTY LIVER DUE TO THE INGESTION OF ALCOHOL

Fig. 4 Liver diagram (17)

## Introduction:

Fatty liver due to the ingestion of alcohol, is primarily caused by an imbalance in the synthesis and break-down of fatty acids. Metabolism of ethanol causes a shift in the liver's redox state, which inhibits  $\beta$ -oxidation and upregulates lipid synthesis. These factors, coupled with impaired fatty acid secretion, leads to an accumulation of triglycerides within the hepatocytes. Although reversible by lifestyle changes, fatty liver is the most prominent alcohol-induced liver disease, affecting 25-30% of the population in Europe. (3)

## How is alcohol metabolised?

Alcohol is mostly metabolised in the liver via 2 pathways. Small amounts can also be metabolised in the gastric mucosa. (20)

The pathway used depends on the volume of alcohol ingested: (20)

- Low-moderate volume  $\rightarrow$  Alcohol dehydrogenase (ADH) pathway
- High volume  $\rightarrow$  Microsomal ethanol oxidising system (MEOS)

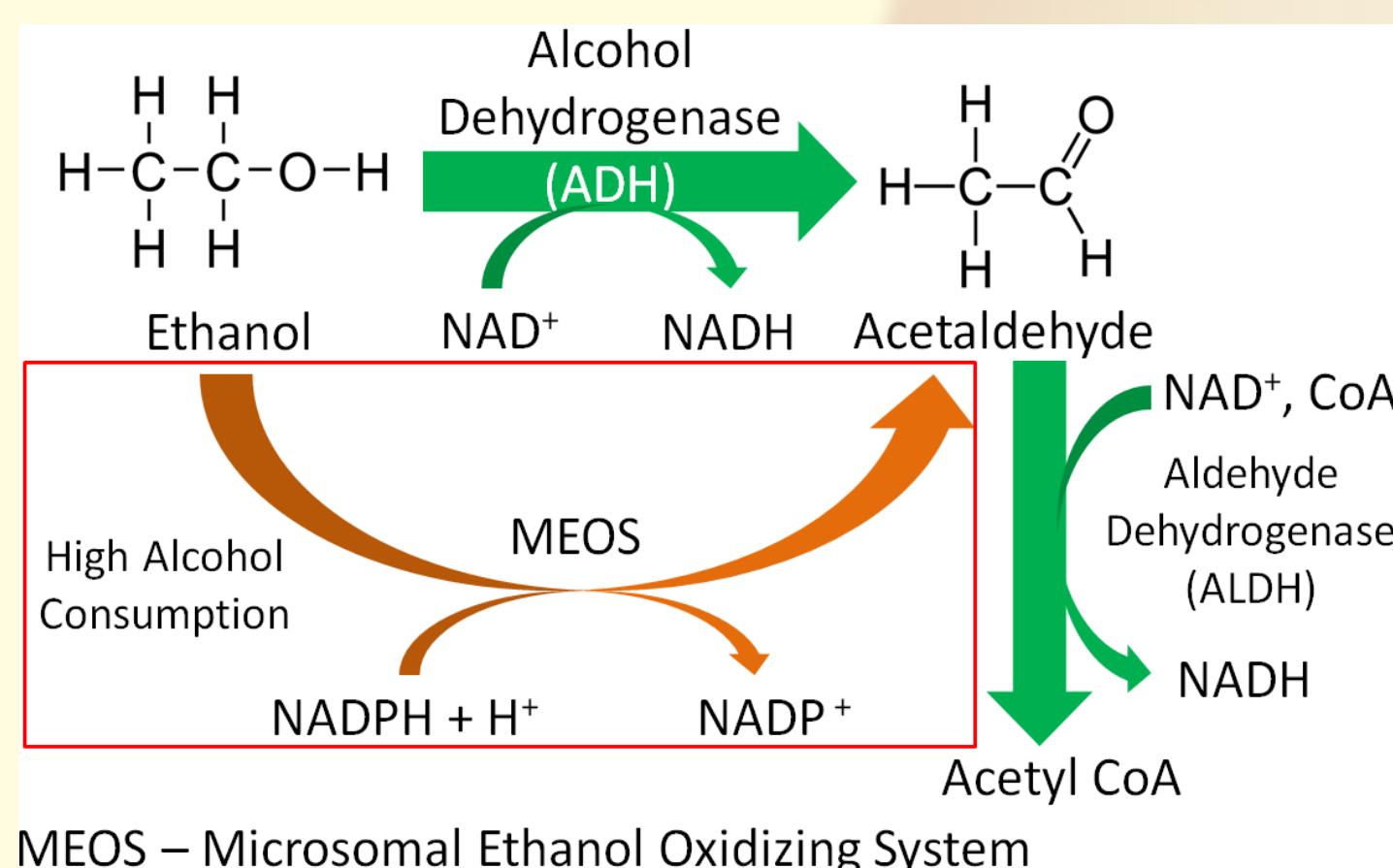


Fig.1 MEOS and ADH pathways (18)

## Effect of excess NADH (13-14):

- NADH is produced during the oxidation of ethanol in the ADH and MEOS pathways.
- This excess NADH donates electrons to the electron transport chain, generating ATP.
  - Increased ATP levels reduce the need to metabolise fatty acids for energy, inhibiting  $\beta$ -oxidation.
- NADH inhibits NAD<sup>+</sup>-requiring gluconeogenesis (15)
  - This reduces the number of substrates available for the tricarboxylic acid cycle.
  - Acetyl-CoA is used in lipid synthesis instead – the excess fatty acids generated are stored as triglycerides in the liver.

### Reference list:

- (1) Zhou Z, Wang L, Song Z, Lambert JC, McClain CJ, Kang YJ. A critical involvement of oxidative stress in acute alcohol-induced hepatic TNF-alpha production. *Am J Pathol*. 2003;163:1137-46.
- (2) Galli A, Pinaire J, Fischer M, Dorris R, Crabb DW. The transcriptional and DNA binding activity of peroxisome proliferator-activated receptor alpha is inhibited by ethanol metabolism. A novel mechanism for the development of ethanol-induced fatty liver. *J Biol Chem*. 2001; 276: 68-75.
- (3) Fatty liver (hepatic steatosis; steatohepatitis) information [myVMC]. [accessed 7 Apr 2019] Available from: <https://www.myvmc.com/diseases/fatty-liver-steatosis-steatohepatitis/>
- (4) Ameer C, Edvardsson U, Ljungberg A, Asp L, Akerblad P, Tunel A, Olofsson SO, Linden D, Oscarsson J. Activation of peroxisome proliferator-activated receptor alpha increases the expression and activity of microsomal triglyceride transfer protein in the liver. *J Biol Chem*. 2005; 280: 1224-1229.
- (5) Winder WW, Hardie DG. AMP-activated protein kinase, a metabolic master switch? Possible roles in type 2 diabetes. *Am J Physiol*. 1999;277:E1-10.
- (6) Vasudevan DM, Sreekumar S. Textbook of Biochemistry for Dental Students. Fifth edition. Jaypee Brothers Medical Publishers (P) Ltd; Jitendar P Vij, 2007.
- (7) Sanders MJ, Grondin PO, Hegarty BD, Snowdon MA, Carling D. Investigating the mechanism for AMP activation of the AMP-activated protein kinase cascade. *Biochem J*. 2007;403:139-48.
- (8) Liangpunsakul S, Wu SE, Zeng Y, Ross RA, Jayaram HN, Crabb DW. Effect of ethanol on hydrogen peroxide-induced AMPK phosphorylation. *Am J Physiol Gastrointest Liver Physiol*. 2008;295:G1173-81.
- (9) Garcia-Ruiz C, Cole A, Mari M, Albert M, Maria C, Carlos E, et al. Defective TNF- $\alpha$  mediated hepatocellular apoptosis and liver damage in acidic sphingomyelinase knockout mice. *J Clin Invest*. 2003;111:197-208.
- (10) You M, Fischer M, Deeg MA, Crabb DW. Ethanol induces fatty acid pathways by activation of steroid regulatory element binding protein (SREBP). *J Biol Chem*. 2002;277:29342-7.
- (11) Rasineni K, Casey C. Molecular mechanism of alcoholic fatty liver. *Indian Journal of Pharmacology*. 2012; 44(3): 299-303. doi: 10.4103/0253-7613.96297
- (12) Horton J, Goldstein J, Brown M. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *The Journal of Clinical Investigation*. 2002;109(9): 1125-1131. doi: 10.1172/JCI15593
- (13) Lieber CS. Hepatic, metabolic and toxic effects of ethanol: 1991 update. *Alcohol Clin Exp Res*. 1991;15:573-92.
- (14) Grunnet K, Kondrup J. The effect of ethanol on the beta-oxidation of fatty acids. *Alcohol Clin Exp Res*. 1986;10:64S-8.
- (15) Alcohol Metabolism. [accessed 7 Apr 2019] Available from: <http://chemistry.elmhurst.edu/chembook/642/alcoholmet.html>
- (16) Wehr H, Rodo M, Lieber CS. Acetaldehyde adducts and autoantibodies against VLDL and LDL in alcoholics. *J Lipid Res*. 1993;34:1237-44
- (17) What Does the Liver Do for the Body? | About Liver Function. UPMC HealthBeat. 2015. [accessed 7 Apr 2019] Available from: <https://share.upmc.com/2015/09/what-does-the-liver-do-for-the-body/>
- (18) 6.5 Alcohol Metabolism | Nutrition Flexbook. [accessed 7 Apr 2019] Available from: <https://courses.lumenlearning.com/suny-nutrition/chapter/6-5-alcohol-metabolism/>
- (19) Alcoholic Liver Disease. [accessed 7 Apr 2019] Available from: <http://www.clevelandclinicmedcom/medicalpubs/diseasemanagement/hepatology/alcoholic-liver-disease/>
- (20) Nutrition lecture (Alcohol), Dr Andrew Shore.
- (21) Hill, M.A. [accessed 7 Apr 2019] Available from: [https://embryology.med.unsw.edu.au/embryology/index.php/Gastrointestinal\\_Tract - Liver\\_Histology](https://embryology.med.unsw.edu.au/embryology/index.php/Gastrointestinal_Tract - Liver_Histology)
- (22) Shimomura I, Ishii H, Korn BS, Bashmakov Y, Horton JD. Nuclear sterol regulatory element binding proteins activate genes responsible for entire program of unsaturated fatty acid biosynthesis in transgenic mouse liver. *J Biol Chem*. 1998;273:35299-35306.

## How does alcohol impair very-low-density-lipoproteins (VLDL) secretion?

- Ethanol inhibits phosphatidylcholine synthesis, a factor key in the formation of VLDL.
  - Production of VLDL decreases, which reduces the export of triglycerides, causing them to accumulate in the liver.
- Acetaldehyde, an intermediate in ethanol metabolism, reduces VLDL secretion by inhibiting the assembly of microtubules. (16)

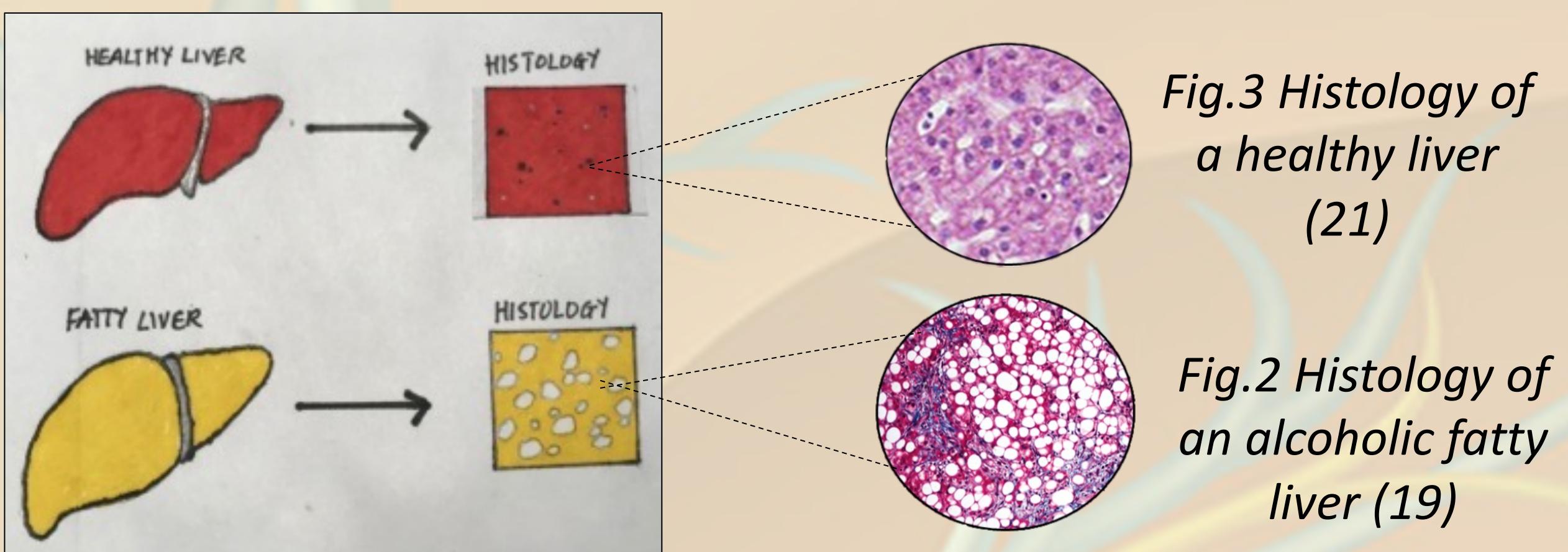


Fig.3 Histology of a healthy liver (21)

Fig.2 Histology of an alcoholic fatty liver (19)

## How does alcohol inhibit $\beta$ -oxidation?

### Peroxisome proliferator-activated receptor- $\alpha$ (PPAR $\alpha$ ):

#### Role of PPAR $\alpha$ (1-2):

- A nuclear hormone receptor which detects high levels of fatty acids, and becomes active.
- Activation causes PPAR $\alpha$  to form a heterodimer with retinoid X receptor (RXR).
- The heterodimer binds to peroxisome proliferator response elements in the genes involved in  $\beta$ -oxidation, enhancing the pathways.
- Upregulates microsomal triglyceride transfer protein (MTP), which is involved in the transport of VLDL. (4)

#### Effect of ethanol on PPAR- $\alpha$ (4):

- Inhibits  $\beta$ -oxidation by:
  - Preventing binding of the PPAR $\alpha$ /RXR heterodimer to the genes in  $\beta$ -oxidation.
  - Inhibiting the expression of genes regulated by PPAR $\alpha$ .
- Reduces the level of MTP and subsequent transport of VLDL, encouraging the accumulation of triglycerides in hepatocytes.

## Critique of Sources:

Throughout my poster I have used information from credible sources such as journal articles. Articles are intended to inform rather than persuade, making them less likely to be biased, and more likely to be reliable. However source 2 was published in 2001 and source 5 in 1999, therefore although these sources are credible, the information is not current – this reduces the reliability of the sources, and accuracy of my poster. In addition, 'Virtual Medical Centre' is only partially reliable, as information from a health centre would be biased towards making the reader abstain from alcohol. Its partnerships with 'Parent Hub' and 'Pregnancy birth & baby' may also influence the information on the website, making it biased and reducing the accuracy of my poster.

## How does alcohol enhance fatty acid synthesis?

### Adenosine Monophosphate-activated Protein Kinase (AMPK):

#### Role of AMPK:

- A heterotrimeric protein activated by elevated AMP levels.
- Activation causes the phosphorylation and inhibition of enzymes involved in lipid synthesis, in particular acetyl-CoA carboxylase (ACC). (5)
  - Catalyses conversion of acetyl-CoA to malonyl-CoA. (6)
- Regulates sterol regulatory element-binding protein 1 (SREBP-1). (5)

#### Effect of Ethanol on AMPK (7-9):

- Increases the level of ceramide, which activates protein phosphatase 2A (PP2A).
- PP2A dephosphorylates and inhibits AMPK.
  - This activates the enzymes involved in lipid synthesis – fatty acids produced are stored in the liver as triglycerides.

### SREBP-1:

#### Role of SREBPs:

- Group of transcription factors which control the enzymes involved in fatty acid synthesis. (10)
- SREBP-1 and 2 enhance lipid synthesis by activating genes which are required to produce NADPH. (12)

#### Effect of ethanol on SREBPs: (11)

- Inhibits AMPK, which activates SREBP-1 and upregulates the SREBP-1 target genes.
  - Increases fatty acid synthesis.
- Evidence: A study conducted on 10 genetically modified mice revealed that overexpression of SREBP-1a caused a 26 fold increase in lipid synthesis, resulting in a huge fatty liver. (22)

## Conclusion:

In conclusion, ethanol's ability to influence the action of receptors, enzymes and coenzymes involved in the synthesis and oxidation of fatty acids, ultimately leads to the formation of a fatty liver.