Alcohol and lipidic metabolism

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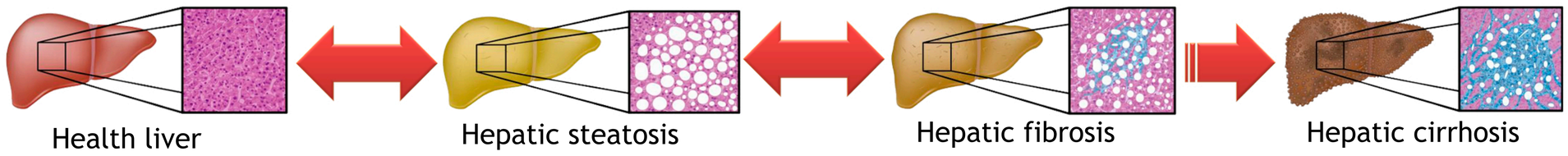
INTRODUCTION

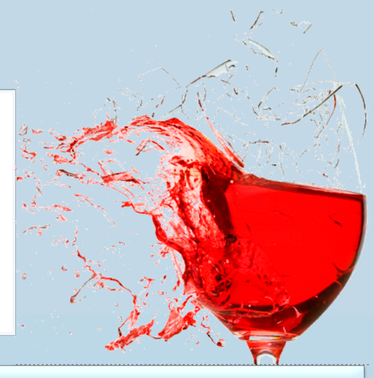
Alcohol is a widely consumed substance everywhere and is considered a drug because it causes dependence and a lot of adverse health effects due to its toxicity. According to the World Health Organization (WHO) in 2014, the European region, that represents a 14,7% of the world population older than 15 years old, consume more than one quarter (25,7%) of the total quantity of alcohol consumed worldwide.
Chronic alcohol consumption is not due to a single factor but the sum of vulnerable factors converging in one person, and developing alcohol-related problems. Prolonged alcohol consumption affects essential organs in the body, such as the liver. Hepatic damage can be divided into different stages:



ALCOHOLIC FATTY LIVER DISEASE (AFLD)

AFLD is characterized by an increase of lipids in the liver, mainly triglycerides, caused by an accumulation of acetaldehyde, a very toxic metabolite of alcohol. The **objective** of this study is to determine the enzymatic alterations which cause AFLD, using as **methodology** searching bibliography information and the results obtained to prove it. The main alterations that have been investigated are:

- Alterations of the enzymes involved in lipid
- Alterations in adipose tissue
- The activation of the immune system, largely initiated by tumor necrosis factor α (TNFα).



ALTERATIONS

SREPB

The alterations in Sterol Regulatory Element-Binding Proteins (SREBP) affected by alcohol are: downregulation of AMPK, increase of homocysteine and reactive oxygen species (ROS).
The upregulation of SREBP transcription promotes an increase in the expression of mRNA of lipogenic genes, like FAS and ACC.

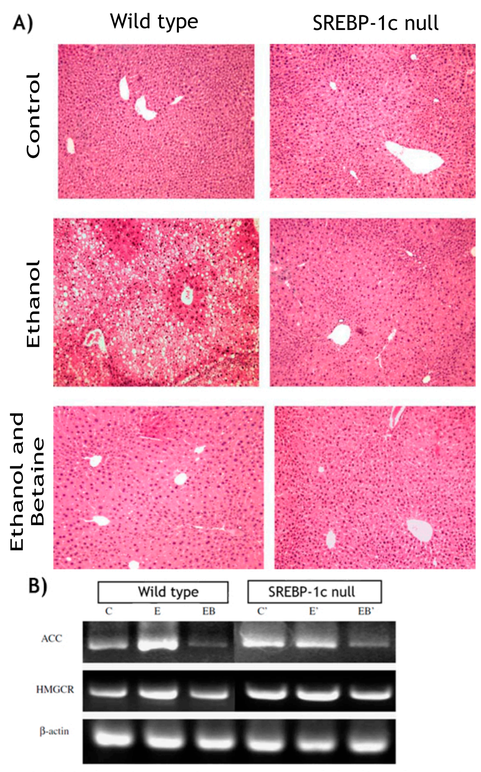


Figure 1. A) Light microscopic appearance of the liver from mice fed control and alcohol diet for 4 weeks and betaine treatment (hematoxylin-eosin staining 100x). **B)** RT-PCR of mRNA[1].

TNF-α

When liver damage occurs, early immune responses are initiated against this damage and the most important cytokine involved in TNFα is produced by the liver immunity cells, called Kupffer cells.

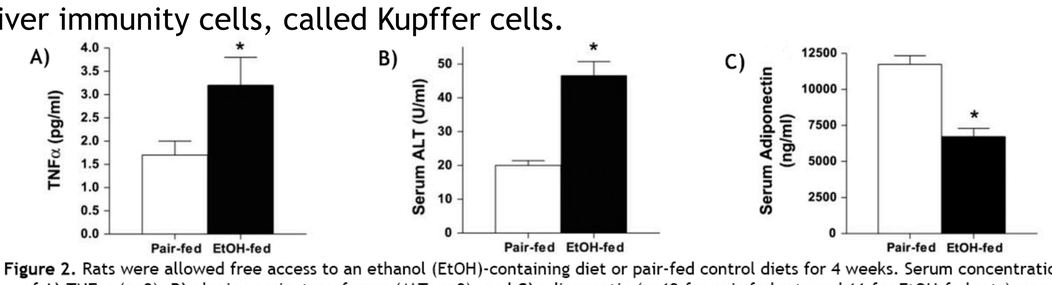
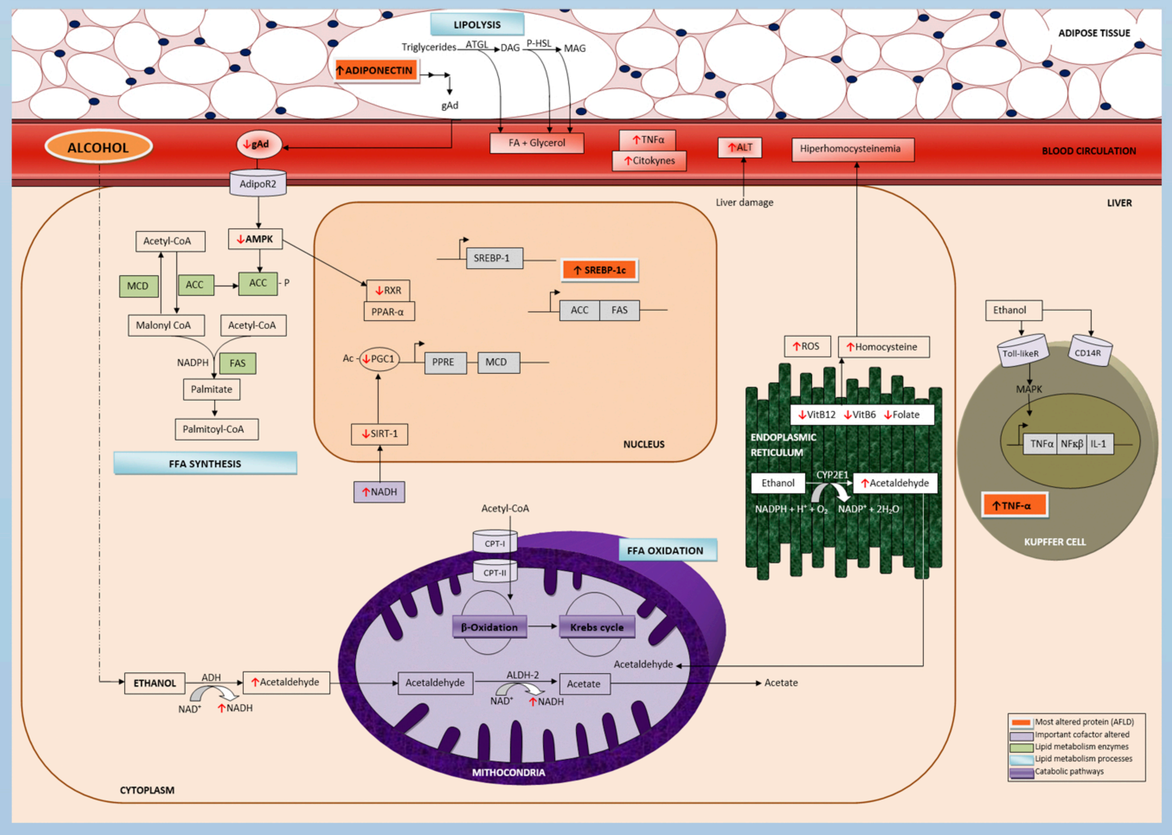


Figure 2. Rats were allowed free access to an ethanol (EtOH)-containing diet or pair-fed control diets for 4 weeks. Serum concentrations of **A)** TNF-α (n=8), **B)** alanine aminotransferase (ALT; n=8), and **C)** adiponectin (n=12 for pair-fed rats and 11 for EtOH-fed rats) were measured. *P < 0.05 compared with pair-fed rats[2]



ADIPONECTIN

Adiponectin is a peptidic hormone secretated only by the adipose tissue and abusive alcohol consumption significantly reduces the levels in circulation. The main action of this protein is promoted by an increase in the oxidation of FFA, but in presence of alcohol this process decreases. Moreover, the increase in TNFα inhibits adiponectin.

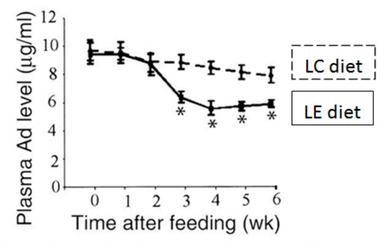


Figure 3. Levels of plasma adiponectin after mice had been fed with control diet (LC) and ethanol diet (LE). *P < 0.05 for ethanol diet versus control diet (n = 6)[3].

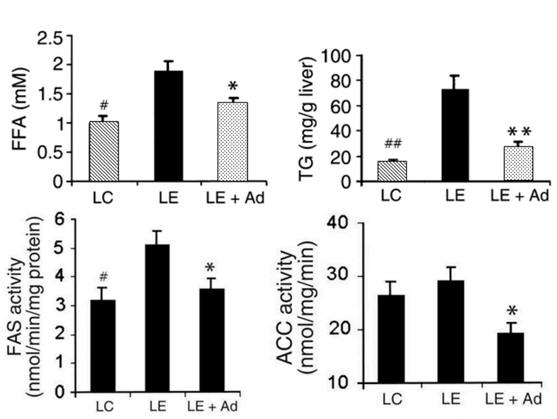


Figure 4. Serum samples and enzymatic activity were collected after 5 weeks of control diet (LC), ethanol diet (LE), or LE + Adiponectin diet in the last 2 weeks. #P < 0.05 for LC-treated mice versus LE-treated mice; *P < 0.05 for LE + Ad-treated mice versus LE-treated mice[3].

TREATMENT

- **Alcohol abstinence** is the most important
- **Naltrexona**: decreases recurrence time
- **Betaine**: antioxidant which reduces AFLD
- **Anti-TNFα antibodies**: downregulate inflammatory responses
- **Metformin**: AMPK activator
- **Clofibrate** and **Wy14,643**: PPARα agonist

CONCLUSIONS and FUTURE RESEARCH

- Alcohol can affect a lot of pathways even in early disease stages.
- Some pathways are not well known yet, like SREBP activation.
- Kupffer cell activation is very important to the worsening of the disease.
- Future studies in TNFα response mechanisms would be very interested.
- It would be necessary to include pathways affected in other organs to fully understand the disease.

References edited:
[1] Ji, C., Chan, C., & Kaplowitz, N. (2006). Predominant role of sterol response element binding proteins (SREBP) lipogenic pathways in hepatic steatosis in the murine intragastric ethanol feeding model. Journal of Hepatology, 45(5), 717-24.
[2] Thakur V, Pritchard MT, McMullen MR, Nagy LE. (2006) Adiponectin normalizes LPS-stimulated TNF-alpha production by rat Kupffer cells after chronic ethanol feeding. American Journal of physiology Gastrointestinal and liver physioloy; 290(5):G998-1007
[3] Xu, A., Et. al (2003). The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice, The Journal of Clinical Investigation 112(1), 91-100.

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