Reactive Oxygen Species Generated in a Chronic Consumption of Alcohol. Pathogenesis in the Liver.

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Introduction

Alcohol is the most accepted drug in the world, it is part of the dialy life and an essential point in social meetings. Chronic alcohol consumption is one of the most important etiological factor in the pathogenesis of liver disease, so knowing the effect that alcohol has in the human body can be really important to avoid it or to fight it. It has been shown that reactive oxygen species (ROS) play an important role in this pathogenesis.

The aim of this bibliographic research is to explain the alcohol metabolism, its contribution to oxidative stress, and the relationship between it and the alcoholic liver disease; highlighting the part of ROS and its dangerous byproducts resulted from the interaction of ROS with other macromolecules.

Methods

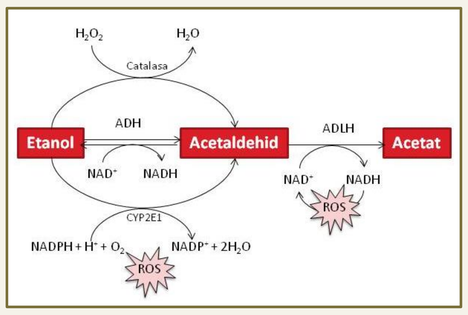
To elaborate this review, various publications, either reviews or conventional articles, were consulted.

- Firstly, a search of the key words *ROS, oxidative stress, alcohol metabolism, ethanol metabolism, alcoholic liver disease* was held in Pubmed, Sciencedirect and Google Scholar.
- Secondly, the most important and related articles were read and summarizes, and their bibliography analyzed.
- Finally, all the information was integrated and some diagrams about it were elaborated in order to complete the review and the poster.

Alcohol metabolism

Alcohol is metabolized in the liver by oxidative pathways mainly (Fig. 1). The first step of the oxidative metabolism is the production of acetaldehyde from ethanol, and this reaction can involve three different enzymes, being alcohol dehydrogenase (ADH) the most important, the other two are cytochrome P450 and catalase.

Cytochrome P450 is a group of enzymes with oxidase function that eliminate toxic substances, not only found in liver, but also in other organs. In the alcohol metabolism, there a really important enzyme, CYP2E1, that is highly activated in a chronic consumption and it is one of the major source of ROS.



Acetaldehyde is a toxic product that contributes to tissue damage. In the metabolism of ethanol, acetaldehyde is transformed to acetate, a product less toxic that can be oxidised to CO_2 or metabolised to Acetil-CoA.

The main consequences of this reactions are the generation of harmful products and ROS, changes in the $NADH/NAD^+$ ratio and hypoxia in liver.

Figure 1. Schematic representation of the oxidative metabolism of ethanol. Adaptation of Zakhari, 2006.

Reactive oxygen species

Reactive oxygen species are free radicals, which can unstable atoms, molecules or compounds. Because of its molecular structure, they are very reactive in order to create a stable compound.

Oxygen (O_2) is essential for life. Without it, there is no production of ATP, necessary for cellular function and survival. ATP is produced in the electronic transport chain, where oxygen is the last acceptor. O_2 can accept 4 electrons and 2 hydrogen. Through this process ROS (Fig.2) can be generated. ROS have harmful effects on cell when their concentration rises. As a consequence cell result in a state called oxidative stress.

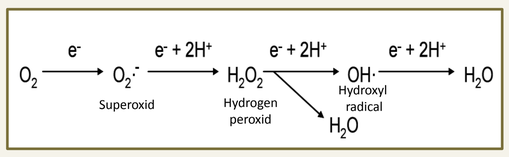
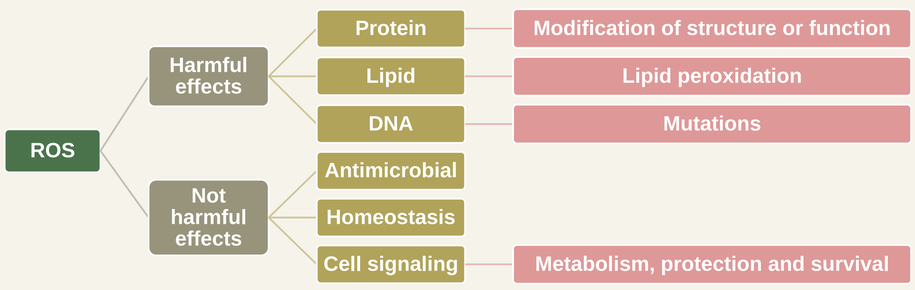


Figure 2. Reduction of oxygen to water, and the intermediate products, ROS.

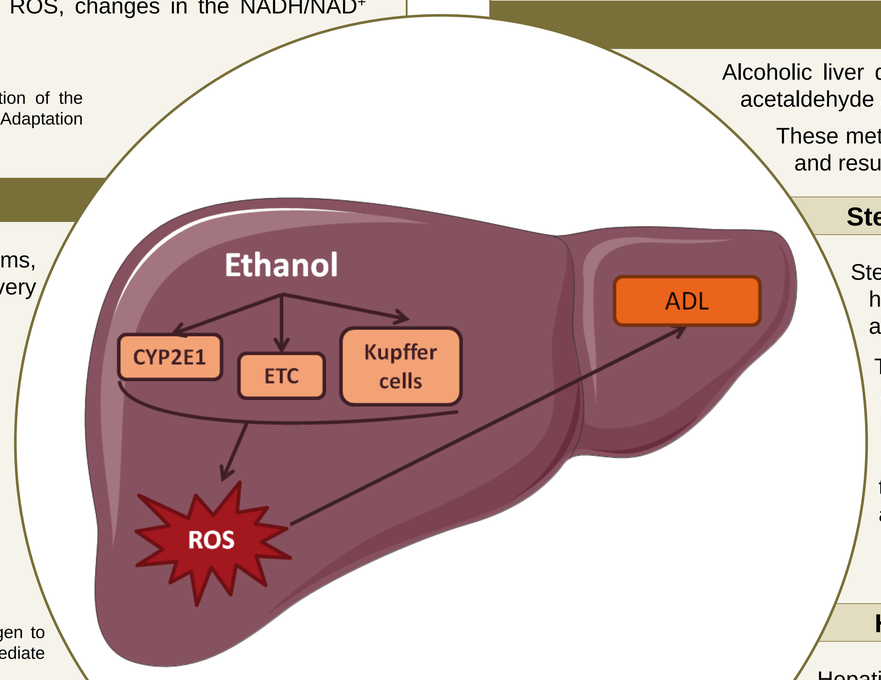
ROS are not always harmful, they also help to eliminate some pathogens, participate in homeostasis and in cell signaling.



ROS related to alcohol

Alcohol consumption promotes ROS formation by:

- Oxidation of ethanol to acetaldehyde by CYP2E1. This pathway is over activated in chronic consumption.
- Oxidation of NADH in electronic transport chain (ETC). Concentration of NADH rises in alcohol metabolism and it has to be oxidised.
- Kupffer cells activated in the liver. This type of cells contain a NADH oxidase complex that produces ROS.



Lipid peroxidation

Cells' lipids can interact with some free radicals as ROS. This reaction is called lipid peroxidation and its products are also radicals (Table1).

The lipid peroxidation products can interact with macromolecules, as ROS do, but they form adducts. These adducts are recognised as strange molecules in body, so immune system react against them. In last term, this reaction can damage normal hepatic tissue.

These products have part of responsibility on the alcoholic liver disease (ALD).

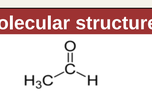
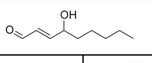
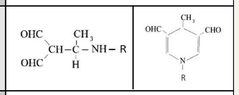
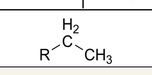
Radicals	Abbreviation	Molecular structure
Acetaldehid	AA	
Malondialdehid	MDA	
4 – hidroxy-2-noneal	HNE	
Híbrid Malondialdehid – Acetaldehid	MAA	
Radical hydroxietil	HER	

Table 1. The 5 main radicals produced in lipid peroxidation. Two structures has been proposed for MAA.

Alcoholic liver disease

Alcoholic liver disease is one of the major causes of morbidity in the world. ROS and acetaldehyde are, directly or indirectly, responsibles.

These metabolites participate in cell signaling disrupting different signaling pathways and resulting in functional losses and in changes in gene expression.

Steatosis

Steatosis or fatty liver is a lipid accumulation state on hepatocytes. It is the first response of the liver after an alcohol abuse and it is reversible.

This clinical effect is produced by different causes in alcohol metabolism and each one affects different pathways.

Specifically, ROS participate in this clinical condition through the AMPK pathway, that turns out in an alteration of lipid metabolism (Fig.3).

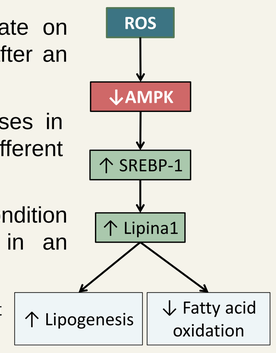


Figure 3. Pathway of how ROS affect lipid metabolism that result in fatty liver.

Hepatitis, fibrosis and cirrhosis

Hepatitis starts due to pro-inflammatory cytokines, which are increased in a situation of chronic alcohol consumption. They damage liver tissue and it results into hepatic inflammation and fibrogenesis, healthy tissue is replaced by extracellular matrix, in particular fibrillar collagens. Progression of this state becomes to cirrhosis.

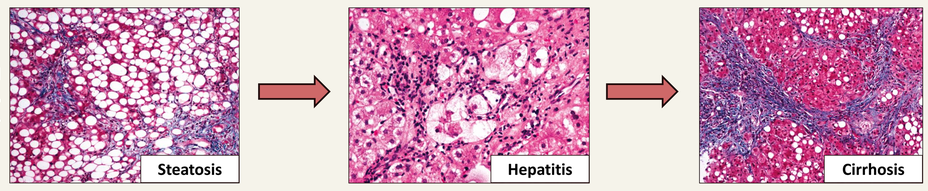


Figure 4. Histological progression of steatosis, hepatitis and cirrhosis. http://www.clevelandclinicmeded.com/

Cancer

ROS and lipid peroxidation products generate DNA adducts (Fig.5), which have mutagenic properties. They produce base repair substitution mutations and other types of genetic damage that can turn into cancer. One of the most important affected gens is TP53 (tumor suppressor). Moreover, cirrhosis is a high risk factor to develop hepatocellular carcinoma, so both pathways facilitate carcinogenesis.

Epigenetic is also modified by these products, DNA results in an hipometilation state which makes that differentiate cells become to progenitor cells or stem cells, and it means that hepatic tissue loses its identity and develops a pathological condition.

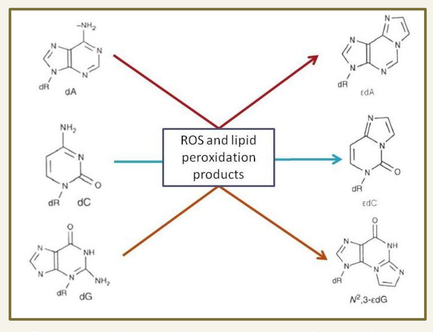


Figure 5. DNA adducts generated by ROS and lipid peroxidation products. Adaptation from Linhart *et al*, 2014.

Concluding remarks

- Alcohol consumption and its metabolism are strongly related to pathogenesis in liver. One important enzyme that participate in this metabolism is CYP2E1, it is overactivated in chronic alcohol consumption.
- ROS generated in alcohol metabolism have harmful effects in lipids, proteins and DNA. It results in a loss of functionality of these molecules.
- Not always ROS has negative effects; they participate in antimicrobial response and cell signaling, even though in pathways of survival.
- The pathological effects due to alcohol consumption are confined to the group alcohol liver disease. It includes steatosis, hepatitis, fibrosis, cirrhosis and hepatocellular carcinoma. Other types of cancer are also possible to be developed in this situation.
- Knowing all the pathways affected by ROS during alcohol metabolism can help to develop some effective therapy.

References

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