Review Paper

Consequences Of Ethanol Consumption

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ABSTRACT

Chronic ethanol consumption is associated with increased incidence of a variety of illnesses. The precise mechanisms leading to alcohol related diseases are still imprecisely known. The metabolic effects of alcohol are due both to its direct action as well as to that of its first metabolite acetaldehyde, and can also be related to the changes in redox state. Ethanol increases the rate of generation of free radicals, decreases antioxidant levels, and potentiates oxidative stress. Cells are protected against oxidation by the action of certain enzymes, vitamins, and other substances, known collectively as antioxidants.

Key words: Ethanol, Acetaldehyde, Oxidative stress, Reactive oxygen species

The term alcohol originated from an Arabic word *al-kohl = subtle*. It is a colorless, volatile liquid with a characteristic odor and taste. From ancient times alcoholic beverages have been used to induce a sense of wellbeing. Alcoholism is the tendency towards excessive use of alcohol. Nowadays alcoholism has become a pervasive problem that threatens most of the countries all over the world. Its incidence is increasing relentlessly among the general population.[1] In 1990, the World Health Organization (WHO) estimated that globally, alcohol accounted for 3.5% of the total days lost to death and disability.[2] The explanation of this finding is that in addition to chronic diseases that affect drinkers after many years of heavy use, alcohol also contributes to traumatic outcomes that kill or disable disproportionately high numbers of young people, resulting in many years of disability-free life being lost.

Psychological disturbances probably are the most important reason. Psychologists have proposed the existence of an alcoholic personality characterized by a psychological vulnerability emerging from immaturity, a desire for inordinate amount of appreciation, high expectations, low level of frustration tolerance, and uncertainty about one's ability to play the correct role adequately. Researchers have found that a specific gene is responsible for susceptibility of an individual towards alcoholism. Environmental and cultural factors also play a significant role in the acquirement of alcoholism. Alcoholics are generally found to be extroverted, sensation-seeking, and neurotic, as compared to normal people. They tend to have depressive sociopathy, experience vague anxieties, and react pathologically to undesirable stresses in life. Alcoholics also have low levels of self-concept, high anxieties in interpersonal relationships, ambivalence towards authority, and isolationism.[3] Being a depressant drug, alcohol has major effects on higher nerve centers. Its first effect is to reduce feelings of worry, and thereby to promote a

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feeling of wellbeing. It also loosens powers of imagination. Alcohol even in small doses impairs judgment and inhibits the skills necessary for fine movements.[4] When alcohol is consumed above recommended levels, it makes the nervous system alcohol-dependent. Once the actions of alcohol are over, the opposite effects (rebound symptoms) begin to appear. If one carries on drinking in spite of reverse or rebound symptoms, tension, nervousness, restlessness, etc., can creep on the individual, depending on the tolerance of the body.

Reasons for alcohol consumption

Scientists and sociologists have put forward the following reasons for people taking up alcohol consumption:

Self-gratification: Some people drink only for enjoyment, or to remove boredom, or to get rid of monotony.

Symbolic participation: Some individuals take to alcohol to project themselves as "heroes". Many people also drink to maintain their status. They tend to consider alcohol drinking as a status symbol.

Psychodynamic relief: In this case, alcohol consumption is indulged in to remove psychological disturbances, and to get relief from sorrow, grief, etc.

Alcohol related diseases

Excessive consumption of alcohol may lead to a variety of gastrointestinal, neurologic, cardiovascular, and malignant diseases.[5,6] Alcohol intoxication can lead to various disorders such as gastritis, gastric ulcers, fatty liver, liver cirrhosis, alcoholic hepatitis, etc. Pancreatitis is very common among chronic alcoholics.

Alcohol in heavy doses can cause muscular weakness and acute alcoholic myopathy. It can also lead to elevation of blood pressure. In binge drinkers, the incidence of atherosclerosis is very high.[7] Alcoholism is associated with hypoparathyroidism and low testosterone and other sex steroids levels; thus resulting in low serum calcium levels and diminished reproductive capacity in both males and females.

Heavy drinking increases the risks of carcinoma of tongue, mouth, larynx, oesophagus, and liver. Even in small doses, alcohol can produce ataxia, alcoholic neuropathy, and Wernicke's encephalopathy.[8] Alcohol consumption during pregnancy could lead to fetal alcohol syndrome characterized by low birth weight, greater susceptibility to infections due to immune deficiency, congenital malformations, increased tortuosity of the retinal artery and vein, and high serum uric acid levels.[9] Alcohol stimulates the pancreatic β cells to produce insulin, which reduces blood sugar level and produces hypoglycemia. Low blood sugar level inhibits the formation of liver glycogen. Alcohol also inhibits glucose formation from lactate, and from other glucogenic amino acids in the liver. Chronic alcoholism is associated with derangement in sulphur amino acid metabolism producing ethanol-induced hyperhomocysteinemia. Homocysteine induces neuronal cell death. Alcohol in high doses induces DNA damage and impairs DNA repair system.[10] These mechanisms induce apoptosis and early aging. There is a three to seven fold increase in premature mortality, enhanced susceptibility to chronic liver disease, and increased tendency to traumatic injuries and drowning.[11]

In terms of mortality, even if allowance is made for alcohol's supposed protective effects with regard to coronary heart disease, globally in 1990, alcohol still caused over ¾ million more deaths than it prevented. The burden of alcohol-related disease is highest in the developed countries, particularly Europe, the continent with the highest levels of alcohol consumption. Within WHO European Region, alcohol products are responsible for around 9% of the total disease burden. As well as deaths from chronic diseases such as alcohol-related liver disease and

cirrhosis, between 40% and 60% of all deaths from intentional/ unintentional injury are alcohol-related.[2]

However, alcohol related diseases are not observed in everyone who drinks excessive amounts of alcohol, and it would be useful to have tests by which one could predict their occurrence. Although epidemiological studies have shown that alcohol intake correlates with increased risk of cirrhosis,[12] many decades of research have not yielded the exact reasons why only a relatively small proportion of individuals who consume excessive quantities of alcohol develop clinically significant alcohol related diseases.[13] The increased susceptibility is related not only to the total amount of alcohol consumed, but also to drinking patterns and type of alcoholic beverage ingested. Other potential influencing factors include age, gender, genetic background, nutritional status, intestinal microflora, reactions with xenobiotics, occupational hazards, and viral diseases.[14, 15]

Liver disease has long been associated with alcoholics as the liver is the major organ concerned with the removal of ethanol from the body. It is clearly established that excessive alcohol intake can lead to liver cirrhosis. When patients with a history of heavy alcohol abuse were assessed, liver damage severity correlated well with quantity of alcohol consumed.[16] Most patients develop fatty liver, which reverses on withdrawal of alcohol and is unlikely to progress to liver cirrhosis. In the liver, the acetaldehyde produced by oxidation of ethanol interacts with lipids and proteins, generating free radicals and impairing protein function. The toxic metabolites and free radicals stimulate fibrogenesis in the liver. Proinflammatory cytokines are especially important in the development of hepatitis, although the pathogenesis is unknown. Seventy-five percent of esophageal cancers are alcohol related; yet alcohol is not a carcinogen. Ethanol may promote carcinogenesis via increased free radical products during its metabolism.[17]

Pathogenesis

One approach to establish the mechanisms that give rise to ethanol-induced liver damage is to investigate those alterations that occur very early in the pathogenesis of the disease. One of the earliest effects of ethanol consumption on the liver is a change in the structure of mitochondrion. The mitochondria are often enlarged and misshapen, appearing either as swollen or elongated structures, with the cristae disrupted or without normal organization.[18] In the rat model, these structural changes in the mitochondria are accompanied by development of fatty liver,[19] suggesting the possibility that hepatic energy metabolism was compromised by chronic ethanol consumption, given the central role of mitochondrion in energy conservation. Since the viability of aerobic tissues such as the liver is compromised by a decrease in ATP concentration, it was also recognized that changes in energy metabolism could be an etiological factor in ethanol-related liver disease. Ethanol-elicited alterations in mitochondrial structures and functions may also result in elevated levels of mitochondrial reactive oxygen species (ROS).[20] The ethanol-related decrease in hepatocyte viability, observed under oxygen tensions similar to those in the liver lobule, is one of the earliest indicators that chronic ethanol consumption compromises the structural integrity of the predominant cell type in the liver, even when more classical indicators of alcoholic liver disease, e.g., tissue necrosis, stellate cell activation, and/ or perivenular fibrosis are not observed.[21]

Absorption and Metabolism

Although alcohol has high caloric value, it reduces nutrient intake from other foods by decreasing appetite. Alcohol consumption decreases the absorption of a number of nutrients and can alter their storage, metabolism, and excretion. Further, it affects the metabolism and storage

of fat-soluble vitamins, and also causes deficiency of many water-soluble vitamins. Decrease of many antioxidant levels also occur in the body due to alcohol consumption.

Ethanol being soluble both in water and lipids and having a small molecular size, can diffuse rapidly through the mucous membranes of the esophagus and stomach. After absorption, ethanol appears in both expired air and in urine, since it diffuses out from the lungs and kidneys. It is not stored in the body, as whatever is ingested is oxidized. It is metabolized entirely in the liver.

The impact of ethanol on generation of reactive oxygen species (ROS) in the cell is linked to its metabolism via oxidative processes.[22] The major mechanisms for ethanol oxidation are represented by the following reactions. In the individual consuming moderate amounts of ethanol, most of the metabolism is accomplished by alcohol dehydrogenase.

$$CH_3CH_2OH + NAD^+ \rightarrow CH_3CHO + NADH + H^+$$

In this reaction a hydride ion is being transferred from ethanol to NAD^+. This enzyme is produced mainly by the liver cells and partly by the kidneys. This mechanism for ethanol metabolism is the most predominant one.

The microsomal electron transport system also participates in ethanol oxidation via catalysis by the cytochrome P_{450} isoenzymes.[23] This Microsomal Enzyme Oxidizing System (MEOS) is not present normally in liver, but may be induced by repeated ingestion of ethanol. Alcohol stimulates the proliferation of the smooth endoplasmic reticulum of the liver cells, enhancing the capacity of the microsomal enzyme oxidizing system that metabolizes drugs and alcohol. MEOS is included in the mixed function oxidase system that is also induced by many drugs. The system is dependent on NADPH and cytochrome P_{450} and catalyses the direct utilization of molecular oxygen without formation of ATP. The enzymes in this family vary in their capacity to oxidize ethanol, including the 2E1, 1A2 and 3A4 isoforms.[24] They catalyze the following reaction sequence:

$$CH_3CH_2OH + NADPH + H^+ + O_2 \rightarrow CH_3CHO + NADP^+ + 2H_2O$$

One H_2O is derived from the reducing equivalents of $NADPH + H^+$ and the other from the reducing equivalents transferred from ethanol. The cytochrome P_{450} isozymes in the liver, which are active in ethanol oxidation, have Km values of about 10-15 mM that translates to tissue levels of ethanol in the range of ~50-75 mg%. Ethanol at hepatic levels below these concentrations is metabolized mostly by alcohol dehydrogenase. An important consideration with the microsomal electron transport system is that the cytochrome P_{450} 2E1 isoform is induced to higher tissue concentrations as a result of chronic ethanol consumption and becomes more important quantitatively in ethanol oxidation in the alcohol abuser. In addition to the mitochondrion, the 2E1 isoenzyme may also be a significant catalyst for formation of ROS in the alcohol consumer, as it has been demonstrated to generate higher amounts of H_2O_2 in the presence or absence of oxidizable cosubstrate.[25] Its elevation in the livers of ethanol consumers has also been linked to increased generation of hydroxyl radicals.[26] Ethanol enhances the activity of cytochrome P_{450}2E1 (Cyp2E1) probably by stimulating the translation of Cyp2E1 mRNA.

Peroxisomal activity also contributes to ethanol oxidation in the liver, as is seen in the following reactions:

$$RCH_2CH_2COSCoA + O_2 \xrightarrow{\text{AcylCoA oxidase}} RCH = CHCOSCoA + H_2O_2$$

$$CH_3CH_2OH + H_2O_2 \xrightarrow{\text{Catalase}} CH_3CHO + 2H_2O$$

In heavy ethanol consumers where there is usually an elevation in fatty acids in the liver, it is possible that this mechanism might be more prominent due to increased peroxisomal

oxidation of fatty acids. Ethanol oxidation gives rise to acetaldehyde, which is further oxidized by hepatic aldehyde dehydrogenase that is quite efficient in keeping acetaldehyde levels low.

$$CH_3CHO + NAD^+ \rightarrow CH_3COOH + NADH + H^+$$

The mitochondrial form of aldehyde dehydrogenase plays a prominent role in maintaining low concentrations of acetaldehyde. The acetate is then activated by acetyl CoA synthase to acetyl CoA. Chronic alcohol consumption results in a decreased rate of acetaldehyde oxidation in intact mitochondria.

As a result of oxidation of ethanol by alcohol dehydrogenase and subsequent oxidation of acetaldehyde there is a significant increase in the hepatic NADH + H^+ /NAD^+ ratio. This shift occurs both in the cytoplasm and the mitochondrion, as measured by the lactate/pyruvate and β-hydroxybutyrate/acetoaetate ratios, respectively. Acetaldehyde levels in the liver after ethanol administration are only 100–350 μM, and this has led to the conclusion that mitochondrial NAD^+ dependent acetaldehyde dehydrogenase (apparent K_m for acetaldehyde is about 10 μM/L) is the main pathway for acetaldehyde oxidation. The mitochondrial, low Km aldehyde dehydrogenase generates much of the NADH within the mitochondria, and the reducing equivalents of the cytoplasmic NADH are transported into the mitochondrion primarily via the malate-aspartate shuttle that is predominant in the liver. The increased level of NADH occurring as a result of ethanol oxidation is readily reoxidized by the mitochondrial electron transport system if the tissue is not anaerobic. Thus, ethanol oxidation increases the availability of oxidizable NADH to the mitochondrion. During oxidation of ethanol, NADH is generated, which in turn affects the metabolism of lipids, carbohydrates, proteins, and purines.

About 90% of the acetaldehyde formed from alcohol is oxidized in the liver. Alcohol is hepatotoxic not only because of secondary malnutrition, but also through metabolic disturbances associated with oxidation of ethanol. Ethanol metabolism produces two types of adducts, *viz.*, acetaldehyde derived adducts and α-hydroxyl ethyl radical derived adducts. Both are shown to be immunogenic and antibodies are produced against these adducts.[27] Alcohol dehydrogenase (ADH) is also involved in the reversible oxidation of vitamin A or retinol to retinal for retinoic acid synthesis. Retinoic acid is a potent transcriptional regulator and a morphogen. It is assumed that the competition of consumed ethanol with retinol for oxidation by ADH might explain developmental disorders seen with fetal alcohol syndrome.[28]

Immunomodulator activity

Ingestion of ethanol has been shown to be associated with immunodeficiency.[29] Researchers have shown that alcohol administration is directly related to immunosuppression. Alcohol intake increases the susceptibility of the individual to different types of infections. Both humoral and cell mediated immunity have been shown to be suppressed in chronic alcoholics.[30] Ethanol reduces the number of lymphocytes, as well as phagocytosis by macrophages.[31,32] It can suppress the host defence mechanisms to bacterial infections and inhibit neutrophil function. Ethanol modifies the specificity of antibody functions against a defined epitope, probably due to changes of the conformation of the antibodies, and this effect is concentration dependent.[33] Ethanol administration impairs cell-mediated immune response, probably by inhibiting early events in T-lymphocyte activation.

Ethanol is also involved in impairment of IgM synthesis and secretion by plasma cells especially in the mesenteric lymph node.[34] It further suppresses the synthesis of IL-1, 2 & 4 in the spleen, probably by inhibiting translation of mRNA for the cytokines.[35]

Lipid metabolism

Levels of free fatty acids and fatty acid ethyl esters are elevated in ethanol-treated rats' liver, kidney, brain, and heart. These are probably the possible mediators in the production of alcohol dependent syndromes.[36] These esters were found to be toxic to the cells.[37] Fatty acid ethyl esters are non-oxidative products of ethanol metabolism and have been implicated as mediators of cholesterol induced organ damage.[38] Fatty acid ethyl esters bind with lipoproteins and albumin in human plasma and are carried to the different parts of the body, and induce organ damage. Ethanol administration to pregnant rats during gestation period leads to significant accumulation of saturated fatty acids and ethyl esters of long chain fatty acids in both maternal and fetal organs. Maternal ethanol consumption during pregnancy leads to decrease of decosahexaenoic acid content in fetal brain, and phosphatidyl choline and phosphatidyl ethanolamine content in the liver due to reduction of polyunsaturated fatty acids levels.[39]

Ethanol is associated with increased levels of triglycerides and HDL cholesterol. Ethanol ingestion leads to severe alteration of cholesterol metabolism, resulting in both elevated serum cholesterol and hepatic cholesterol ester levels. It causes alteration of the plasma membrane cholesterol domains that alter transbilayer fluidity gradients in plasma membrane, and are associated with decreased Ca^{2+}, Na^{+}, K^{+}-ATPase activities.[40] Probably there is decreased expression of LDL receptors' gene and HMG-CoA reductase gene as evidenced by decreased amount of LDL mRNA content, and high HMG-CoA reductase mRNA in hepatocytes. Alcohol induces defective lipoprotein metabolism. The accumulation of VLDL and LDL in blood of ethanol-ingested individuals is due to reduced expression of LDL-receptors. Ethanol provoked a change in apolipotrotein β conformation that was observed by electronic spin resonance.[41] Chronic ethanol exposure affected the deacylation and reacylation of membrane phospholipids.[42] The increase of LDL level is probably the main risk factor in the formation of atherosclerosis, and oxidation of LDL to ox-LDL increased atherogenicity. This ox-LDL that is produced due to ethanol oxidation, induced smooth muscle proliferation through the activation of phospholipase D.[43]

Lipid peroxidation

Ethanol consumption is associated with increased hepatic lipid peroxide content. This plays some important roles in the pathogenesis of alcohol related diseases.[44] Increased production of oxygen radicals due to ethanol may promote lipid peroxidation that induces tissue injury. Lipid peroxidation mediated by free radicals is considered to be the primary mechanism of cell membrane destruction and cell damage.[45] Involvement of reactive oxygen species and lipid peroxidation products can be clearly demonstrated in fundamental events of hepatic fibrogenesis like activation and effects of stellate cells, as well as expression of metalloproteinases and their specific inhibitors.[46] Lipid peroxidation and low molecular weight iron augmentation are linked to ethanol metabolism.

Role of Reactive Oxygen Species

Ethanol administration increases the rate of generation of reactive oxygen species in liver and brain.[47] Oxidation of ethanol by alcohol dehydrogenase produces NADH and NADH–dependent reactive oxygen species by various organelles. These free radicals have a role in the development of oxidative stress. Formation of superoxides probably plays a key role in the development of alcohol-induced pathogenesis.[48]

Oxidative stress is well recognized to be a key step in the pathogenesis of ethanol-associated liver injury.[49] The metabolic effects of alcohol are due both to its direct action and to that of its first metabolite acetaldehyde, and can also be connected to the changes in redox state. Differences in ethanol distribution, bioavailability, and hepatic metabolism can provide insights

into the protective and predisposing factors in alcoholism, as well as gender differences of alcohol toxicity.[50]

The major energy-generating structures within cells (i.e., mitochondria) may be especially sensitive to oxidative stress, resulting in diminished energy production. Under normal circumstances the mitochondrion contributes a significant proportion of the reactive oxygen species in the hepatocyte. In the chronic ethanol consumer, the levels can be expected to be elevated, not only due to alterations in the mitochondrial electron transport chain related to chronic ethanol consumption, but also as a consequence of decreased concentrations of mitochondrial antioxidants in the ethanol consumer.[51] Active oxidants generated during ethanol metabolism produce mitochondrial membrane permeability transition. In addition, acetaldehyde, and ethanol consumption-associated endotoxemia with subsequent release of inflammatory mediators may cause hepatocyte injury via both oxyradical-dependent and oxyradical-independent mechanisms. These cytotoxic processes may lead to lethal hepatocyte injury.

Ethanol-inducible cytochrome P_{450} and catalase may also be involved in the generation of free radicals. Ethanol itself can be transformed into a free radical [hydroxyethyl radical] following interaction with hydroxyl radical. Accumulation of nitric oxide may be another source of free radical formation. Alcohol can stimulate the excess formation of nitric oxide through calcium-calmodulin mediated induction of nitric oxide synthase. Nitric oxide can combine with superoxide radical to form peroxynitrite. Decomposition of peroxynitrite leads to the formation of more reactive hydroxyl and nitroxide free radicals. Oxidative stress may also occur following acidosis and hypoglycemia, which can occur after ethanol administration. An increase in low molecular weight iron and its putative links to ethanol metabolism may contribute to the generation of radicals.[52]

Effects of vitamins

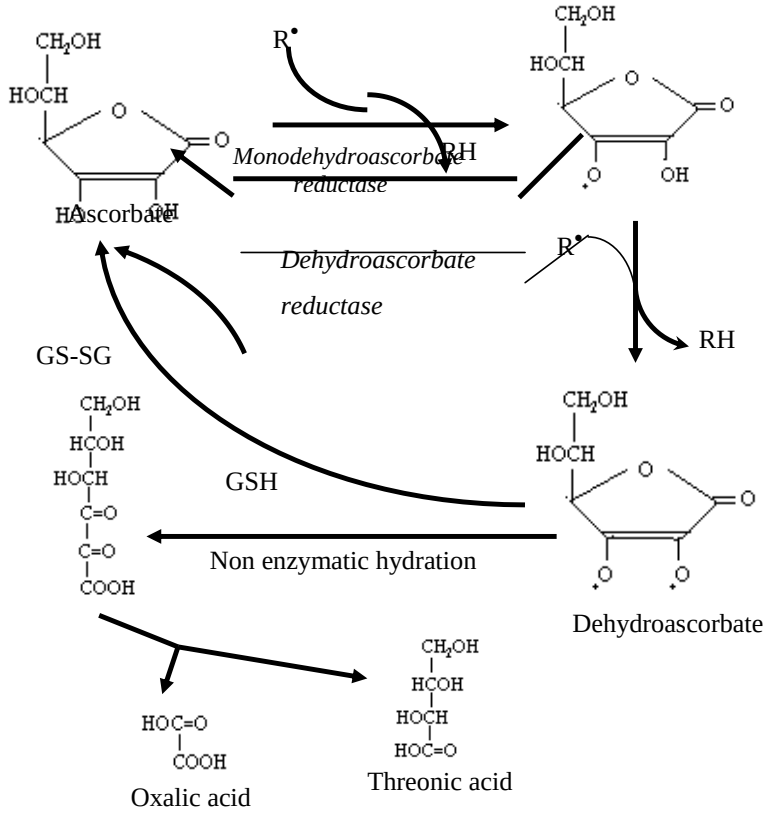
Cells are protected against oxidation by the action of certain enzymes, vitamins, and other substances, known collectively as antioxidants. Ethanol-mediated oxidative stress is mitigated when pregnant rats are treated with folic acid, concomitant to ethanol administration. The antioxidant capacity of folic acid seems to be involved in its protective effect.[53] Chronic ethanol feeding enhanced hepatic consumption of vitamin E in ethanol-treated animals, irrespective of the vitamin E level of the basal diet; and the effect was observed in both the microsomal and mitochondrial fractions.[54] Ethanol-induced stress can be partly prevented by vitamin E supplementation. Pharmacological antioxidants could have beneficial effects in reducing the incidence of ethanol-induced changes in cellular lipids, proteins, and nucleic acids. The antioxidants could act by reducing free radical production (e.g. chelators of redox-active iron derivatives), trapping free radicals themselves, interrupting the peroxidation process, or reinforcing the natural antioxidant defence. Vitamin A supplementation attenuates the changes in lipid peroxidation, glutathione, and testicular morphology.[55] Supplementation of ascorbic acid along with alcohol reduced the lipid peroxidation products in the liver and enhanced the activities of scavenging enzymes.[56]

Ascorbate can act as a radical trapping antioxidant reacting with superoxide and the two protons to yield H_2O_2, or with the hydroxy radical and a proton to yield H_2O. The ascorbate in the first case oxidizes to dehydroascorbate radical, and in the second case to monodehydroascorbate radical.

$$O_2^- + \text{Vit C} + 2H^+ \longrightarrow \text{Vit C} + H_2O_2$$

$$OH^\bullet + \text{Vit C} + H^+ \longrightarrow H_2O + \text{Vit C}^\bullet$$

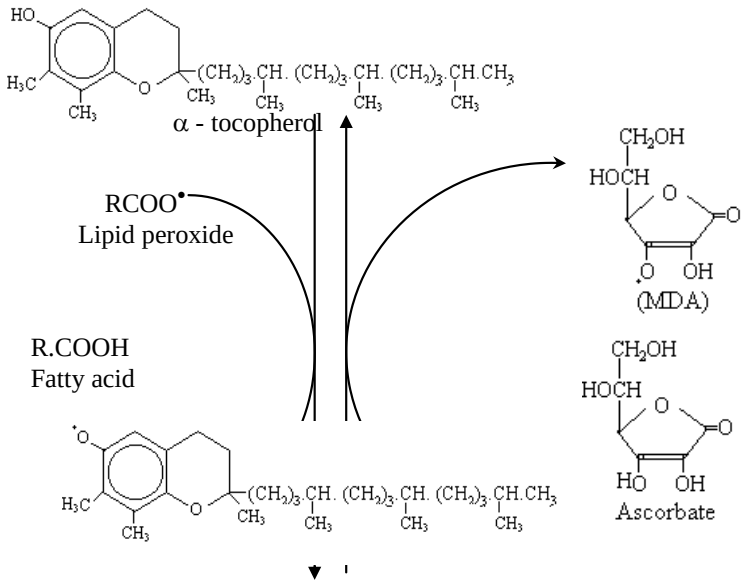
The cytotoxicity of acetaldehyde was shown to be reduced if vitamin C is applied prior to the ethanol ingestion.[57]



One of the major roles of vitamin E as an antioxidant is the trapping of radicals at membrane surfaces. α-tocopherol reacts with lipid peroxides and free radicals, donates its phenolic hydrogen to reduce the lipid peroxide and free radicals, and itself is oxidized to α-tocopheroxyl radical, the quinone form. This quinone then reacts with ascorbate in the aqueous phase, regenerating α-tocopherol, and forming monodehydro ascorbate radical, which reacts to yield ascorbate and dehydroascorbate. The dehydroascorbate can be degraded non-enzymatically to diketogluconate. Vitamin C may then have a vitamin E-sparing antioxidant action, coupling lipophilic and hydrophilic reactions.[58]

α-tocopherol resides close to the polyunsaturated fatty acid tail of membrane phospholipids, and near the membrane enzymes like NADPH-dependent mixed function oxidase, which form free radicals. The isoprenoid side chain of α-tocopherol remains bound hydrophobically to the nonpolar tail of membrane phospholipid. The chromane ring of tocopherol is oriented towards the polar head group of membrane phospholipids near the water-adjoining surface of lipid layer. Tocopherols can prevent peroxidation of fatty acids by reducing

free radicals, and preserve the structural and functional integrities of membrane bound organelles. In the absence of ascorbate, physiological concentrations of α-tocopherol have less radical-scavenging activity. However, the tocopheroxyl radical can be reduced to tocopherol by reaction with glutathione, catalysed by a membrane specific isozyme of hydroperoxide glutathione peroxidase, which is a selenoenzyme.



Conclusions

Although many factors related to the pathogenesis of alcoholic liver disease have been considered, hepatotoxic effects of ethanol and its metabolites, effects of excessive hepatic NADH generation, oxidative stress, hypoxia, alterations of the immune system, genetic factors, and nutritional factors may play more important roles to produce alcohol dependent diseases, than the others. Genetic polymorphism of key enzymes related to metabolism of ethanol and acetaldehyde, alcohol dehydrogenase, cytochrome P_{450}2E1 (CYP2E1) and aldehyde dehydrogenase have recently been elucidated.[59] Increased oxidative stress has been put forward as one possible mechanism behind alcohol-related tissue damage.[60] Unlike many selective pharmacological agents, ethanol clearly has several major loci of action. One deleterious factor in ethanol metabolism is the potential for generation of excess amounts of free radicals. The extent to which this activity accounts for the overall toxicity of ethanol is unknown. Acetaldehyde catabolism also has the likelihood of contributing to ethanol-related oxidative stress. In the final analysis, abstinence from alcohol and intake of proper nutrition are the only guaranteed preventive approaches for alcoholic liver diseases.

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