Indian Journal of Clinical Biochemistry, 2008 / 23 (1) 4-9

REVIEW ARTICLE

ALCOHOL INDUCED EFFECTS ON KIDNEY

Subir Kumar Das and D M Vasudevan

Department of Biochemistry, Amrita Institute of Medical Sciences, Elamakkara P.O., Cochin 682026, Kerala

ABSTRACT

After administration ethanol and its metabolites go through kidneys and are excreted into urine, and its content in the urine is higher than that of the blood and the liver. Chronic ethanol administration decreases the renal tubular reabsorption and reduces renal function. Multiple functional abnormalities of renal tubules may be associated with ethanol-induced changes in membrane composition and lipid peroxidation. The vulnerability of the kidney to oxidative damage has been partly attributed to its high content of long-chain polyunsaturated fatty acids. Renal ultra structural abnormalities due to ethanol exposure may be important in the genesis of functional disturbances. Increased oxidative stress and endothelial dysfunction with their complex interrelationships are relevant aspects of atherogenesis in chronic renal failure. Antioxidants, particularly polyphenols are expected to decrease the vulnerability of the kidney to oxidative challenges.

KEY WORDS

Alcohol, Electrolyte, Kidney, Oxidative stress, Renal function,

The kidney is an important organ having not only excreting function but also other functions such as production of the substances that activates a living body, enzymatic reaction, immunization etc. After ethanol administration, ethanol and its metabolites go through kidneys and are excreted into urine, and its content in the urine is higher than that of the blood and the liver. The kidney is often involved in the development, maintenance and counter regulation of complex electrolyte disturbances like phosphate and potassium hypoglycemia etc. (1). Some studies suggest that chronic ethanol ingestion per se is not nephrotoxic (2). The kidney seems to be the only vital organ generally spared in chronic alcoholics without advanced alcoholic liver disease or hepato-renal syndrome. But, regular alcohol consumption raises the blood pressure, which per se is a risk factor for renal damage (1). Large amounts of ethanol have deleterious effects on the kidney. Structural and functional abnormalities of the kidney are reported with increasing frequency in the fetal alcohol syndrome seen in children who have been prenatally exposed to ethanol (3).

Address for Correspondence :

Dr. Subir Kumar Das
Department of Biochemistry
Amrita Institute of Medical Sciences
Elamakkara P.O., Cochin, Kerala
E-mail : drsubirkdas@yahoo.co.in

Alcohol-fed animals were found to have significantly reduced renal function, interstitial edema and renal hypertrophy, characterized by significantly increased absolute amounts of protein, fat and water (4). Lactate dehydrogenase, succinate dehydrogenase, aspartate aminotransferase, glutamate dehydrogenase, AMP deaminase, ornithine transcarbamylase, arginase and glutamine synthetase activities were increased in the kidney of the rat during repeated ethanol loading (5).

Folate and other vitamins

Decreased plasma levels and increased urinary levels of folate due to chronic ethanol consumption may contribute to the development of folate deficiency. The folate binding protein, which is located in the brush border membrane (BBM) of proximal tubule cells, is thought to be involved in renal folate reabsorption. Ethanol probably affects in the renal uptake and metabolism of folate (6). Folic acid transport across the epithelial cell membrane of kidney tubules is an essential step for its reabsorption, conservation and homeostasis in the body. Chronic ethanol administration decreases the renal tubular reabsorption (7). Importantly, ethanol feeding interferes with

disulfide bond status, temperature sensitivity and Na^+ and divalent cation dependency of the transport process. The transport is transmembrane pH dependent, and ethanol does not have any effect on the pH optimum of the folate transport. The reduction in uptake in the ethanol-fed group is more pronounced at pH less than 6. However, the binding component was found to contribute an appreciable extent to the total folate uptake (7). Ethanol exerts its effect on the renal brush-border membrane by causing a structural change in the phospholipid bilayer, which activates sodium intake (8).

Ethanol directly impairs the renal conservation of 5-CH_3-H_4PteGlu (9) and decrease thiamine accumulation in the kidney by inhibiting phosphorylation of thiamine to thiamine phosphate (10).

Electrolytes

Acute ethanol administration in rats alters renal sodium and potassium excretion (11). Chronic alcoholic patients may experience low blood concentrations of key electrolytes as well as potentially severe alterations in the body's acid-base balance (12). In addition, alcohol can disrupt the hormonal control mechanisms that govern kidney function. By promoting liver disease, chronic drinking causes further detrimental effects on the kidneys including impaired sodium and fluid handling and even acute kidney failure (12).

The long-term effect of chronic alcohol over consumption is water and salt retention with expansion of extracellular volume. Depletion of magnesium, phosphate and calcium is also frequently found in alcohol-dependent patients. These electrolyte disturbances may be associated with the alcohol-induced hypoparathyroidism and parathyroid hormone resistance of the skeletal muscle as well as with the decrease of serum osteocalcin. Metabolic acidosis with lower arterial blood pH and plasma bicarbonate concentration was revealed in alcoholic patients. A significant correlation between chronic alcohol over consumption and increased incidence of hyperuricemia and gout attack was also reported. Alcohol seems to have dual effects on the blood pressure. Increased blood pressure was demonstrated in men above 80 g and in women above 40 g ethanol consumption daily. In contrast, young adults consuming only 10 to 20 g per day had lower blood pressure indicating a J-curve relationship. This is in line with the lowered risk for coronary heart disease associated with regular consumption of small alcohol amounts. Severe alcohol abuse predisposes to acute renal failure and seems to be associated with the general catabolic effects (13).

Tubular dysfunction has an important pathophysiological role in a wide range of electrolytes and acid-base disturbances commonly observed in these patients. These renal abnormalities are often reversible, disappearing with abstinence (3). Due to its high permeability, alcohol concentration in the tubular fluid approaches that of peritubular fluid and under steady state conditions alcohol concentration in the final urine is almost the same as in serum water (14).

Alcohol dehydrogenase

It seems that renal tissue is almost free from alcohol dehydrogenase. Thus, acetaldehyde, the cytotoxic intermediate of alcohol metabolism, should not accumulate in effective doses. If applied directly in micropuncture experiments alcohol is without distinct effect while acetaldehyde inhibits the main parameters of cellular vitality as measured by electrical membrane potential and intracellular ion activities (14). However, when mature rats were fed 20% ethanol for 10 weeks, an increase in alcohol dehydrogenase and catalase activities were observed in the kidney (15).

ATPases

Multiple functional abnormalities of renal tubules may be associated with ethanol-induced changes in membrane composition and lipid peroxidation of epithelial cells. Ethanol interferes with the carrier function by decreasing Na^+K^+-ATPase activity, but this activity is enhanced by chronic exposure (16). In another study, when adult rats were fed 20% ethanol for 10 weeks, renal Na^+K^+-ATPase activity increased but the sensitivity of the enzyme to ethanol inhibition *in vitro* was not altered (17). The kinetic parameters of Mg^{2+}-ATPase were not affected under the same conditions. The rise in renal Na^+ K^+-ATPase activity was consistent with the renal sodium retention found in ethanol-fed rats (18). The mechanism of ethanol-induced enhancement of renal Na^+ K^+-ATPase activity could be explained through an increase in the number of catalytic units (19). Ethanol affects the selectivity of the Na^+ K^+-ATPase for Na^+ and/or for K^+, enhancing the Na^+ affinity for the K^+ sites and/ or reducing the K^+ affinity for its own sites (20). The Na^+ and the Na^+ K^+-ATPase activities of basolateral plasma membrane from rat kidney proximal tubular cells are affected differentially by ethanol (21).

Growth factors and steroidal activity

The insulin-like growth factor (IGF) is the major growth factor related to alcohol consumption. Alcohol reduced the level of IGF-I in a dose-dependent manner in the serum, liver and

kidney, while increased the level of IGF-II in the serum and kidney. Alcohol decreased IGF-I receptor mRNA in the liver and kidney, and increased serum levels of IGF-binding proteins (IGFBP)-1. However, alcohol had no effect on serum levels of IGFBP-2, -3 and -4. These effects were also observed in the kidney. These may contribute to the metabolic dysfunction following chronic alcohol consumption (22).

Ethanol consumption showed a decrease in renal 11- beta-hydroxysteroid dehydrogenase activity and plasma aldosterone level, while increase in plasma corticosterone level (23).

Fatty acid metabolism and cytochrome P 450

Long-term ethanol consumption is associated with modifications of fatty acid metabolism. One and two month ethanol treatment led to a 3 to 4 fold rise of the cytochrome P 450 (CYP) 2E1 protein in kidney microsomes. Ethanol intake does not act on the kidney microsome capability to hydroxylate unsaturated fatty acids. CYP2E1 is strongly inducible by ethanol and therefore accounts for the tolerance of this hepatotoxicant (24). While in one study ethanol appeared to induce CYP2E1 in the kidney (25), others did not find any change in renal cytochrome P450 after chronic ethanol consumption (26).

Ethanol may mildly perturb the redox state of isolated kidney tubules without inhibiting glucose synthesis, and that ethanol and oleate interact to inhibit renal gluconeogenesis by a mechanism highly dependent on the fatty acid concentration (27). Renal microsomal and peroxisomal oxidation of fatty acids increased due to chronic ethanol treatment and results in an increased extramitochondrial disposition of fatty acids and ethanol oxidation by the kidney (15). Chronic but not acute ethanol treatment leads to depletion of the renal stores of prostaglandin precursors in the rat (28). It decreased arachidonic and docosahexaenoic acids in the kidney lipids (29). However, the water diuresis produced by acute ethanol administration is not mediated by enhanced renal PGE2 production (30).

Increasing evidence suggests that fatty acid ethyl esters (FAEE) play a central role in ethanol induced organ damage. Ethanol treatment caused a significant increase in the levels of FAEE, particularly in the brain and heart but also in the kidney and liver. Increase in FAEE were associated with a significant increase in FAEE synthase activity (31).

Reactive Oxygen Species (ROS)

Over the last decade, oxidative stress has been implicated in the pathogenesis of a wide variety of seemingly unrelated renal diseases. The kidney is an organ highly vulnerable to damage caused by reactive oxygen species (ROS), likely due to the abundance of long-chain polyunsaturated fatty acids in the composition of renal lipids. ROS are involved in the pathogenic mechanism of conditions such as glomerulosclerosis and tubulointerstitial fibrosis (32).

Chronic alcohol administration led to a significant increase in the level of protein oxidation in the kidney of rats (33). There was a rapid fall in non-proteinic free sulfhydryl (NPFSH) content in the kidney, followed by constantly reduced levels during ethanol intoxication (34). Glutathione transferase activity (31), manganese-superoxide dismutase activity (35) and lipid hydroperoxide levels (31) were also increased. Increased reactive oxygen species, partly generated from acetaldehyde oxidation, may also contribute to the occurrence of oxidative stress and nephrotoxic effects of ethanol ingestion (16).

Ultrastructure

Rats prenatally exposed to ethanol have renal ultrastructural abnormalities that may be important in the genesis of functional disturbances (36). More cases of appearances of basophilic renal tubular, swelling of tubular epithelial cells, urinary casts in tubular lumens, PAS (periodic acid-Schiff staining) positive deposits in glomerulus and atrophy of glomerulus were observed (37).

In one study the rats that were orally administrated with ethanol (4 g/kg bw/ day) for a week, swelling of glomerula and tubules, proliferation of mesangial cells, and hyaline drop in tubular epithelial cells were seen in the kidney (38). In another study one month ethanol (4 g/kg b.w./day) exposure showed swelling of glomerulus, thickening of basement membrane of glomerulus, PAS positive deposits in glomerulus, proliferation of mesangial cell, proliferation of juxtaglomenular cell, dilation of tubular lumen, swelling of tubular epithelial cell, its falling, hyaline droplet in tubular epithelial cell, cell infiltration to interstitial tissue, and basophilic tubule in the kidney. Changes in indices related to renal function were also observed (39).

Ethanol metabolites-protein adducts and hyaline in tubular epithelial cells in the kidney were observed after two-month ethanol administration. However, under long administration of six and eleven months, kidney showed atrophy of tubular

epithelial cells, urinary casts, and cell infiltration to interstitial tissue. In addition thickening of basement membrane of glomerulus, PAS positive deposits in glomerulus, and proliferation of mesangial cell were observed in the kidney (38).

Other effects

Atherosclerosis development is accelerated in chronic renal failure (CRF) and is the major cause of death in chronic alcoholism. An increased oxidative stress and an endothelial dysfunction, with their complex interrelationships are relevant aspects of atherogenesis in CRF patients and might be targets for treatment (40).

Role of antioxidants in alcohol

Reactive oxygen species (ROS) play a key role in the pathophysiological processes of a wide range of renal diseases. Many studies have underlined the cardiovascular protection provided by moderate wine consumption. Thus, antioxidants are expected to decrease the vulnerability of the kidney to oxidative challenges. Polyphenols, particularly abundant in red wine could act as ROS scavengers, iron chelators and enzyme modulators. This beneficial effect is due to both alcohol and nonalcoholic components of wine including several phenolic molecules such as quercetin and resveratrol. Wine polyphenols have antioxidant properties and favorably influence endothelial function, in particular by stimulating nitric oxide-mediated vasodilation and inhibiting the endothelin-1 pathway (40). Although phenol concentration of red wine does not influence the activity of antioxidant enzymes of the kidney, amelioration of myoglobinuric renal damage was found in rats following chronic exposure to flavonol-rich red wine (41). Wine polyphenols could reinforce the endogenous antioxidant system thereby diminishing oxidative damage. The antioxidant capacity of wine *in vitro* implicates a homologous effect *in vivo*, thus helping to modulate tissue lipid peroxidation (42).

Ethanol decreases the content of long-chain PUFA, whereas red wine maintain the levels of arachidonic (20:4n-6) and eicosapentaenoic (20:5n-3) acids and alcohol-free red wine increase the levels of 20:4n-6. Lipid peroxidation in the red wine and alcohol-free red wine groups was reduced. The diminished renal lipid peroxidation was associated with an increased antioxidant capacity of plasma. These suggest that moderate red wine consumption could contribute to the preservation of the contents of n-3 and n-6 PUFA, particularly 20:4n-6, in rat kidney (43). Red wine diminished the malondialdehyde (MDA) production and elevated the GSH/GSSG ratio and the activities of catalase and glutathione peroxidase (44). Red wine administration attenuates the ethanol-induced enhancement of microsomal activities dependent on CYP 2E1 of rat kidney (43, 45). The non-alcoholic, mainly polyphenols constituents of red wine could account for this modulation (43, 45, 46).

CONCLUSION

Because of the kidneys' important and varied role in the body, impairment of their function can result in a range of disorders, from mild variations in fluid balance to acute kidney failure and death. Alcohol, one of the numerous factors that can compromise kidney function can interfere with kidney function through acute or chronic consumption or indirectly as a consequence of liver disease.

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