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World J Gastroenterol 2006 December 14; 12(46): 7421-7427
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

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Pathophysiology of alcoholic pancreatitis: An overview

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Received: 2006-07-29 Accepted: 2006-08-22

Abstract

Use of alcohol is a worldwide habit regardless of socio-economic background. Heavy alcohol consumption is a potential risk factor for induction of pancreatitis. The current review cites the updated literature on the alcohol metabolism, its effects on gastrointestinal and pancreatic function and in causing pancreatic injury, genetic predisposition of alcohol induced pancreatitis. Reports describing prospective mechanisms of action of alcohol activating the signal transduction pathways, induction of oxidative stress parameters through the development of animal models are being presented.

Key words: Alcohol; Metabolism; Pancreatic function; Pancreatitis; Mechanism of action

Chowdhury P, Gupta P. Pathophysiology of alcoholic pancreatitis: An overview. *World J Gastroenterol* 2006; 12(46): 7421-7427

http://www.wjgnet.com/1007-9327/12/7421.asp

INTRODUCTION

Alcohol abuse and dependence are the major cause of morbidity and mortality in the United States. About three-fourths of individuals of 18-26 years of age and two-thirds of those 26 and older are current drinkers. The age related pattern for concurrent alcohol and tobacco dependence was similar to that found for tobacco dependence[1,2]. In a recent survey it was found that approximately 17.6 million adult Americans abuse alcohol or is alcoholic. Alcohol related problems cost society approximately $185 billion per year. In a study conducted at the population level, mortality from pancreatitis due to alcohol addiction was reported[3]. The mechanism of induction of alcoholic pancreatitis is not well understood.

Pancreatitis due to alcohol abuse is a very painful and potentially fatal condition. About one-third of acute pancreatitis cases in the United States are alcohol induced and 60%-90% of pancreatitis patients have a history of chronic alcohol consumption. It is estimated that drinking more than 80 gm of alcohol/d or about 10-11 standard U.S. drinks for a minimum of 6-12 years is required to produce symptomatic pancreatitis[4]. The risk of developing the disease increases with both amount and duration of alcohol consumption. Only 5% of clinically documented alcoholics develop disease but at autopsy only 5%-10% of alcoholics are found to have evidence of chronic pancreatitis[5-7]. Chronic pancreatitis is mostly caused by heavy alcohol consumption and is characterized by onset of symptoms in the 4th or 5th decade[8]. Due to this discrepancy in data of alcoholic and diseased patients, it is thought that other factors like environmental, genetic, race and concomitant risk factors are also involved.

Cigarette smoking might have an additive effect with alcohol in inducing pancreatitis. In the rat model of alcohol-induced pancreatitis, ethanol induces pancreatic ischemia while cigarette smoke potentiates the impairment of pancreatic capillary perfusion caused by ethanol[9]. Cigarette smoking accelerates progression of alcoholic chronic pancreatitis[10,11]. A dietary component may also interact and modify effects of alcohol on the pancreas. A protein and fat rich diet along with continued consumption of alcohol exacerbate the course of chronic pancreatitis[12,13]. African Americans are affected more than Caucasians and this could be due to differences in diet, type or quantity of alcohol consumption[14]. It can be due to differences in metabolism of alcohol in liver and pancreas. Alcohol consumption at intoxicating concentrations induces pancreatic cellular injury that may involve class Ⅲ isoenzymes of ADH[15].

ALCOHOL METABOLISM

It is well known that alcohol is metabolized *via* an oxidative and a non-oxidative pathway in the liver. Various studies have been conducted to demonstrate alcohol metabolism in isolated pancreatic acini and cultured acinar cells. Haber *et al*[15] have studied oxidative metabolism of alcohol using cultured pancreatic cells. His findings corroborate a study reported by Gukovskaya *et al*[16], conduced with isolated pancreatic acini. In the cytosol of acini, ethanol is oxidized to acetaldehyde by alcohol dehydrogenase. At physiological

blood alcohol concentrations, cytochrome P-450 accounts for approximately 20% of ethanol metabolism[17,18]. The presence of cytochrome P-450 CYP2E1 has been demonstrated in rat pancreas[19] as well as human pancreas[20]. Chronic use of alcohol has been shown to induce the expression of CYP2E1 in rat pancreas[19] similar to that in liver[21].

The non-oxidative pathway of ethanol metabolism involves the formation of FAEE using FAEE synthase[22]. Gukovskaya *et al*[16] have confirmed the presence of FAEE synthase activity in pancreas that may explain the accumulation of FAEE in pancreas after ethanol exposure. Werner *et al*[23,24] studied correlation between oxidative and non-oxidative pathways of ethanol metabolism in the pancreas. Their studies show that ethanol causes a dose-dependent injury to pancreas due to a shift to non-oxidative metabolism following inhibition of the oxidative pathway. This results in an increase of FAEE. Carboxyl ester lipase (CEL) has been known to catalyze FAEE synthesis from fatty acids and ethanol. CEL gene polymorphism, especially an increase in the frequency of the L-allele, was found to be associated with alcohol induced pancreatitits[25]. The aspect that inhibition of the oxidative pathway can cause an increase in flux of ethanol metabolism *via* the non-oxidative pathway needs to be clarified further.

GENETIC PREDISPOSITION OF ACUTE AND CHRONIC PANCREATITIS: ROLE OF ALCOHOL

In alcoholic pancreatitis, mutations of the cationic trypsinogen gene and of pancreatic secretory trypsin inhibitor (SPINK-1) have been implicated in its pathogenesis[26]. The discovery of genetic cause of hereditary pancreatitis has renewed interest in genetic predisposition to alcoholic pancreatitis. Various gene mutations like cationic trypsinogen (especially at codon 29 and 1220), SPINK1 mutation, and CFTR gene mutation are associated with development of chronic pancreatitis[27]. In idiopathic pancreatitis, both variants of SPINK1 (N 291 and R 122H) and CFTR were identified. Alteration of both genes was found in patients with alcoholic chronic pancreatitis and the increase of those genes is related to higher levels of alcohol consumption[27]. The SPINK1 inhibits the autoactivation of premature trypsinogen within the pancreas[28]. The most frequent mutation in the SPINK1 gene was the N34S mutation in Exon-3. Kuwata *et al*[29] detected intronic polymorphism in the SPINK1 gene in 4 alcoholic patients but found no differences when the data were compared with other patients. Similar findings have been reported in five other alcoholic chronic pancreatitis patients with an N34S mutation[30]. Truninger *et al*[31] and Monaghan *et al*[32] screened 58 and 46 alcoholic pancreatitis patients respectively for cationic trypsinogen gene mutation activation but no mutations have been found.

Alcohol metabolizing enzymes such as aldehyde dehydrogenase (ADH), metabolizing alcohol to acetaldehyde, exist as different isoenzymes. ADH polymorphism has been identified in ADH-2 and ADH-3[33]. Increased prevalence of ADH-1 isoenzyme in patients with alcoholic pancreatitis has been reported[34]. With regard to ADH-2 isoenzyme, results are not conclusive and further studies need to be done. Kimura *et al*[35] and Frenzer *et al*[36] found no correlation between ADH-2 polymorphism and chronic pancreatitis in Japanese and Austrian patients respectively while Maruyama *et al*[37] demonstrated elevated risk for chronic alcoholic pancreatitis for different genotypes of ADH-2. Cytochrome P-450 is involved in metabolizing alcohol in endoplasmic reticulum. Several studies have been done to evaluate the association between polymorphism of enzyme Cyto-P4502E1 (CYP2E1) and alcoholic pancreatitis with no success[36,38,39]. Verlaan *et al*[40] analyzed DNA samples from chronic pancreatitis -alcoholic, idiopathic and hereditary. They observed that the frequency of ADH-3 and CYP2E1C1C2 genotypes did not differ between chronic pancreatitis patients, alcoholic and healthy controls. But they conclude that the presence of CYP2E1 intron 6DD genotype might confer a higher risk of alcoholic chronic pancreatitis. Kim *et al*[41] compared the genotype and allele frequencies of ADH-2, ADH-3, ALDH-2, Cyto P450-2E1, IL-1, IL-6, IL-8 and TNF-alpha in patients with chronic pancreatitis and alcoholic liver cirrhosis with those from controls. No difference in frequencies of genotype and allele of enzymes and cytokines amongst three groups were found. Frequency of ADH-2 was significantly higher and those of CYP2E1 and ALDH-2 were significantly lower than control.

Polymorphism of other enzymes involved in free radical stress and acinar cell damage, such as glutathione -S-transferase (GST) family has also been investigated[42]. Bartsch *et al*[43] found a moderate increase in susceptibility of pancreatitis due to polymorphism of GSTM1 but Frenzer *et al*[36] and Scheider *et al*[44] were not able to confirm it. The enzymes GSTM1, GSTT1, GSTP1, CYP1A1 and CYP2E1 are involved in bioactivation and detoxification of a variety of xenobiotics present in smoke, alcoholic drink among others. A higher frequency of the Val/Val genotype in alcoholics and pancreatitis in comparison to alcoholics without the disease was found[45]. In the same study the investigators found an association between the occurrence of Val/Val GSTP1 genotype and chronic pancreatitis and also an association between m2/m2, CYP1A1 and alcoholic liver cirrhosis suggesting that these genotypes are genetically more prone to the development of alcoholic pancreatitis and alcoholic cirrhosis respectively.

EFFECT OF ETHANOL ON GASTROINTESTINAL AND PANCREATIC FUNCTION

Ethanol had a stimulatory effect on gastric acid secretion[46]. Singer *et al*[47] found that the effect of ethanol on gastric acid secretion is concentration dependent. Gastric instillation of 1.4% and 4.0% (v/v) of ethanol has a small stimulatory effect while higher concentrations (up to 40% v/v) have either no effect or an inhibitory one. Different studies under controlled conditions have been conducted to determine the action of pure ethanol on gastric acid secretion but results were very different from each other[48-54]. Alcohol is oxidized by ADH enzyme

present in all parts of the gut[55,56]. Ethanol has a direct toxic effect on the mucosal epithelium leading to loss of epithelium and hemorrhagic erosions in the duodenum[57,58]. In large bowel, gut flora plays an important role in ethanol metabolism[59]. Due to increased amounts of conversion of ethanol to acetaldehyde, than to further oxidize to acetate, the toxic acetaldehyde accumulates thereby damaging colonic mucosa and after being absorbed into the portal blood may contribute to liver injury. Alcohol when taken orally is known to increase mucosal perfusion[60] and also to stimulate production of secretin[61]. Both can affect pancreas microcirculation indirectly. Ethanol is also known to affect pancreatic blood flow when given intravenously[62,63] and *via* intragastric route[64]. McKim *et al*[65] investigated the effect of chronic intragastric ethanol administration which induced pancreatic hypoxia and oxidative stress *in vivo*. Pancreatic hypoxia induced by chronic alcohol appears to be secondary to increase in oxygen consumption by pancreas or to decrease in local blood supply without alteration of hemodynamic patterns. Chronic ethanol ingestion was associated with dose related inhibition of basal pancreatic protein secretion which was reversed upon alcohol withdrawal[66]. Increased susceptibility to chronic alcoholic pancreatitis may be through a hyperstimulation mechanism due to combination of neurohormonal factors. In exocrine pancreas, alcohol induces secretory alteration which varies by manner and duration of alcohol exposure. Ethanol effects on pancreatic secretion appear to be primarily caused by systemic cholinergic mechanisms of the vagus nerve[67].

ROLE OF ETHANOL METABOLISM IN PANCREATIC INJURY

Various studies have been done to understand the mechanism of ethanol induced pancreatic injury but till now the exact mechanism is not clear. Earlier it was thought that the Sphincter of Oddi spasm induced by alcohol may be one of the mechanisms responsible but due to a lack of consensus, the later proposal includes the Ductal-Plug hypothesis by Sarles and his colleagues[68]. The secretion of pancreatic juice rich in protein may "plug" the small ductules leading to acinar atrophy and fibrosis. It was not clear whether protein precipitation within pancreatic ducts precedes acinar damage. So protein plugs may be a cause or an effect of pancreatic injury. Saluja and Bhagat[69] investigated the mechanism by which alcohol may induce pancreatitis in an animal model. Ethanol administration resulted in a transient increase of pancreatic amylase output and plasma cholecystokinin (CCK) levels. This phenomenon was mediated by a trypsin-sensitive CCK-releasing factor from the duodenum. The studies suggest that ethanol-induced stimulation of pancreatic digestive enzyme secretion plays an important role in the development of pancreatic injury. Chronic ethanol exposure alone in animals inhibits apoptosis through an intrinsic pathway and the downstream apoptosis executor caspase-3 when compared with the controls[70]. Alcohol exposure accelerates pancreatic necrosis in response to endotoxin. The results from this study showed that the pancreas exposed to alcohol is more sensitive to LPS-induced damage because of increased sensitivity to necrotic cell death rather than apoptotic cell death suggesting that this mechanism may occur in acute alcoholic pancreatitis patients[70].

Due to inability to explain the pathogenesis of alcoholic pancreatitis by theories as mentioned above the focus was directed to pancreatic acinar cells. It is now believed that acinar cells are capable of metabolizing alcohol and the toxic effect may predispose the gland to injury in the presence of an appropriate triggering factor. The characteristics of pancreatic stellate cells showing the involvement of acinar cells in pancreatic fibrosis may be another possible link[71] . It is speculated that metabolites of ethanol like acetaldehyde and FAEEs have direct effects on acinar cells/or induce metabolic alterations within cells indirectly. Acetaldehyde is believed to interfere with the binding of secretagogue to their receptors[72] and thereby inhibit stimulated secretion from isolated pancreatic acini[72]. It also causes microtubule dysfunction thereby affecting exocytosis from acinar cells[73].

During oxidation of ethanol, hydrogen ions and reducing equivalents are released[74]; increase NADH, thereby leading to an imbalance between free radicals and antioxidant defense mechanism. It leads to a loss of mitochondrial glutathione and inactivation of GPx and other respiratory complexes[75]. Also, chronic ethanol ingestion upregulates CYP2E1[19] and catalase[76] for metabolism These pathways will require increased oxygen that will compete with mitochondrial electron transport system leading to localized and transient hypoxia in tissues. These transient conditions of hypoxia and re-oxygenation would further enhance ROS formation through the respiratory chain.

FAEEs, products of non-oxidative ethanol metabolism, have been shown to induce pancreatic injury *in vivo*[77] and *in vitro*[78]. FAEE undergo hydrolysis to FFA which impairs mitochondrial function by uncoupling of mitochondrial and oxidative phosphorylation[79]. Also its direct binding to the intracellular membrane leads to alteration in function and permeability of cell membrane[80]. The generation of cholestryl esters is responsible for the increase in lysosomal fragility releasing hydrolase's which act on the zymogen granule membrane and increase release of trypsin[81,82].

Impairment of blood flow to pancreas by ethanol causes hypoxia without any change in hemodynamic parameters. McCord[83] explained reoxygenation induced injury following hypoxia. Hypoxia can decrease the ability of cells to detoxify free radicals[84] and secondarily, hypoxia/reoxygenation causes more free radical formation leading to formation of α-hydroxyethyl radical and subsequent tissue damage and functional impairment. McKim *et al*[65] found 4-hydroxy nonenal protein adduct accumulation and increasing hypoxia in the pancreas following chronic intragastric alcohol administration in rats. These studies support the hypothesis that hypoxia contributes to oxidative stress caused by alcohol.

EFFECT OF ALCOHOL ON CELL SIGNALING PATHWAY

The mechanism of acute and chronic ethanol mediated

pancreatic injury is unclear in the literature. Feeding alcohol to animals could not reproduce pancreatitis, suggesting that alcohol alone is not sufficient to induce pancreatitis. It sensitizes pancreas to other risk factors, thereby injuring pancreas[85]. Studies using CCK or its analog are done to induce pancreatitis both *in vivo* and *in vitro*[86]. CCK at supra-physiological doses causes pancreatitis with increased blood levels of amylase and lipase and acute inflammatory response along with parenchymal cell damage[87-89]. Katz *et al*[90] showed that ethanol with low dose CCK-8 caused 6-fold more zymogen conversion than that caused by CCK alone**.** To evaluate a mechanism for the development of alcoholic pancreatitis, Pandol *et al*[91] fed animals intragastrically with ethanol diet followed by infusion of CCK-8. Ethanol exposure in the presence of CCK-8 resulted in activation of pro-inflammatory transcription factors, NF-κB, AP-1 and other cytokine and inflammatory molecules thereby resulting in increased trypsin release. On the other hand alcohol when given alone causes less activation of NF-κB as compared to that given with CCK alone indicating that ethanol has inhibitory effects on the inflammatory response alone. Ca^{2+} and PKC contribute to NF-κB activation induced by CCK-8 in acinar cells. Ethanol differentially affects the Ca (2^{+})/calcineurin- and PKC-mediated pathways of NF-kappaB activation in pancreatic acinar cells[16,92]. These effects may play a role to sensitize pancreas to the inflammatory response and pancreatitis. Acute oxidative stress modulates secretion and repetitive Ca^{2+} spiking in rat pancreas[93]. Thus perturbations in Ca^{2+} signaling do not fully explain the secretory block caused by oxidative stress in acute pancreatitis.

CIGARETTE SMOKING AND PANCREATITIS: EFFECT OF ALCOHOL

Cigarette smoking is a known risk factor for alcoholic and chronic pancreatitis. About 80%-95% of people who abuse alcohol also smoke while 25%-30% of smokers do not drink alcohol[94]. The incidence of alcoholism is 10 times more likely in smokers than nonsmokers. Cigarette smoking accelerates the progression of alcohol induced pancreatitis[10,11]. Blomqvist *et al*[95] reported that intermittent nicotine administration to rats enhances ethanol intake and preference to ethanol in a free choice between ethanol and water. He suggested that subchronic nicotine doses increased the responsiveness of mesolimbic dopamine neurons to both nicotine and alcohol. Potthoff *et al*[96] found similar results in their experiments in rats administering chronic nicotine. Ericson *et al*[97] reported the involvement of nicotinic acetylcholine receptors (nAChR) in nicotine induced increased uptake of ethanol. He gave antagonist to peripheral nAChR to mice and rats subchronically for 15 d and after stopping drug, ethanol intake and preference as well as ethanol induced locomotor stimulation increased. This may be due to compensatory enhanced autonomic ganglionic and/or muscarinic neurotransmission. The mechanism (hormonal or metabolic) by which increased peripheral neuronal activity affects the brain dopaminergic system in the brain is not known.

The mechanism by which alcohol causes the pancreatic injury is not entirely clear. Metabolic as well as microcirculatory changes and other theories were proposed to explain this phenomenon. Cigarette smoking is known as a potentiating factor in the development of alcohol induced pancreatic injury. Hartwig *et al*[9] investigated the effect of cigarette smoke on alcohol induced pancreatic injury. They gave cigarette smoke alone or with ethanol intravenously to rats. Ethanol alone impairs pancreatic blood flow without any change in systemic hemodynamic parameters and inflammatory change. Cigarette smoke potentiates pancreatic microcirculatory impairment by ethanol and also induces leukocyte aggregation and adhesion.

Nicotine is metabolized by cytochrome P450 into cotinine[98,99]. Tissue distribution of ^{3}H-nicotine in rats demonstrated that nicotine is distributed and accumulated significantly in the pancreas and parts of the gastrointestinal tract[100]. But nicotine metabolism in pancreas has not been reported yet. In liver, low doses of nicotine and ethanol induces CYP2E1 activity as reported by Howard *et al*[101]. The study suggests that nicotine may increase CYP2E1-induced toxicity and contribute to cross-tolerance in smokers and people treated with nicotine. It may be possible that nicotine might have some effect on pancreatic CYP2E1 induction leading to increased metabolism of ethanol in pancreas by cytochrome and thereby potentiate the damage caused by ethanol.

CONCLUSIONS

Alcohol abuse/alcoholism are a major cause of pancreatitis. Combining alcohol abuse with smoking aggravates the condition further. Despite numerous reported studies the pathogenesis of alcoholic pancreatitis remains obscure. During recent years it has been possible to evaluate the mechanism of development of alcoholic pancreatitis in the animal model and in *in-vitro* acinar cell cultures. The summary of events relating to alcohol exposure that may lead to induction of alcoholic pancreatitis is shown in the flow diagram below (Figure 1).

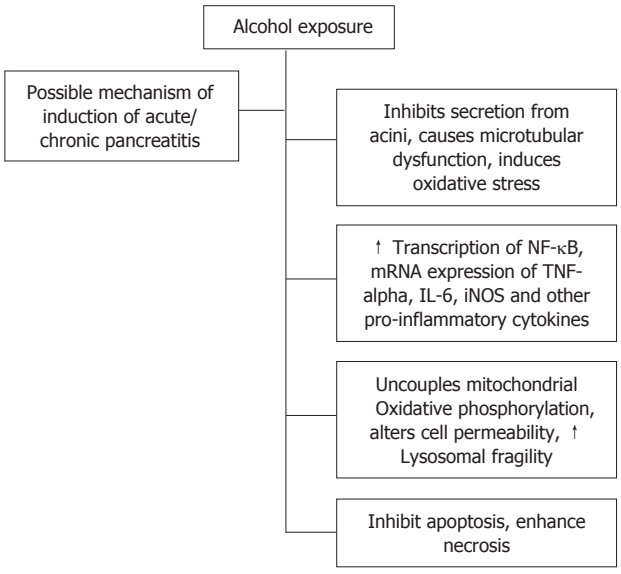

Figure 1 The summary of events relating to alcohol exposure that may lead to induction of alcoholic pancreatitis.

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