Effect of Non-Alcoholic Compounds of Alcoholic Drinks on the Pancreas

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Key Words

Alcohol · Alcoholic beverages · Non-alcoholic compounds · Pancreatitis

Abstract

Over the past 30 years the role of alcohol (ethanol) in the development of acute and chronic pancreatitis has been intensively investigated. However, ethanol is generally consumed in form of alcoholic beverages which contain numerous non-alcoholic compounds. At least on gastric acid secretion it has been convincingly demonstrated that alcohol and alcoholic beverages have markedly different effects. In the present article, we provide an overview about the effect of different non-alcoholic constituents of alcoholic beverages on the pancreas and their possible interaction with molecular mechanisms leading to 'alcoholic' pancreatitis. The present data indicate that pancreatic enzyme secretion in humans is stimulated by non-alcoholic constituents of beer which are generated by alcoholic fermentation of glucose. In addition, it has been shown that natural phenolic compounds (e.g. quercetin, resveratrol) of alcoholic beverages exert different effects on the pancreas *in vitro*, such as inhibition of pancreatic enzyme output, of pancreatic stellate cell activation and of pancreatic cancer growth as well as protective effects against oxidative stress and on experimental induced acute pancreatitis in rats. However, it should be pointed out that alcoholic beverages contain much more non-alcoholic ingredients. Since the effects of these are still

unknown, caution is required in attempting to define alcoholic etiology of pancreatitis without considering the effect of non-alcoholic compounds of alcoholic beverages.

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Introduction

Chronic excessive consumption of alcoholic beverages is clearly associated with acute and chronic pancreatitis. While the role of alcohol (ethanol) in the development of pancreatitis has been intensively studied over the past three decades, the role of non-alcoholic constituents was hardly investigated. However, alcoholic beverages contain numerous non-alcoholic compounds. For example, up to now in beer more than 2000 and in wine more than 1,000 organic and anorganic constituents were defined. As outlined in detail below at least on gastric acid secretion it has been convincingly demonstrated that alcohol and alcoholic beverages have markedly different effects [1–3].

Some of the non-alcoholic constituents are known to be biologically active, although these compounds were often not studied on the background of the effect of alcoholic beverages. However, there is accumulating evidence that these compounds have a critical role in inducing metabolic, pathological and functional changes *in vivo* and *in vitro*.

This article provides an overview about the effect of alcoholic beverages on the stomach and the pancreas in

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Fig. 1. Effect of ethanol and different types of alcoholic beverages on gastric acid secretion of healthy human subjects. **a** Effect of intragastric instillation of various concentrations of ethanol, isotonic glucose and distilled water on 1-hour incremental gastric acid output. Results are means $\pm$ SEM of 6 subjects. * $p < 0.05$ in comparison to isotonic glucose control solution (5.76 w/v) and distilled water. Adapted from Singer et al. [1]. **b** 1-hour incremental gastric acid output in response to different alcoholic beverages produced by fermentation or distillation, to fermented glucose and to the combination of maleic acid and succinic acid in concentrations found in finished beer. For comparison the maximal acid output in response to pentagastrin is also shown. Results are means $\pm$ SEM from at least 6 subjects. * $p < 0.05$ for the difference with isotonic glucose control solution (5.76 w/v). Adapted from Teyssen et al. [2, 3].

comparison to ethanol. Furthermore, it will focus on the effects of different non-alcoholic constituents of alcoholic beverages on the pancreas and it will discuss their possible interaction with molecular mechanisms leading to 'alcoholic' pancreatitis.

Effects of Ethanol and Alcoholic Beverages on Gastric Acid Secretion

Pure ethanol in low concentrations ($<4\%$ v/v) is a mild stimulant of gastric acid output with a response equal to about 23% of the pentagastrin-stimulated gastric acid output (maximal acid output; (MAO) (fig. 1a). Higher concentrations of ethanol (5–40% v/v) have either no ef-

fect or a mildly inhibitory one [1]. None of the ethanol concentrations tested increase plasma gastrin concentrations.

In contrast, alcoholic beverages with low ethanol content (e.g. beer and wine) are powerful stimulants of gastric acid output (fig. 1b) and gastrin release. Distilled alcoholic beverages with a higher ethanol content (e.g. whiskey and cognac) do not stimulate gastric acid output (fig. 1b) or release of gastrin [1, 2].

The ethanol content in beer (4% v/v) and wine (10% v/v) can be only partially or not at all responsible for the marked gastric acid secretory responses to beer and wine. Therefore, non-alcoholic ingredients in beer and wine are most likely responsible for the stimulatory gastric action of these alcoholic beverages.

Fig. 2. Effect of ethanol, beer and fermented glucose on pancreatic enzyme output of healthy human subjects. The 150-min integrated trypsin response (left) and amylase response (right) to intragastric fermented glucose (11.5% w/v), beer and ethanol (4% v/v) as well as to the corresponding caloric (glucose, 5.76% w/v), osmotic (glucose, 11.5% w/v) and volumetric (water) control solutions were determined. Results are means $\pm$ SEM of 6 subjects. * $p < 0.05$ in comparison to ethanol and all control solutions. Adapted from Chari et al. [4].

The search for the stimulatory substances in alcoholic beverages revealed that the powerful stimulants of gastric acid output are the dicarboxylic acids maleic and succinic acid which are produced during the process of alcoholic fermentation [3]. The surprising finding of this investigation was that these dicarboxylic acids do not stimulate gastrin release.

Acute Effects of Alcoholic Beverages on Pancreatic Exocrine Function

Intragastric administration of beer in a dose (250 ml) that does not alter plasma ethanol concentrations causes a significant stimulation of basal pancreatic enzyme output (fig. 2) [4]. The stimulatory effect might be mediated by the hormones cholecystokinin and gastrin. Intragastric administration of ethanol in concentrations similar to beer (4% v/v) has no effect on pancreatic enzyme out-

put (fig. 2). Therefore, the non-alcoholic constituents might be responsible for the stimulatory effect of beer on pancreatic enzyme secretion in humans. The alcoholic fermentation of glucose might be the essential event generating the stimulatory substances in beer [4].

The intragastric administration of an amount of beer (850 ml) or white wine (400 ml) that elevated plasma ethanol concentrations did not affect the basal pancreatic enzyme output [5]. It was suggested that the direct inhibitory effect of circulating ethanol neutralized the stimulatory effect of non-alcoholic components of beer. The basal enzyme output also remained unchanged after intragastric application of white wine and gin.

The meal-stimulated pancreatic enzyme output was inhibited by intragastric beer, white wine and gin [6, 7]. Concurrently, the ethanol plasma levels were elevated in these studies. Therefore, the inhibitory effect of circulating ethanol on pancreatic secretion might have neutralized a possible stimulatory effect of beer and white wine.

Table 1. Studies on the effects of non-alcoholic constituents of alcoholic beverages on the pancreas

Compound	Experimental design	Effect on pancreas	Species	Ref.
Quercetin	in vitro 10–100 μ M isolated pancreatic acini	inhibition of agonist-induced amylase release and of PKC activity	rat (male Sprague-Dawley)	8
	in vitro 50 μ M cultured pancreas fragments experimentally induced pancreatitis	inhibition of culture growth-induced rise in HSP70 levels and restoration of trypsinogen activation	rat (Wistar)	21
Resveratrol	in vitro 10–100 μ M	inhibition of bile salt-dependent lipase (BSDL) activity reduction of secreted and intracellular BSDL in AR4-2J cell line	human (purified BSDL), rat (purified BSDL, AR4-2J cell line)	9
	in vivo 20 mg/kg b.w. experimentally induced pancreatitis	decrease of elevated amylase, malondialdehyde and myeloperoxidase levels increase of pancreatic superoxide dismutase reduction of turbidity ascitic fluid, pancreatic edema, necrosis and inflammatory cell infiltration	rat (Sprague-Dawley)	10
	in vivo 10 mg/kg b.w. experimentally induced pancreatitis	reduction of elevated serum amylase and lipase activities and reduction of changes of serum glucose, calcium and creatinine and aspartate aminotransferase increase of serum concentration of triglyceride and urea nitrogen to normal level reduction of extent of tissue edema, acinar vacuolization and total histological damage	rat (Wistar)	14
	in vivo 2 mg/day experimentally induced pancreatitis	decrease of elevated serum activity of amylase less pronounced necrotic changes of pancreata	rat (male Wistar)	15
	in vivo 10 mg/kg b.w. experimentally induced pancreatitis	decrease of NF- κ B activation in peritoneal macrophages reduction of iNOS expression and of TNF- α , IL-1 and NO serum levels	rat (Sprague-Dawley)	16
	in vivo 30 mg/kg b.w. experimentally induced pancreatitis	reduction of NF- κ B expression and of TNF- α and IL-8 level in pancreatic tissue	rat (Sprague-Dawley)	17
Ellagic acid	in vivo 1% w/w	increase of glutathione S-transferase expression	rat (male Wistar)	11
	in vitro ≤ 25 μ g/ml pancreatic stellate cells (PSCs)	inhibition of PDGF-induced proliferation and migration of PSCs and of phosphorylation of PDGF β -receptor, ERK and Akt decrease of expression of α -SMA, procollagen I and III and MCP-1 inhibition of transformation of freshly isolated PSCs	rat (male Wistar)	13
Green tea extract	in vivo 0.1% solution (approximately 80% catechins)	protective effect against N-nitrosobis(2-oxopropyl)amine-induced oxidative damage	Syrian golden hamster	12
	in vivo 0.2 % solution (91.2% catechins) experimentally induced pancreatitis	decrease of elevated serum amylase activity and lipid peroxides concentration protection of pancreatic tissue	rat (male Wistar)	18

Effects of Different Non-Alcoholic Constituents of Alcoholic Beverages on the Pancreas

One of the differentiating characteristics among alcoholic beverages is their polyphenol composition. In this context wine contains more abundant polyphenols – more than beer and liquors. A number of polyphenols

have been shown to possess anti-oxidant and anti-cancer properties. The first such polyphenols studied were quercetin and rutin followed more recently by resveratrol.

Quercetin is a naturally occurring flavonoid present in a variety of plants and in wine and has important anti-degenerative properties. Rutin is the glycosidic form of quercetin and is one of the flavonoids most abundantly

consumed in foods. It is mainly found in onions, apples, tea and red wine and has anti-inflammatory and anti-mutagenic properties. Resveratrol is a phenolic phytoalexin present in grape skins and wines, especially red wines. Among a variety of biological effects it has a potent anti-inflammatory function in vitro. Ellagic acid is a polyphenol mainly found in fruits (raspberries, strawberries), nuts (walnuts) and wood, but also in beer and in wine. It has a variety of biological activities including anti-oxidant, anti-inflammatory and anti-fibrotic effects. Catechins are phytoalexins which are found in green tea, various vegetables and fruits and particularly in paring of grapes of red wines. In several studies the anti-oxidative and radical-scavenging properties of catechins have been reported. In the following sections the effects of different polyphenols on the pancreas are described (table 1).

Effect of Non-Alcoholic Constituents of Alcoholic Beverages upon Enzyme Output in vitro

Chronic ethanol consumption significantly increases basal pancreatic enzyme output, protein concentration in the pancreatic juice and the viscosity of pancreatic juice. Investigation of the effects of non-alcoholic compounds of alcoholic beverages have been undertaken to facilitate our understanding of their direct effects.

In a former study, the effect of quercetin on stimulated amylase release in isolated rat pancreatic acini was investigated [8]. Quercetin inhibited carbachol-stimulated amylase release both, time- and dose-dependently. In addition, quercetin partially inhibited amylase release induced by various agonists such as cholecystokinin C-terminal octapeptide (CCK-OP), calcium ionophore A23187 and phorbol ester tetradecanoylphorbol-13-acetate (TPA) whereas vasoactive intestinal polypeptide (VIP)-induced amylase release was potentiated. Since quercetin also inhibited protein kinase C activity in a dose-dependent manner the ability of quercetin to decrease agonist-stimulated amylase release may be ascribed – at least in part – to quercetin-induced inhibition of PKC activity.

A recent study compared the effects of resveratrol and a whole red wine polyphenolic extract (RWE) on the pancreatic bile salt-dependent lipase (BSDL) in vitro in the rat pancreatic AR4-2J acinar cell line [9]. Resveratrol and RWE inhibited human and rat BSDL activity in a dose-dependent manner. Furthermore, resveratrol (but not RWE) decreased the expression and secretion of BSDL in AR4-2J cells.

Effect of Non-Alcoholic Constituents of Alcoholic Beverages upon Oxidative Stress

Oxidative stress is another important event that may play a role in pancreatic injury. Evidence of oxidative stress has also been reported in the pancreas of patients with alcoholic chronic pancreatitis. In general, oxidative stress results from an imbalance between the production of free radicals or reactive oxygen species (highly reactive molecules with the potential to damage lipid membranes, intracellular proteins and DNA) and the antioxidant defence mechanisms within the cell (including glutathione, the enzymes glutathione peroxidase, superoxide dismutase and catalase and their co-factors such as vitamin C, vitamin E, zinc and selenium).

The effect of resveratrol on pancreatic oxygen free radicals was investigated in rats with severe acute pancreatitis (SAP) [10]. Histological examinations showed that the resveratrol treatment (20 mg/kg body weight) after SAP induction led to a significant reduction of turbidity ascitic fluid, pancreatic edema, necrosis and inflammatory cell infiltration as compared to the SAP group. In addition, serum amylase was significantly diminished by resveratrol. Furthermore, resveratrol treatment inhibited the formation of the lipid peroxidation product malondialdehyde (MDA) and increased the pancreatic superoxide dismutase (SOD, an internal anti-oxidase). Measurement of myeloperoxidase (MPO) as degree for neutrophil sequestration which is another source of oxygen free radicals during acute pancreatitis showed a reduction of this enzyme in the *resveratrol*-treated group. In conclusion, resveratrol had a protective effect on pancreatic damage by lowering oxidative free radicals and reducing tissue infiltration of neutrophils.

A chemoprotective effect of ellagic acid and flavone has been shown by enhancing the glutathione S-transferase (GST) detoxification system in the pancreas of male Wistar rats [11]. Studies on GST class α , μ and π isozyme expression levels showed an ellagic acid-increased expression of GST- μ by 160% and a flavone-induced increase of GST- π expression by 200%. Ellagic acid and flavone had no significant effect on pancreatic GST enzyme activity and glutathione content.

Certain catechins have anti-oxidative properties by eliminating superoxide and hydroxyl radicals, the latter being oxygen-reactive agents that damage DNA and initiate lipidic peroxidation processes. Thus, it could be shown that a 0.1% solution of green tea catechins (GTC) as drinking water had a protective effect against the oxidative stress in pancreas and liver induced by the

pancreatic carcinogen N-nitrosobis(2-oxopropyl)amine (BOP) in Syrian golden hamsters [12]. The increase of 8-hydroxydeoxyguanosine (8-OHdG) content in nuclear DNA which is a biomarker of DNA oxidative damage was inhibited by GTC. In addition, an inhibitory effect of GTC was also shown on lipid peroxidation confirming the protective effect of catechins on oxidative stress.

Effect of Non-Alcoholic Constituents of Alcoholic Beverages upon Pancreas Stellate Cells

Pancreatic stellate cells (PSCs) are the main source of extracellular matrix synthesis leading to pancreatic fibrosis and are activated by growth factors, inflammatory cytokines, alcohol, its metabolite acetaldehyde and oxidative stress.

Recently, it has been shown, that ellagic acid has crucial effects on a number of cell functions including activation of PSCs in vitro [13]. Ellagic acid inhibited the platelet derived growth factor (PDGF)-induced proliferation and migration in a dose-dependent manner (1–25 µg/ml) without affecting cell viability. Further experiments showed that ellagic acid significantly inhibited several key functions of PSCs including AP-1 and MAP kinases activation, α-SMA gene expression, MCP-1 production and collagen expression in a dose-dependent manner. In addition, ellagic acid blocked the transformation of freshly isolated PSCs from quiescent to myofibroblast-like phenotype in culture. Because of its crucial effects on cell functions and the activation of PSCs ellagic acid is a potential candidate for the treatment of pancreatic fibrosis and inflammation.

Effect of Non-Alcoholic Constituents of Alcoholic Beverages upon Pancreatitis Induced in Animals

Several experimental animal models have been developed to induce acute pancreatitis. In some studies which have been published recently, a protective effect of resveratrol on experimentally induced acute pancreatitis could be demonstrated.

Szabolcs et al. [14] examined the effect of resveratrol on CCK-OP-induced acute pancreatitis in male Wistar rats. Pretreatment with 10 mg/kg body weight resveratrol ameliorated CCK-induced changes of laboratory parameters such as amylase, lipase, glucose, calcium, creatinine and aspartate aminotransferase activities as well as the serum concentration of triglyceride and urea nitrogen.

However, resveratrol showed no effect on the reduced pancreatic Cu/Zn-SOD and glutathione peroxidase activity in the pancreatitis rats. Histological investigation of the pancreas showed a reduced extent of tissue edema, acinar vacuolization and total histological damage after resveratrol treatment. Since no inhibition of NF-κB activation by resveratrol has been found it was concluded that the beneficial effects of resveratrol seem to be mediated by the anti-oxidant effect of resveratrol or by an anti-inflammatory mechanism independent of NF-κB.

An attenuation of various pathological manifestations (less pronounced necrotic changes of rat pancreata such as focal edema, acinar cell vacuolization, and focal tissue necrosis) as well as a decrease of serum amylase activity by resveratrol has been shown in free radicals (tert-butyl hydroperoxide = Bu^tOOH)-induced acute pancreatitis in male Wistar rats [15].

Activation of NF-κB in macrophages is involved in the inflammatory response of rats with sodium taurocholate-induced severe acute pancreatitis (SAP). *Resveratrol* decreased the NF-κB activation as well as iNOS expression in peritoneal macrophages [16]. In addition, in resveratrol-treated SAP rats serum levels of TNF-α, IL-1 and NO were also reduced. Histological examinations of the pancreas showed an attenuation of various pathological manifestations by resveratrol as compared to the untreated SAP group. These results were confirmed by a second study [17] showing the inhibitory effect of resveratrol on expression of NF-κB and the levels of TNF-α and IL-8 in pancreatic tissues of SAP-rats. In summary, resveratrol may be considered as an agent for reducing the inflammatory response in acute pancreatitis.

Similar effects were found for the effect of catechins on DL-ethionine-induced acute pancreatitis in male Wistar rats [18]. Morphological analysis of rats that were supplied with 0.2% solution of green tea extract (GTE, 91.2% catechins) for 13 days prior injection of 800 mg/kg DL-ethionine showed few lesions on pancreatic tissue except for mild interstitial edema whereas in rats with DL-ethionine-induced acute pancreatitis inter- and intrastitial edema and necrosis of acinar cells were found. Furthermore, the GTE-drinking rats showed a significant decrease in serum amylase activity and tissue lipid peroxides concentration, as compared to the DL-ethionine-treated group supplied with water. Similar results were found by the same author for the effects of catechins on cerulein-induced pancreatitis [19]. Taken together, catechins were shown to have a protective effect on experimentally induced pancreatitis in rats.

Previous studies have shown that hepatocyte growth factor (HGF) reduced pancreatic damage in experimental pancreatitis. Warzecha et al. [20] investigated the effect of resveratrol on HGF in cerulein-induced pancreatitis in Wistar rats. Treatment with 10 mg/kg resveratrol alone had no effect on the development of pancreatitis. In addition, resveratrol did not affect the protective effect of HGF. Since it has been shown that resveratrol is an inhibitor of cyclooxygenase-1 activity, it can be concluded that this activity is not involved in the protective effect of HGF in acute pancreatitis.

In cerulein-induced pancreatitis heat shock protein 70 (HSP70) prevents secretagogue-induced cell injury in the pancreas by preventing intracellular trypsinogen activation [21]. Incubation with quercetin completely blocked culture-induced upregulation of HSP70 expression and restored the culture-dependent loss of trypsinogen activation in the cerulein-induced pancreatitis. Studying non-pancreatic tissues it was shown that quercetin inhib-

its synthesis of HSP110, HSP90, HSP40, and HSP28, in addition to HSP70.

In summary, there is accumulating evidence that natural phenolic compounds of plants found in alcoholic beverages exert different effects on the pancreas. Particularly resveratrol protected the pancreas against pro-oxidative activity of hydroperoxide and inhibits inflammation by suppression of platelet aggregation and cytokine production. It is anticipated that resveratrol could serve as a therapeutic compound in managing acute pancreatitis through different pathways. In addition, other non-alcoholic constituents of alcoholic beverages also exert protective effects in vitro. However, it should be pointed out that alcoholic beverages contain much more non-alcoholic ingredients. The effects of these ingredients are still unknown and thus, caution is required in attempting to draw firm conclusions on the effect of non-alcoholic compounds of alcoholic beverages on defining alcoholic etiology of pancreatitis.

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