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Review article

How does cigarette smoking cause acute pancreatitis?

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ABSTRACT

Introduction: Acute Pancreatitis (AP) is an emerging health problem world-wide and it is a major cause of admissions for gastrointestinal disease in many countries. Amongst the more common causes (alcohol and gallstones), recent evidence has emerged indicating that smoking is an independent risk factor for AP. However, the mechanisms involved in smoking-induced AP have not been completely elucidated. This review puts together all the published evidence in literature to present the clinical and laboratory evidence relating smoking to the causation of AP.

Discussion: The two main metabolites from cigarette smoke, namely nicotine and NNK are able to induce functional and histological changes within the pancreas consistent with AP. The major mechanisms involved include their action on acinar cells and zymogen secretion through pathways involving CCK and the nicotinic preganglionic receptors. Effects on the pancreatic microvasculature may be mediated through the nitric oxide pathway. There is indirect evidence to suggest that nicotine and acrolein may lead to CFTR dysfunction thereby influencing ductal secretion. However, direct evidence for this effect is needed. The effect of cigarette smoke metabolites on stellate cells and the islets warrants further investigation in the context of pathogenesis of AP.

Conclusion: Using a step-wise approach, the review revisits the effects of the various metabolites of cigarette smoke on the constituents of the pancreas (exocrine, endocrine, neurohormonal, stellate cells, ductal system) and highlights their proven, and potential, mechanisms in triggering off an attack of AP.

Introduction

With a rising incidence across the world [1,2] mirrored by an increase in hospital and emergency department admissions [3–6], and the lack of specific treatment for the disease itself [7,8], acute pancreatitis (AP) represents a significant burden on global health care systems [4,9,10]. AP is characterized by an acute inflammation of the pancreas that results in a clinical spectrum ranging from the more common, mild and self-limiting course, to severe disease that is even associated with the risk of mortality [11]. While alcohol and gallstones are the two most common factors linked to the causation of an attack of AP [4,12–14], other associated causes include diet [15,16], drugs [17], pancreatic tumours and certain genetic predispositions [18].

The habits of cigarette smoking and consuming alcohol quite often co-exist [19]. Hirota and colleagues [19] noted that alcoholic patients suffering from pancreatitis were more likely to smoke when compared to non alcoholics. The association between smoking and AP was initially overlooked possibly due to the general perception that alcohol was a more likely risk factor for AP [20,21]. However, over the last 2 decades [22–25] there has been a steady increase in our appreciation of the effect of cigarette smoking on pancreatic function and the causation of pancreatic diseases, especially pancreatic cancer [26] and pancreatitis [27]. Within the last year itself, there have been 4 published meta-analyses [28–31] highlighting the clinical/epidemiological association between smoking and the development of AP. While the importance of patient, as well as, public education on the ill-effects of smoking, in general, requires strong advocacy, the above data heralds the need for a better understanding of the mechanisms by which cigarette smoking contributes to the pathogenesis of AP.

This review will systematically explore the clinical and experimental data correlating cigarette smoking and its mechanisms involved in the causation of AP.

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Smoking in the causation of AP

The effect of smoking on the causation of AP, independent of alcohol, was initially appreciated in studies from Italy [23,32]. Thereafter, the dose-dependent relationship between number of cigarettes smoked and the development of AP was noted by Lindkvist et al. [20] who also found that smoking was associated with a relative risk of 3.57 (95% CI 0.98–13.0) for AP in patients who did not consume alcohol. Similar studies that followed suggested that based on a critical analysis within the cohort 46% of the aetiology of pancreatitis was attributable to smoking [21].

In addition to smoking being able to trigger the sentinel attack of AP, data has begun to emerge suggesting that smoking may also be linked to recurrent AP (RAP) (depending on the severity of smoking [33]) and that it may even further lead to the progression from AP to chronic pancreatitis (CP) [34]. These findings have now been confirmed by a recent meta-analysis [28].

There are now 4 meta-analyses published clearly indicating a role of cigarette smoking in the causation of AP [28–31] not only in current, but even former, smokers compared to never-smokers. Sadr-Azodi et al. [35] showed that the risk for AP amongst smokers reduced to a level comparable to non-smokers in those who had given up the habit for 2 decades. Within a large cohort of 484,624 patients, Munigala and colleagues [36] were able to clarify that heavy smoking not only increased the risk of the first attack of AP, it did so at a younger age and with the additional likelihood of developing recurrent AP (RAP). Besides being an independent risk factor, smoking may also serve as a co-factor in the causation of non-gallstone related AP (including alcohol, idiopathic and drug-induced AP) [35,29].

The next section addresses the constituents/metabolites of cigarette smoke and the clinical evidence to support their penetration of the pancreas.

Constituents of cigarette smoke and pancreatic penetration

Cigarette smoke contains various metabolites including gases such as carbon monoxide (CO), hydrogen cyanide (HCN) and nitrogen oxide, volatile chemicals contained in the liquid–vapour portion of the smoke aerosol such as formaldehyde, acrolein, benzene, and certain nitrosamines, chemicals contained in the submicron-sized solid particles suspended in cigarette smoke, namely nicotine, phenol, polyaromatic hydrocarbons (PAH) and tobacco-specific nitrosamines (TSNA), namely and N′-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) [37].

Of all the chemicals present in cigarette smoke, nicotine and NNK are the two most well studied in pancreatic disease. Nicotine is the major biologically active substance in cigarette smoke [38]. These metabolites are capable of penetrating pancreatic tissue. Cotinine, the predominant metabolite of nicotine, and NNK were detected in 100% and 83% of pancreatic juice samples from smokers that were analyzed by gas chromatography with mass spectrometric detection using a selected ion monitoring technique (GC-SIM-MS) [39]. Additionally, nicotine has been found to be retained longer in the pancreas in case of constant/prolonged exposure determined by radioactive [3H] labelled nicotine studies in mice [40]. In patients with CP, chronic cigarette smoke inhalation has been shown to result in higher expression of the inflammatory marker interleukin-6 and enzymes in acinar, islet and duct cells favouring a role for increased oxidative stress [41].

Considering that metabolites of cigarette smoke penetrate the pancreatic tissue, the next section will provide the experimental evidence for the effects of these metabolites on the various anatomical components of the pancreatic tissue.

Effects of smoking on the pancreas

Neurohormonal considerations

The predominant regulation of pancreatic secretion is mediated via the parasympathetic nervous system (the vagus nerve) [42] with the sympathetic nervous system exerting its influence through the innervation of microvasculature and spinal afferent nerves [43]. Neurotransmission at the pancreatic ganglia from the dorsal motor nucleus of vagus/DMV-derived preganglionic fibres are mediated by acetylcholine acting through the nicotinic receptors while the postganglionic neurotransmission is mediated by acetylcholine acting through muscarinic receptors [44].

Another important neural network between the enteric nervous system and the pancreas is termed the enteropancreatic innervation [45]. It mediates enteropancreatic reflexes that are important not only for stimulatory mediators of the intestinal phase of pancreatic exocrine secretion, but also for stimulating pancreatic secretion when chyme enters the duodenum [46,47]. Cholecystokinin (CCK) and secretin are two of the main enteropancreatic hormones responsible for the stimulatory effect on pancreatic exocrine secretion.

The exocrine pancreas

Studies from Poland had suggested that smoking may influence exocrine function based on estimations of amylase and lipase activity in serum and urine samples from smokers and non-smokers with AP [48,49]. These human studies mirrored the murine experiments in which nicotine (in a concentration of 12.5 mM) was noted to stimulate amylase and trypsinogen release by 95 and 400% from rat pancreatic acini [50]. In addition, nicotine stimulated the secretion of preformed zymogen granules and newly synthesized proteins. These stimulatory effects of nicotine on the exocrine pancreas (serum enzymes [51] and secretory proteins [52]) were observed not only in diseased, but even in non-diseased states under the influence of stimulatory hormones such as secretin. The mechanism involved appears to be distinct from the pathways involved in nicotine-induced cell proliferation [53]. The intracellular morphological changes in the exocrine pancreas that are indicative of the effect of nicotine on enzyme secretion precede the functional or metabolic alterations [54].

In the experimental setting, caerulein (an octapeptide analogue of CCK) has been shown to stimulate exocrine secretion at least in part by nicotinic receptors at concentrations comparable to physiological concentrations of CCK [55]. In the early 90s, Chowdhury et al. [24] in their murine experiments had noted that nicotine in high doses over 16 weeks resulted in functional as well as morphological changes in the exocrine pancreas. In this experiment they found that while plasma levels of CCK were significantly elevated with nicotine, the amylase secretory response of pancreatic acinar cells to CCK-8 and carbachol was inhibited. At the histopathological level, high doses of nicotine enhanced the appearance of numerous vacuoles in the pancreatic acinar cell cytoplasm which on close examination demonstrated pyknotic nuclei and fusion of vacuoles. CCK activates the inositol triphosphate/diacyl glycerol signalling pathways which raises cytosolic Ca^{++} concentration with concurrent activation of protein kinase C and the consequent triggering of Ca^{++}-dependent exocytosis. Nicotine, too, has been shown to affect calcium-activated events regulating the exocytotic secretion in rat pancreatic acinar cells via a mechanism completely abolished by nicotinic receptor antagonist, calcium channel receptor antagonists and inositol trisphosphate (IP3) receptor blockers [56] indicating a common pathway of action of nicotine and CCK. The possibility of nicotine acting via CCK receptors [57] has also been suggested although this remains less likely.

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