British Journal of Applied Science & Technology
3(2): 206-213, 2013

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Genetic and Environmental Attributes of Chronic Pancreatitis

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SS and SA designed the study, performed the statistical analysis, and wrote the first draft of the manuscript. Authors SS and SA managed the analyses of the study as well as literature searches. Author GC managed the identification of the disease, and analysis of clinical parameters of patients. All authors read and approved the final manuscript.

Research Article

Received 5th September 2012
Accepted 10th December 2012
Published 19th February 2013

ABSTRACT

Chronic pancreatitis (CP) is a chronic progressive inflammatory disease of the pancreas. Tropical chronic pancreatitis is a severe form of CP with multifactorial aetiology. In addition to the growing evidence of attributes of genetic factors, the environmental factors may also play crucial roles in the progression and pathogenesis of CP as these factors may interact with the genetic components of individuals and cause aberrations. Oxidative stress related genes may modify the effects of ambient tobacco smoking and alcohol on CP. This review presents an updated account of the contribution of gene-environment interactions on the onset and progression of CP.

Keywords: Environmental factors; chronic pancreatitis; oxidative stress; smoking; alcohol.

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1. INTRODUCTION

CP is a progressive inflammatory disorder ultimately leading to irreversible structural changes resulting in functional impairment of exocrine and/or endocrine physiology [1, 2]. The existing reports indicate that despite the involvement of some genetic factors, the environmental factors also influence the onset as well as progression of the disease. Alcohol is recognised as the major cause of CP. In developed countries, 60–70% of patients with CP have a long history of heavy alcohol consumption; whereas smoking has been described as an additional risk factor [3-4]. Since 1982 [5] smoking has been recognized as one of the major risk factors for CP, particularly in alcohol-related CP compared to CP arising from other causes [6]. Alcohol is used by a far greater number of people than those who actually go on to develop CP, indicating variable genetic susceptibility.

Environmental factors such as cigarette smoking, alcohol, high-fat diets, fossil fuel products and high temperature cooked meat sources may expose the human pancreas to toxins released by these factors [7,8]. Induction of phase I xenobiotics metabolising enzymes in the pancreas, principally cytochrome monooxygenases in response to a number of these agents, have been reported to produce cytotoxic lipophilic intermediates that can potentially overcome their abilities to detoxify such products [9]. Initially in 1994, Cavallini and coworkers had described the effect of tobacco and alcohol on pancreatic lithogenesis during the course of CP. They found that medium to heavy smokers had a significantly increased risk of developing calcifications in pancreas but found no effects in those using alcohol [10].

The results of recent studies suggest that CP has a strong genetic basis. The increasing knowledge of gene-environment interaction has provided new insight in the pathogenesis of CP [11]. Tobacco smokings are known to contain free radicals and to induce their direct formation at the tissue level causing damage of cell membranes, proteins, DNA, chronic tissue inflammation and their remodelling in the long run [12,13]. Upon exposure, different protein systems including those scavenging reactive oxygen species (ROS) are up-regulated, and the level of response is influenced by variation in expressions of underlying genes. Likewise, polymorphisms in oxidative stress related candidate genes like glutathione s-transferases (GSTs), microsomal epoxide hydroxylase or heme-oxygenase 1, have been associated with decline in CP function. The other environmental factors such as ethanol, smoking and some putative etiologic factors may contribute to chronic pancreatic injury. In this review, an endeavour has been made to present an updated account of the contribution of gene-environment interactions on the onset, progression and severity of chronic pancreatitis.

2. ALCOHOL CONSUMPTION MAY ADVERSELY AFFECT THE DIGESTIVE SYSTEM AND CAUSE PANCREATITIS

Alcohol abuse was proposed as a causative agent of pancreatitis in 1878 by Freidrich [14]. In 1970s Sarles proposed that alcohol causes pancreaitis via precipitation of the secreted proteins (protein plug formation) within small pancreatic ducts leading to acinar atrophy and fibrosis [14,15,16]. Some animal experiments have shown that chronic alcohol administration produces changes in the acinar cells. It has been shown that the pancreatic content of the digestive enzymes such as trypsinogen, chymotrypsinogen, lipase and the lysosomal enzyme such as cathepsin B is increased in alcohol fed rats [17]. The risk for developing pancreatic disease occurs when there is a daily consumption of greater than 100 g of

ethanol for men and 80 g for women for more than five years. Therefore, there is variability in the susceptibility of males and females to the alcohol in disease progression.

3. SMOKING INDUCED GENERATION OF FREE RADICALS AND OXIDATIVE STRESS DURING CP

Smoking has been proved to be independently associated with CP [18]. The pancreatic disease is a complex disorder resulting from multiple defects, which, when combined, leads to failure of control systems and metabolic homeostasis. The developmental factors like protein, genes and other pathways that govern interaction between environmental factors and their impacts on the cellular level lead to make the pathogenesis more complicated. The central role of free radicals in tobacco smoke mediated carcinogenesis and oxidative stress has been established by a series of studies [19-20]. An important finding by Pryor and co-workers was that cigarette tar has high concentrations of stable free radicals, identified as a semiquinone (QH•) and carbon-centered radicals (-C•) as detected by electron paramagnetic resonance (EPR) [21]. The most interesting is a quinone/semiquinone/hydroquinone (Q/QH•/QH2) system in the tar polymeric matrix [22]. The stable free radicals were identified as o- and p-benzosemiquinone radicals and their role in the DNA damage through the formation of HO• were detected by EPR spin-trapping [23]. The following mechanisms have been identified: the QH• radicals reduce O_2 into O_2•−, which can dismutate to form H_2O_2 and then with Fe^{2+} (cigarette tar itself contains high concentrations of iron) can generate highly oxidizing hydroxyl radicals through the Fenton reaction shown as following:

$$(1)\ Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\cdot + OH-$$
$$(2)\ Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + OOH\cdot + H$$

4. FREE RADICALS ADVERSELY INFLUENCE MULTIPLE FACTORS IN PANCREATIC CELLS

The reactions of free radicals especially OH· with these membrane constituents lead to lipid peroxidation within the membranes followed by disintegration of the cells and ultimately to cell death. ROS can also disrupt mitochondrial membrane potential (øm), leading to release of cytochrome c and subsequent DNA fragmentation due to H_2O_2-induced mitochondrial damage [24]. In other pathways, switching on proinflammatory cascades not only exerts direct effects on the pancreatic cells, but also initiates the migration, adhesion, and infiltration of inflammatory cells into the exocrine pancreas. Genes to be involved in migration and adhesion process are chemokines. The intercellular adhesion molecules are under the regulation of the redox-sensitive kinases or transcription factors such as MAPKs, (Mitogen-activated protein kinase), NF-kB (Nuclear factor kappa-light chain enhancer of activated B cells) and activator protein-1 [25,26,27]. So the mechanism by which smoking contributes to pancreatic injury or by which smoking accelerates the pancreatic inflammatory process, is associated to the activation of multiple signal transduction pathways due to nicotine exposure explained in Fig. 1. This event results in high levels of intracellular calcium release and may be responsible for cell cytotoxicity and cell injury [28].

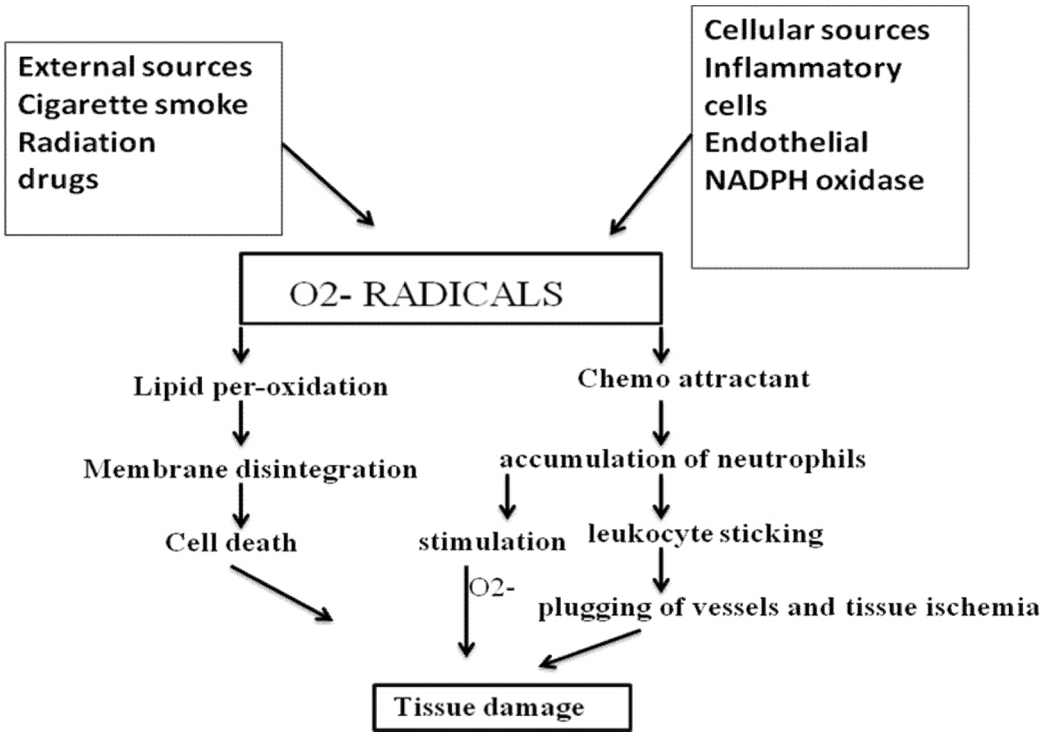

Fig. 1. Direct and indirect effects of oxygen free radicals

5. SMOKING AND DEVELOPMENT OF ACUTE AND CP

The large effects of tobacco smoking were caused by long-term cumulative exposure in current smokers as well as the remaining effects in former smokers, especially in men. The recent advances in basic research have revealed that stimulus or upstream signals regulating the ROS/RNS-generating enzymes might also play a role in the pathogenesis of pancreatic inflammation, thus opening a possible new therapeutic avenue against these diseases [29]. Oxidative stress plays a critical role in both acute and chronic pancreatic inflammation. Generation of ROS/RNS from numerous enzymatic systems, including xanthine oxidase, nitric oxide synthase, CYP2E1, and NADPH (Nicotinamide adenine dinucleotide phosphate) oxidase, not only directly oxidizes a wide range of biomolecules, but also switches on several stress-activated pathways like MAPK, NF-kb, cytokines and other pro-inflammatory pathways [30, 31]. Apart from the epidemiologic evidence of an association between smoking and development of acute and CP, a biological effect of smoking seems plausible because both animal studies and human studies have demonstrated changes into the pancreas and in pancreatic functioning after exposure to tobacco smoke.

6. INTERACTION OF CP WITH VARIOUS OTHER ENVIRONMENTAL FACTORS

A review article presented by Morinville and Whitcomb [32] has indicated that some environmental factors can cause injury to the pancreas. The different environmental factors, metabolic and oxidative stress can lead to pancreatic injury via premature activation of zymogens within the pancreas. Certain environmental factors such as infections by bacteria, viruses and parasites, medications such as aminosalicylic acid derivatives, anticonvulsants,

antineoplastics, antimicrobials, estrogens, diuretics and immunomodulators etc.; toxins such as alcohol, organophosphates, scorpion bite toxins, methylene chloride; or trauma including blunt trauma (motorcycle accidents etc.) and child abuse; and metabolic factors such as biochemical disturbance including hyperglycemia, hypertriglyceridemia, inborn errors of metabolism, diabetic ketoacidosis and uremia can cause damage to the pancreas to an irreparable extent. However, the reports available indicate that environmental factors alone do not account for a significant percentage of acute pancreatitis episodes [32]. In addition, other factors such as obesity, diets containing high animal protein, fat and antioxidant deficiencies etc. may contribute to pancreatitis. The diets containing highly processed or red meat or deficient in fruits and vegetables or phytochemicals (lycopene and flavonols) may also act as risk factors [33].

7. ASSOCIATION OF GENETIC FACTORS IN CP

The sequencing of numerous genes has suggested that the genetic polymorphisms may act as predisposing risk factors for pancreatitis disorders. It has been observed that not all individuals exposed to a known environmental factor develop pancreatitis, and also that not all individuals possessing a genetic mutation associated with pancreatitis express it phenotypically. It suggests involvement of a complex gene-gene and gene-environmental interactions [32]. The mutations in the genes such as *PRSS1* with chromosomal location at 7q35 (which encodes cationic trypsinogen) with mutations such as R122H, N29I, A16V, K23R, E79K etc.; *SPINK1* located at 5q32 (which encodes serine protease inhibitor Kazal type 1) contain mutations N34S, P55S, -253C alleles etc. and cystic fibrosis transmembrane conductance regulator *(CFTR)* having chromosomal location at 7q31.2 (which encodes cystic fibrosis transmembrane conductance regulator) with multiple mutations are associated with chronic pancreatitis. The mutations in *PRSS1* and *CFTR* manifest within the acinar cells and ductular system, respectively. *SPINK1* mutations appear to have a disease-modifying effect (eg, it has a synergistic effect in the presence of *CFTR*) [32, 33]. Mutations causing loss of function in other genes such as chymotrypsinogen C (*CTRC*) and calcium-sensing receptor *(CASR)* are also reported to contribute in chronic pancreatitis [34]. The detailed roles of these factors are described in a couple of recently published reviews [35, 36].

8. STONE FORMATION, DUCT OBSTRUCTION AND NECROSIS-FIBROSIS IN CP

The stone formation and duct obstruction due to excessive alcohol consumption have been found to increase the lithogenicity of pancreatic juice which finally culminates into stone formation. Upon chronic contact with the stones, the epithelial cells of pancreatic duct produce ulceration and scarring. The chronic obstruction of the acini leads to atrophy and fibrosis [37]. The underlying cellular mechanisms of pancreatic fibrogenesis involve pancreatic stellate cells. The alcohol and oxidative stress are the key players which stimulate the stellate cells which upon activation migrate to the periacinar areas and deposit collagen and fibronectin. In addition, some specific cytokines emitted during the inflammatory phase of acute pancreatitis have been shown to stimulate the pancreatic stellate cells [38]. Also, the transforming growth factor beta 1 has been shown to mediate onset of pancreatic fibrosis and its pathogenesis [37,38].

9. CONCLUSION

Among the numerous environmental factors reported so far playing crucial role in influencing the health of humans, consumption of alcohol and smoking has been found not only to generate toxic free radicals but also adversely influence the oxidative pathway and transcription processes into pancreatic cells resulting into further aggravation of CP. These factors may exert synergistic effect with those of genetic factors making the disease conditions even worse as they interact with the genetic components of individuals.

ACKNOWLEDGEMENTS

Authors are grateful to Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow-India for providing infrastructural facilities. SS is thankful to DST for financial support in the form of a INSPIRE fellowship.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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