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Clinical and experimental aspects of free radicals in chronic pancreatitis

Koji Ochi, Naoki Matsumura, Takaaki Mizushima, Fumihiro Mitsunobu*, Yosiro Tanizaki*

Department of Laboratory Medicine,
Okayama University Medical School
*Misasa Medical Branch,
Okayama University Medical School

Summary : Free radicals have been suspected to play an important role in the pathogenicity of chronic pancreatitis. We reviewed studies on free radicals in chronic pancreatitis in both clinical and experimental aspects. Many clinical studies have provided circumstantial evidence for the close relation between free radicals and chronic pancreatitis. However, few experimental studies in animals on relation between free radicals and chronic pancreatitis have been reported, because adequate experimental models for elucidating a pathological role of free radicals in chronic pancreatitis have not been established. The research concerning the role of free radicals in chronic pancreatitis is expected to improve our understanding the pathological mechanisms of the disease.

Key Word : chronic pancreatitis, free radicals

Introduction

Free radicals have been suspected to play a role in the pathogenicity of chronic pancreatitis[1]. The research concerning the role of free radicals in chronic pancreatitis is expected to improve our understanding the pathological mechanisms of the disease. In this paper, we reviewed studies on free radicals and chronic pancreatitis in both clinical and experimental aspects.

Clinical aspects

Basso et al[2]. found increased malonyl dialdehyde (MDA) serum concentrations in patients of chronic pancreatitis. MDA is known to be a marker of lipid peroxidation[3]. Schoenberg et al.[4] also reported, in the pancreatic tissue of chronic pancreatitis that MDA and conjugated dienes levels were significantly higher, as compared with normal pancreatic tissue obtained from organ donors. Conjugated diene is reported to be a more sensitive marker of lipid peroxidation[4].

Guyan et al[5]. demonstrated that patients with chronic pancreatitis exhibit high-lipid-peroxidation markers (9 cis, 11 trans isomer of linoleic acid, conjugated dienes and ultra-violet fluorescence products) in the duodenal juice and serum. These data suggest that ongoing lipid peroxidation within the pancreas of chronic pancreatitis is possibly induced by enhanced generation of oxygen radicals[4].

In addition, dietary and biochemical studies revealed that patients with chronic pancreatitis are often deficient in several antioxidants such as vitamin C, and E, riboflavin, and selenium[6-8].

Based on above-mentioned data, supplement of antioxidants has applied to patients with chronic pancreatitis[9, 10]. Uden et al[11, 12]. demonstrated that treatment of selenium, β-carotene, vitamin C, vitamin E and methionine was effective in reduction of pain of patients with chronic pancreatitis in a 20-week, double-blind, placebo-controlled, switch-over trial.

Braganza[13] hypothesized that exposure of xenobiotics induced chytochrome P450 monooxygenase. in pathogenesis of idiopathic chronic pancreatitis, Xenobiotics stand for toxicity from exogenous factors, including petrolic products in fumes[14-16], smoke from cigarette[17], foods (cassava in some tropical areas[16]), and drugs[18, 19].

Cytochrome P4502E1 (CYP2E1) is ethanol inducible form of cytochrome P450. This enzyme is a major pathway of ethanol metabolism in heavy drinkers[20]. Free radicals are formed in metabolism of ethanol via CYP2E1. In tropical chronic pancreatitis, Chaloner et al[21]. reported evidence for induction of cytochrome P-450I by analyzing theophylline kinetics. Furthermore, Foster et al[19]. reported that in material from patients with chronic pancreatitis, cytochrome P-450 enzyme levels were greater in both the liver and the pancreas than those seen in controls. The pathway of metabolism via cytochrome P-450 leads to production of free radicals, which cause tissue damage through peroxidation of cell membranes.

Clinical studies have provided circumstantial evidence that free radicals might be associated with pathogenicity of chronic pancreatitis.

Experimental aspects

Few experimental studies in animals on relation between free radicals and chronic pancreatitis have been reported. Iimuro et al[22]. reported that free radicals are formed in the pancreas during the early phases of chronic alcohol intake in rats before the development of overt pathology. Norton et al[23]. also demonstrated that chronic ethanol administration leads to oxidative stress in the rat pancreas in the absence of histologic evidence of inflammation or necrosis.

As for CYP in animal models, Norton et al[24]. demonstrated that CYP2E1 is present in the pancreas of rats and is induced in response to chronic ethanol administration. Rutishauser et al[25]. studied long-term effects of CYP inducer on pancreatobiliary secretion and pancreatic histology in hamsters. CYP inducer results in pancreatic hypersecretion of protein and biliary hypersecretion of lipid peroxidation products, although it does not cause fibrosis or the ductal abnormalities in the pancreas. Further experimental studies on association between CYP and chronic pancreatitis need to be done.

Acetaldehyde, which is ethanol's first metabolite, is also another source of free

radicals. According to studies in rats by Altomare et al[26], acetaldehyde might be responsible for oxidative stress that occurs in pancreatic cells after ethanol ingestion in rats.

Conclusion

Although circumstantial evidence supports that free radicals might be play a important role in pathogenesis of chronic pancreatitis, adequate experimental models for elucidating the pathological role of free radicals are expected to be established.

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臨床的および実験的側面からみた慢性膵炎とフリーラジカル

越智浩二，松村直樹，水島孝明，光延文裕*，
谷崎勝朗*

岡山大学臨床検査医学
*岡山大学三朝分院

慢性膵炎の発症機序は不明な点が多いが、フリーラジカルがそれに関与することが示唆する報告も多い。しかし，その直接的な証明はなされていない。慢性膵炎の病態にフリーラジカルがどのように関与するかを理解することは慢性膵炎の発症機序の解明の一助になると考え，臨床的および実験的側面から慢性膵炎とフリーラジカルの関係を概説した。

検索用語：慢性膵炎，フリーラジカル