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ROUND TABLE

Action of Antiproteases on the Inflammatory Response in Acute Pancreatitis

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Summary

The spectrum of acute pancreatitis ranges from mild edematous disease to a severe necrotizing process which is usually accompanied by local or systemic complications and even mortality. Early deaths (within the first week) due to severe acute pancreatitis are generally caused by massive inflammatory responses which result in multiple organ failure. Although the exact mechanisms which trigger the inflammatory and necrotizing processes are not completely understood, it is generally accepted that autodigestion and activated leukocytes play important roles in the pathogenesis of acute pancreatitis. Proinflammatory cytokines are associated with systemic inflammatory response syndrome and multiple organ failure syndrome in acute pancreatitis. A compensatory anti-inflammatory response occurs in parallel with systemic inflammatory response syndrome. Trypsin secreted by the pancreatic acinar cells activates protease-activated receptor-2 which can result in the production of cytokines. Protease inhibitors such as aprotinin, gabexate mesilate, nafamostat mesilate, ulinastatin, etc. can inhibit the various enzymes and inflammatory response in experimental and clinical studies. Thus, protease inhibitors have been considered as a potential treatment to inhibit the pancreatic inflammation in acute pancreatitis. The beneficial effects of antiproteases on experimental severe acute pancreatitis may be, in part, due to the modulation of inflammatory cytokine responses. The effect of protease inhibitors on the inflammatory response in human acute pancreatitis deserves further study.

Introduction

Acute pancreatitis ranges from a mild, self-limiting disease to a life-threatening condition with multiple organ failure. The mortality rate of acute necrotizing pancreatitis (about 25% of acute pancreatitis) has been reported to be between 10% and 30% [1]. Effective therapies for acute pancreatitis are still limited. The currently accepted pathogenic mechanism of acute pancreatitis includes autodigestion and acute inflammation of the pancreas by the activation of proteases of the pancreas and acute inflammatory cells [2, 3]. Thus, protease inhibitors have been considered to be a potential treatment to inhibit the pancreatic inflammation in acute pancreatitis. Protease inhibitors have been shown to be effective in experimental acute pancreatitis [4, 5, 6, 7, 8, 9, 10]. However, the efficacy of antiproteases on acute pancreatitis in clinical human trials is still controversial [11, 12, 13, 14, 15]. The prophylaxis of endoscopic retrograde cholangiopancreatography (ERCP)-related pancreatitis by administering protease inhibitors is still being debated [16, 17, 18]. In recent years, protease inhibitors were shown to have anti-inflammatory effects

in *in vitro* and *in vivo* studies. The content of this paper will focus on the action of antiproteases on the inflammatory response in acute pancreatitis.

The Role of Proteases and Inflammatory Response in Acute Pancreatitis

Although the exact mechanisms which trigger the inflammatory and necrotizing processes are not completely understood, it is generally accepted that autodigestion and acute inflammatory response of the pancreas by the activation of proteases of the pancreas and acute inflammatory cells play important roles in the pathogenesis of acute pancreatitis [2, 3, 19]. The premature activation of pancreatic zymogens may be the first step leading to pancreatic autodigestion and inducing other pathways leading to pancreatic injury. Trypsin produced in and secreted by the pancreatic acinar cells activates protease-activated receptor-2 (PAR-2), which is present in high concentrations on the luminal surfaces of pancreatic acinar cells and duct cells [20]. The results of PAR-2 activation are the production of cytokines and the regulation of the exocrine function by means of a negative feedback loop [20].

In cerulein-induced pancreatitis, large amounts of trypsinogen are present in the interstitium and drain by means of the portal and lymphatic circulation [21]. The activation of this extracellular trypsinogen by enterokinase infusion induces hemorrhagic necrosis in a setting of mild edematous pancreatitis. These results have demonstrated that interstitial trypsinogen activation may be the central event in the progression of mild pancreatitis to fulminant necrotizing pancreatitis [21]. Pancreatic proteases were also suggested to be one of the critical factors leading to the development of pancreatitis associated with lung injury [9].

In addition to pancreatic proteases, activated leukocytes play an important role in the pathogenesis of acute pancreatitis [19, 22]. The serum levels of major proinflammatory cytokines, including tumor necrosis factor alpha (TNF-alpha), interleukin-1 beta (IL-1beta), interleukin-6 (IL-6), interleukin-8 (IL-8), and platelet activation factor, have been reported to be significantly higher in severe acute pancreatitis as compared to mild pancreatitis [2, 21, 23, 24]. Proinflammatory cytokines are associated with systemic inflammatory response syndrome (SIRS) in acute pancreatitis [25]. A compensatory anti-inflammatory response occurs in parallel with SIRS. Anti-inflammatory cytokines including interleukin-10 (IL-10), IL-1beta receptor antagonist, and soluble interleukin-2 receptor are also significantly higher in patients with severe acute pancreatitis [26, 27]. Using endoscopic retrograde cholangiopancreatography (ERCP)-induced pancreatitis as a model, a significant increase in proinflammatory and anti-inflammatory cytokines was confirmed in the early stages of post-ERCP pancreatitis [28]. An imbalance between proinflammatory and anti-inflammatory response leads to localized tissue destruction and distant organ damage [21]. Early deaths (within the first week) due to severe acute pancreatitis are generally caused by massive inflammatory responses which result in multiple organ failure.

The recognition of the early involvement of inflammatory cytokines in acute pancreatitis and cytokines as the mediators of the acute phase protein response has generated significant research interest in the utility of using cytokine levels as early prognostic indicators. Although no single serum test is optimal, current evidence concluded that serum IL-6 level at admission has the best sensitivity and specificity for the early assessment of the severity of acute pancreatitis among the proinflammatory and anti-inflammatory cytokines [29, 30].

Action of Antiproteases on the Inflammatory Response

A variety of naturally occurring protease inhibitors is present in the circulation and plays an important role in limiting tissue damage. The major plasma protease inhibitors include alpha 2-macroglobulin, alpha 1-antitrypsin, antichymotrypsin, serum trypsin inhibitor and C1 esterase inhibitor [31]. Their action is, however, insufficient when the

protease activity increases such as occurs in acute pancreatitis [31]. Decreased amounts of circulating protease inhibitors and the delayed clearance of serum protease-inhibitor complexes by the reticuloendothelial system have been associated with the more severe forms of pancreatitis [32].

Aprotinin, also known as bovine pancreatic trypsin inhibitor, is the first antiprotease drug to be used in clinical trials for acute pancreatitis. In the 1960s, aprotinin was widely used for the treatment of patients with acute pancreatitis. A high dose of aprotinin was reported to reduce the mortality rate in biliary and idiopathic acute pancreatitis [33]. However these findings were not confirmed in subsequent trials [34, 35]. In the 1970-1980s, new protease inhibitors including gabexate mesilate, nafamostat mesilate and ulinastatin (urinastatin) were developed in Japan. These compounds have a broad spectrum of inhibitory activity against various enzymes, including trypsin, chymotrypsin, plasmin, kallikrein, thrombin, r subunit of complement 1, s subunit of complement 1, and phospholipase A_2 [36]. Both gabexate and nafamostat are synthetic protease inhibitors of low molecular weight (417 and 540 Dalton). Ulinastatin is an intrinsic trypsin inhibitor purified from human urine which inhibits several enzymes (neutrophil elastase, trypsin, alpha-chymotrypsin, lipase, amylase, and carboxylase). Unlike aprotinin and ulinastatin, nafamostat and gabexate inhibited alpha 2-macroglobulin bound trypsin and free trypsin to the same extent [37]. In *in vitro* experiments, nafamostat inhibited the pancreatic protease activity 10 to 100 times more potently than gabexate [38]. Protease inhibitors have multiple functions, but not all of them are mediated by enzyme inhibition. They have complex effects on many homeostatic functions including platelet function, coagulation and inflammation [39].

Aprotinin has been reported to have anti-inflammatory properties in many basic and clinical studies. Aprotinin was shown to inhibit IL-6 secretion through a blockade of protease-activated receptor-1 (PAR-1) on platelets *in vitro* and *in vivo* [40]. Aprotinin was demonstrated to reduce IL-8 production and lung neutrophil accumulation after cardiopulmonary bypass [41]. Aprotinin has been used clinically to reduce transfusion requirements and the inflammatory response to cardiopulmonary bypass [41, 42]. Aprotinin can improve the hemodynamic effects of septic shock by blocking the formation of kinins [43].

Gabexate mesilate was shown to inhibit lipopolysaccharide-induced TNF-alpha production in human monocytes by inhibiting activation of both nuclear factor-kappaB and activator protein-1 [44]. Gabexate can attenuate the ischemia-reperfusion-induced acute lung injury in dogs by ameliorating the degree of change of alveolar membrane permeability, neutrophil aggregation, and activation [45]. Administration of gabexate mesilate before an esophagectomy has been shown to suppress the increase of serum IL-6 levels and reduce SIRS through the suppression of TNF-alpha production by lipopolysaccharide stimulated monocytes [46].

Nafamostat mesilate inhibits the production of IL-6 and IL-8 in human monocytes stimulated with lipopolysaccharide [47]. Nafamostat treatment has protective effects against lipopolysaccharide-induced hepatotoxicity through the downregulation of TLR4 and CD14 in the liver, which decreased TNF-alpha, IL-1beta, and IFN-gamma production in the liver [48]. Nafamostat mesilate downregulated the expression of TNF-alpha, IL-1beta, IL-6, inducible NO synthase, CD86 and nuclear factor-kappaB activation, but enhanced the expression of IL-12 and IL-10 in *Dermatophagoides pteronyssinus*-stimulated alveolar macrophages [49]. Nafamostat and gabexate exerting a therapeutic effect in allergen-induced airway inflammation was a result not only of their inhibitory action in the early phase of mast cell activation, but also of immunoregulatory function in the late phase of allergic inflammation [49].

Ulinastatin inhibited the lipopolysaccharide-stimulated activity of polymorphonuclear leukocytes and the production of IL-8 in

vascular endothelial cells [50]. The perioperative administration of ulinastatin was reported to decrease the production of serum IL-6 and C-reactive protein in patients with hepatic resection [51]. Like aprotinin, ulinastatin treatment attenuated the elevation of IL-6 and IL-8 release immediately after cardiopulmonary bypass [52]. The administration of ulinastatin attenuated the postoperative increases in plasma concentrations of TNF, IL-6, and C-reactive protein in rat recipients of small bowel transplantations [53].

Action of Antiproteases on the Inflammatory Response in Acute Pancreatitis

Protease inhibitors have been shown to be effective in experimental acute pancreatitis. The administration of gabexate mesilate has significantly reduced serum amylase and trypsinogen concentrations and the extent of acinar cell vacuolization in the pancreas in cerulein-induced acute pancreatitis in rats [5]. Gabexate mesilate has been shown to decrease serum lipase levels and reduce the severity of the pancreatic pathology and lung edema [8]. It has also been found to improve microcirculation in the pancreas by increasing flow velocity and reducing leukocyte sticking [8]. Nafamostat reduced the mortality of rats in experimental acute pancreatitis in a dose-dependent manner [38].

There have been few studies investigating the effects of protease inhibitors on the inflammatory response in acute pancreatitis. We used the model of retrograde bile salt-induced necrotizing pancreatitis in rats to evaluate the effects of gabexate mesilate on the serum levels of proinflammatory and anti-inflammatory cytokines [10]. We demonstrated that gabexate significantly reduced the serum levels of TNF-alpha and IL-6 (proinflammatory cytokines) and increased the serum levels of IL-10 (anti-inflammatory cytokine) at 5 hours after the induction of acute pancreatitis. The severity of pancreatic histopathology, the reduction of mean arterial pressure, the volume of ascites and pancreatic wet weight/body weight ratios were also significantly improved by the administration of gabexate. Furthermore, 24-hour mortality was significantly reduced by the use of gabexate. The results indicated that the beneficial effects of gabexate on severe acute pancreatitis may be, in part, due to the modulation of inflammatory cytokine responses. Pezzilli *et al*. [54] reported that gabexate mesilate reduced the serum levels of C-reactive protein in patients with severe acute pancreatitis.

Mikami *et al*. [55] demonstrated that the levels of serum IL-6 and the mortality rate were significantly reduced after continuous regional arterial infusion or intravenous infusion of nafamostat in experimental severe acute pancreatitis as compared to control rats. Intra-arterial infusion of nafamostat significantly decreased serum IL-6 concentrations as compared to the intravenous infusion of nafamostat. Maeda *et al*. [56] also showed that nafamostat reduced IL-6 and interferon-gamma production and alleviated distant organ injury in rat cerulein-induced acute pancreatitis. These results indicated that the beneficial effects of nafamostat on the inflammatory response of acute pancreatitis may be explained not only by its inhibitory action on pancreatic enzymes but also by its modification of the complement system, coagulation and fibrinolytic system [55].

Ulinastatin administration contributed to the recovery of the immune function by improving proliferative responses and the cytokine release of splenocytes from rats with severe acute pancreatitis [57]. The release of IL-2, IL-10 and interferon-gamma was significantly decreased in the splenocytes from rats with pancreatitis as compared to those from sham operation and control groups. In contrast, treatment with ulinastatin significantly increased the proliferative as well as the cytokine-releasing capacity of the splenocytes in rats with pancreatitis [57].

Shi *et al*. [58] reported that pretreatment with protease inhibitors (aprotinin, pefabloc, trypsin inhibitor) significantly prevented the elevation of plasma IL-10 and pancreatic and pulmonary levels of myeloperoxidase in taurodeoxycholate-induced acute pancreatitis

in rats. However, plasma concentrations of IL-6 did not significantly decrease following pretreatment with protease inhibitors. The immunomodulatory effect of aprotinin in acute pancreatitis needs further investigation.
The topic "Antiproteases in the Treatment of Acute Pancreatitis" is discussed by Drs. Kitagawa and Hayakawa in another contribution to this Round Table [59].
In conclusion, protease inhibitors can inhibit the various enzymes and inflammatory response in experimental and clinical studies. Further large scale studies are required to clarify the role of protease inhibitors in the treatment of human acute pancreatitis. The timing, dosage and route of the administration of protease inhibitors may be closely related to the success of the treatment.

Keywords Aprotinin; Cytokines; Gabexate; nafamostat; Pancreatitis; Protease Inhibitors; urinastatin

Conflict of interest The authors have no potential conflicts of interest

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