Therapy for acute pancreatitis with platelet-activating factor receptor antagonists

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Abstract

Acute pancreatitis (AP) causes release of platelet-activating factor (PAF), which induces systemic effects that contribute to circulatory disturbances and multiple organ failure. PAF is a cell surface secretion of bioactive lipid, which could produce physiological and pathological effects by binding to its cell surface receptor called platelet-activating factor receptor (PAF-R). Studies showed that PAF participates in the occurrence and development of AP and administration of platelet-activating factor receptor antagonists (PAF-RAs) could significantly reduce local and systemic events after AP. PAF has also been implicated as a key mediator in the progression of severe AP, which can lead to complications and unacceptably high mortality rates. Several classes of PAF-RA show significant local and systemic effects on reducing inflammatory changes. As a preventive treatment, PAF-RA could block a series of PAF-mediated inflammatory injury and thus improve the prognosis of AP. This review introduces the important role of PAF-RA in the treatment of AP.

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INTRODUCTION

Acute pancreatitis (AP) is a kind of inflammatory disease that can develop into severe acute pancreatitis (SAP). SAP refers to AP associated with organ failure and/or local complications such as necrosis, pseudocyst or abscess[1]. The overall mortality of SAP has decreased in recent years to around 15%-20%. A variety of inflammatory mediators play a crucial role in AP. Synthesis of platelet-activating factor (PAF) is sensitive to biologically active mediators seen in many inflammatory processes, which could produce physiological and pathological effects by binding to its cell surface receptor called platelet-activating factor receptor (PAF-RA). PAF significantly potentiates pancreatic tissue damage and increases serum amylase and lipase levels, causes scattered haemorrhages and may serve as a primary mediator of inflammation. Many identified PAF-RAs exhibit varied structures, and interact with the PAF-RA in different ways. It has been postulated that these differences could be due to conformation changes in the receptor protein itself, by G-protein coupling or changes on the cell membrane. Several classes of PAF-RA show significant local and systemic effects on reducing inflammatory changes. PAF-RAs used as a preventive treatment can block a series of inflammatory injury caused by PAF, thereby improving AP prognosis. Research on such as a potential therapy has helped to elucidate the role of PAF in AP. Progress in treatment of AP with PAF-RAs is summarized below.

BIOLOGICAL ACTIVITY OF PAF

PAF released by various cells including endothelial,
RELATIONS BETWEEN PAF AND AP

In the development of AP, the pancreas and its surrounding tissues secrete digestive enzymes to digest their own components, causing acute inflammation. AP is divided into acute edema and acute hemorrhagic pancreatitis according to its histology and clinical manifestations. Acute hemorrhagic pancreatitis is also called as severe acute pancreatitis (SAP). Studies found that SAP is closely related to neutrophil excessive activation and cytokines-mediated cascade of systemic inflammatory response syndrome (SIRS) [14]. The considerable release of PAF and direct or indirect systemic response facilitates formation of SIRS and causes circulation dysfunction, resulting in multiple organ dysfunction syndrome (MODS) [26]. In vitro experiments showed that PAF can stimulate a large number of trypsin release [22], while in vivo experiments showed that PAF could induce and aggravate AP through injection into pancreatic arteries [19]. PAF is increased in pancreas, ascites, immune complexes, cerulein and liver induced by cows iodine acid salt.

PAF-RA

PAF-RA can successfully repress the effect mediated by PAF in AP. PAF-RAs are divided into five categories according to their chemical structure and properties: nitrogen heterocyclic compounds (such as WEB2086, WEB2170, etc.), PAF analogues (such as CV3988, SDZ63072, etc.), dihydropryridines (such as PCV4233, PVA4248, etc.), natural medicines (such as BN52021, Kadsurenone, etc.), and others (such as 52770 RP, TCV309, etc.).

PAF-RAs exert their effects by inhibiting the activity of neutrophils and depressing pulp peroxidase, competing targets with PAF and inhibiting the activity of PAF [14], inhibiting increasing PAF in AP, reducing vascular permeability and improving microcirculation of blood flow velocity, reducing plasma cytokines and inflammatory mediators, enzyme activity and the role of self-digestion of pancreatic tissue. At present, there are several compounds with obvious antagonism of PAF, their chemical codes are BN52021, WEB2170, TCV309, WEB2086 and BB882 (lexipafant), which can reduce the inflammatory response and significantly affect local and systemic status in AP.

WEB2170

WEB2170 is a nitrogen heterocyclic compound. Nitrogen binds to the receptor through the hydrogen bond, facilitating the activity of PAF-RAs, thus reducing the NO production by liver cells in pancreatitis. PAF is likely to be the main contributing factor for endotoxin effect. WEB2170 can significantly reduce intestinal necrosis mediated by lipopolysaccharide (LPS) [19] and TCV2170 does not affect the TNF levels [20]. WEB2170 can reduce vascular permeability and infiltration of neutrophils and macrophages.

WEB2086 (Apafant) can inhibit angiogenesis in atherosclerotic plaque [27]. Oral WEB2086 can elevate low blood pressure induced by PAF.

TCV309

TCV309 is an important PAF antagonist, which can inhibit the biological activity of PAF both in vivo and in vitro. Oral TCV309 can significantly reduce the concentration of neutrophil chemokine, but does not lead to significant changes in amylase [21]. TCV309 has more advantages than PAF analogues in avoiding hemolysis and vascular injury when the inhibitory activity of PAF binding to its receptor is higher. In addition to injection, TCV309 can be taken orally.

Lexipafant

Lexipafant has entered clinical trials. Lexipafant is a molecule specifically designed to bind to PAF-R [28] and an imidazole derivative of heterocyclic sp2 nitrogen compounds and has been shown to be considerably more potent than other PAF receptor antagonists with a much greater affinity than PAF itself for its binding to human platelet PAF-R.

Lexipafant can prevent liver ischemia/reperfusion injury [19] and reduce the severity of inflammatory response to liver injury induced by bile duct ligation in rats [29], leading to impairment of AP endothelial barrier function, leukocyte accumulation and IL-1 level in the pancreas [21]. Treatment of pancreatitis with lexipafant reduces the severity of pancreatitis-associated intestinal dysfunction, systemic IL-1 concentration and local leukocyte recruitment [29].

Animal experiments showed that lexipafant improves inflammation of AP [23]. Lexipafant treatment can improve acute necrotizing pancreatitis caused by bacteria shift [24]. In clinical trials, it was shown that lexipafant could reduce the morbidity and mortality of acute pancreatitis, but may not reduce the morbidity and mortality of severe acute pancreatitis. Further investigation is expected about the effect of lexipafant [25].

Vincent et al. [28] also claimed that there is no difference in survival, hemodynamics, respiratory function and MOF score between treatment with lexipafant and...
placebo. Johnson et al. used lexipafant intervention therapy to study 290 cases of AP patients and found that the organ failure scores of AP are significant reduced, suggesting that lexipafant cannot change the SAP organ failure process in patients. Further study is needed to observe the effect of lexipafant.

**BN52021**

BN52021 is a terpenoid extracted from Ginkgo biloba leaves. In 1988, Jancar found that treatment of AP in immune-complex-induced mouse model with BN52021 could significantly relieve edema of pancreas\(^{(29)}\). Since BN52021 competitively inhibits the binding to PAF and its platelet receptor, PAF cannot activate phospholipase C through G-protein transduction, adenosine cyclase and tyrosine protein kinase, thereby blocking the PAF receptor signal transduction and the biological effects of PAF. BN52021 exerts its biological effects by competitively inhibiting the expression of PAF and PAF-R rather than by decreasing the expression of PAF receptor in pancreatic tissues\(^{(29)}\). BN52021 is a non-competitive GABA receptor antagonist\(^{(30)}\) and inhibits gene transcription of adrenal peripheral benzodiazepine receptor and synthesis of steroids\(^{(31)}\).

BN52021, a most promising PAF-R antagonist, can effectively inhibit PAF-induced neutrophil chemotaxis, adhesion, aggregation and other inflammatory factors, thus reducing inflammation injury. BN52021 significantly reduces the mortality of AP, prolongs the average survival time, maintains a lower serum amylase activity, reduces pancreatic injury as well as Ca\(^{2+}\) content and malondialdehyde (MDA) level and superoxide dismutase (SOD) activity in pancreatic tissue. Bedirli et al.\(^{(32)}\) reported that BN52021 can inhibit intestinal bacterial shift to the pancreas. BN52021 protects the stability of macrophage membrane against lysis\(^{(33)}\). PAF may play an important role in liver injury and regeneration. Ginkgolide B attenuates liver damage, thus improving liver function following acetaminophen intoxication\(^{(34)}\).

To sum up, BN52021 has a wide range of pharmacological effects. Currently, pharmacology of BN52021 mainly focuses on the PAF-R antagonists. Whether other mechanisms of BN52021 exert effects through different pathways is worthy of further study.

**CONCLUSION**

Progress has been made in research about the therapy for AP, especially for SAP, with PAF-RA. However, there is still a long way to go. Further study is needed to confirm the encouraging results obtained from animal experiments and find other key inflammatory mediators in the pathogenesis of AP.

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