

Research status of the mechanism and treatment for acute pancreatitis complicated with hepatic injury[☆]

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Abstract

Acute pancreatitis(AP) is characterized by its sudden onset and rapid progression and is often complicated by liver injury. AP-induced liver injury may develop into hepatic failure and even result in death. Thus, it is of importance to protect liver function and block injury-related pathways. In the pathogenesis of liver injury in AP, inflammatory cytokines, nuclear factor-kappa B(NF- κ B) and oxygen free radicals play important roles. The complexity of the mechanism underlying the development of liver injury exerts, to some extent, a contribution to the difficulties in the treatment of this disease. Currently, the drugs used to treat the disease include L-arginine (L-Arg), calcium ion antagonists, somatostatin and a variety of inflammatory mediator inhibitors. Additionally, some traditional Chinese medicines such as tripterygium, wilfordii, rhubarb and salvia miltiorrhizae may also have some effects. In this article, the pathogenesis of liver injury in AP and its therapy are reviewed.

Key words: acute pancreatitis(AP); hepatic injury; mechanism; treatment

INTRODUCTION

Acute pancreatitis(AP) requires emergency treatment as it rapidly develops in the common acute abdomen can induce the injury of many organs^[1,2]. AP complicated with hepatic injury will not only aggravate the condition of AP, but also directly influence its prognosis, often resulting liver function failure and can cause death. The liver is one of the organs found in the human body with an animate substance metabolism. When AP develops, it often accompanies hepatic injury, which

becomes an important factor resulting in further aggravation of AP^[3-5]. The permeability of cellular membrane will increase when hepatic cells are injured, causing a large amount of ALT, AST and LDH to infiltrate into the blood. The function of the liver in detoxication and cleaning toxic substances and bioactive compounds will decrease, which will cause the causative agent to enter general circulation through the liver barrier, and establish a foundation for the injury of tissues and organs all over the body. Therefore, it is very important to protect the function of liver and block the cause of its damage. At present, the pathogenesis and treatment for hepatic injury induced by AP has become a hot spot of research, which will be the subject of this review.

Mechanism

The function of AP is influenced by inflammatory cytokines, endotoxin, nuclear factor- κ B(NF- κ B) and oxygen free radical causing AP to be complicated with hepatic injury.

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Inflammatory cytokines

Cytokines are generated by leucocytes of all involved tissues and endothelial systems after being stimulated by activated pancreatin or endotoxin, they are then activated by themselves promoting the generation of other factors, to cause a linkage and magnification effect. This will cause massive cellular necrosis of pancreas and induce multiple organ dysfunction syndrome (MODS) and multiple organ failure(MOF), finally leading to death. Researches in recent years have shown that IL-8, IL-6 and TNF- α are important inflammatory cytokines during AP onset. These factors and other mediators of inflammation constitute the complicated pathomechanism for AP, and they can be used reliably to predict earlier period SAP^[6].

① TNF- α

In SAP, mononuclear phagocytic system is activated by mediators of inflammations and release massive cytokines. In these cytokines and mediators of inflammation, TNF- α plays a key function. Chen *et al.*^[7] found that, after researching the SAP rat model, the expression of TNF- α mRNA in hepatic tissue increased, and its extent was positively correlated with the severity of the pancreatitis. This suggested that TNF- α was correlated with the extent of hepatic injury in SAP. Gloor *et al.*^[8] found that TNF- α can injure the liver in the early period of AP, from which SAP onset to MOF develops. TNF- α can mediate hepatic injury by the following ways:(1)the toxicity of TNF- α directly causes sinus hepatic endotheliocyte swelling, resulting in hepatic sinusoid microcirculation disturbance;(2)it can stimulate neutrophilic granulocyte to express CR1 and CR3, activate complement system;(3)causes a stimulation of neutrophilic granulocyte to generate an active oxygen medium such as oxygen free radical, and further stimulates Kupffer cells to produce perhyride and induce the release of cytokines such as IL-1,IL-6 and PGE₂; (4) induce the expression of adhesion molecule(ICAM) in endotheliocyte and leukomonocyte, and hyper-express ICAM-1 which can cause migration and adhesion of neutrophilic granulocyte from lumen of blood vessel to tissue substance, finally resulting in hepatic injury;(5)mediate hepatic injury in coordination with other cytokines such as IL-1 and IL-6; (6)TNF- α can induce apoptosis of hepatic cells. Sindram *et al.*^[9] found that, in hepatic cells, Kupffer cell and platelet activate apoptosis path by releasing TNF- α conent.

② IL-6, IL-8, IL-10, IL-18

Gu CJ *et al.*^[10] demonstrated that IL-6 is one of the key mediums in AP complicated with hepatic injury. A significant increase of IL-6 can reflect AP severity, and often develop into hepatic lesion. It stimulate inflammatory reaction by regulating the function of

mature inflammatory cells. It can reinforce the effect of inflammatory cells on mediators of inflammation, and induce multisystem organ failure(MSOF). In AP, IL-6 is released before C-reactive protein(CRP), inducing hepatic cells to produce C-reactive protein^[9]. IL-6 can induce the generation of ICAM-1 which induces neutrophilic granulocyte to migrate to the liver and injure hepatic cells.

IL-8 also can mediate inflammation expanding from the pancreas to other organs such as the liver^[6]. IL-18 is a kind of new proinflammatory cytokine, and is similar significantly with IL-1 β in structure and function. It can induce the gene expression and synthesis of IL-1, TNF and other chemotatic factors^[11,12]. Therefore, IL-18 may play an important role in SAP complicated with hepatic injury. In addition, IL-10 has the function of down regulation for maintaining cytokine network balance, is a kind of self protection mechanism of the body^[13].

③ Platelet activating factor

In recent years, platelet activating factor(PAF) is considered as a critical mediator of inflammation during external secretion and topical and systemic inflammatory reaction syndrome(SIRS) in SAP. The main function of PAF is to activate the platelets, promoting them to adhere and collect, result in thrombosis, upregulate adhesion factor b2-integrin and change skeleton protein in the endothelial cell; this leads to capillary permeability increase and blood plasma effusion(a blood viscosity increase and blood flow rate decrease) participating in ischemia-reperfusion injury; stimulating the generation of other vasoactive substances, cytokines and mediators of inflammation.

Disequilibrium between PAF and vasoactive substances induces a vicious cycle, resulting in a series of chain reactions and magnification reactions, i.e. cascade effect, which will aggravate the injury of tissues and organs, leading to SIRS, which can further develop to multiple organ dysfunction syndrome(MODS) and(or) multiple organ failure(MOF), and in some cases death^[14,15]. PAF can result in a sudden increase of Ca²⁺ in hepatic cells, which is associated with hepatic cell injury and apoptosis. Therefore, the increase of PAF plays an important role for the onset and development of SAP.

Endotoxin

In SAP, when massive endotoxin(LPS) is increased in the portal vein, phagocytosis function of hepatic endothelial system is decreased, therefore systemic resistance to endotoxin is depressed, causing endotoxemia to develop. In SAP, endotoxin in blood plasma play an important promoting role during the development of multiple organ damage. Qiao *et al.*^[16] found that, endotoxin in the blood is originated mainly

from the intestinal tract. In early stages of SAP, immune suppression of intestinal function resulting in the transposition of bacteria and endotoxin. SAP is a kind of disease involving multiple organs in the body, and hepatic injury is just a topical manifestation. Mole *et al.*^[17] found that, in vitro livers in an SAP rat model (induced by intravenous injection of caerulein by being infused with endotoxin through portal vein as 'second invasion') the concentration of TNF- α , IL-1, IL-6 and activated production of neutrophilic granulocyte did not increase significantly. Therefore, it was demonstrated that the 'second invasion' induced by endotoxin is a systemic inflammatory reaction.

The mechanism of endotoxin induced hepatic injury might be: ① many kinds of endotoxin related receptor such as CD14, TLR4 exist at the surface of hepatic macrophage. In SAP, these receptors are activated by enterogenic endotoxin, then generate massive cytokines (mediators of inflammation and reactive oxygen free radical) thus the liver is damaged; ② endotoxin activate vasoactive substances, such as bradykinin, histamine, 5-hydroxytryptamine, to cause Vasomotor function disorder, which will lead to hepatic microcirculation disturbance; ③ endotoxin can induce membrane phospholipids degradation and produce free radicals by directly activating serum phosphatidase A₂ (PLA₂), mediate lipid peroxidation of hepatic cell and cause hepatic injury; ④ lipopolysaccharide binding protein (LBP) is a kind of acute phase reactive protein, which can bind with endotoxin to produce dissolubility LBP-endotoxin complex. This complex can bind with CD14 receptor in the surface of hepatic cell, directly causing hepatic injury; ⑤ endotoxin also can cause hepatic injury by interfering with the energy metabolism process of hepatic cell.

Nuclear factor - κ B (NF- κ B)

Nuclear factor is a kind of protein which can bind with B sequence in some gene promoter and enhancer regions. A recent study found that, NF- κ B is an important multipolar nuclear factor of cellular transcription, which can regulate the transcription of many cytokines relative with inflammation, such as TNF- α , IL-6, IL-10, IL-8 and intercellular adhesion molecule-1 (ICAM-1), which is associated with the process of immunization, inflammation, cell regeneration and apoptosis in the body.

In the silent cell, NF- κ B exists in cytoplasm in inactive form. When stimulated by pancreatin, inflammatory cytokines and endotoxin, NF- κ B is activated to cause nuclear transposition, and bind with κ B site to promote or enhance the transcription of these genes^[18,19]. In AP, pancreatic elastinase activate hepatic Kupffer cells by NF- κ B to express TNF- α which induce he-

patic injury. In the rat SAP model^[20] it was also found that when AP developed, the activation of NF- κ B in the liver may have stimulated the expression of TNF- α mRNA, and therefore participate in the development of hepatic injury. Other studies^[18,21,22] demonstrate that, NF- κ B can stimulate the transcription of multiple genes related to inflammation, thus participate in the tissue damage process induced by many causes. When AP complicated with hepatic injury develops, the activation of hepatic NF- κ B also plays an important role^[19]. Thus, NF- κ B transmit promoting signal activated abnormally by pancreatint to release cytokines, the latter will damage pancreatic cell, and extend inflammation from pancreas to multiple organ all over the body.

Oxygen free radical

Oxygen free radical (OFR) is a group containing oxygen with hyper chemical reaction activity, mainly including superoxide anion radical (O²⁻) and hydroxy radical. When they cause lipid oxidation, they can increase mucosal permeability to enhance phagocyte action, and produce more oxygen free radicals, thus inducing tissue and cell damage^[23]. Scott *et al.*^[24] showed that excessive oxygen free radicals in a pathologic state can cause tissue and cell damage. OFR participates in the pancreas edema process in AP, and may participate in the pancreas necrosis process. It is also known to mediate leukocyte and platelets and is activated by TNF- α in multiple organs, and releases lysosome, OFR and lipid mediators of inflammation. OFR can react with protein and enzyme, and result in protein denaturation and enzyme inactivation. The production LPO of OFR peroxidation can inactivate membrane-bound enzyme, damage the cellular membrane and increase vasoprmeability. The velocity of OFR production exceeds in vivo antioxygenic capability, or in vivo antioxygenic capability is exhausted greatly, which causes a series of oxidizing reactions resulting in lipid peroxidation of cells and organelle plasma membrane, directly damaging cells, destroying lysosome and mitochondrion in the hepatic cell, even leading to hepatic cell lytic necrosis, and hepatic intercellular lymphocyte infiltration. OFR can not be removed immediately. The change of inflammation mediators generate OFR and stimulate self secretion increase, which cause waterfall linkage magnification effect, resulting in an inflammatory reaction increase in all tissues, following capillary permeability increase and ischemia, this will aggravate SAP development.

Treatment

In pancreatic necrosis, multiple system organ failure frequently occurs in AP patients. Ideal therapy uses specific NF- κ B inhibitor (including antioxidant, NF- κ B dependent protein kinase inhibitor and I κ B kinase

inhibitor, corticosteroids, protein body inhibitor, antisense NF- κ B, pseudo heterozygote of transcription factor and IL-10) to block the NF- κ B over activated signal conduction pathway^[25]. But excessive or long term inhibition of NF- κ B activity can result in hepatic apoptosis, leading to the body's immune function decrease, and the possibility of bacterial infection increase. Therefore how to control therapy time and find an appropriate dose must be studied, allowing it to be safely used in clinic. In recent years, some traditional Chinese medicines(owing to a better efficacy with fewer adverse effects and lower cost) have become a research focus. The main research advancement in recent years is reviewed as follows.

Western medicine therapy

At present, the protection of L-arginine(L-Arg), Ca²⁺ antagonist, somatostatin and many mediators of inflammation(TNF- α , NF- κ B-inhibitors in SAP) complicated with hepatic injury has been noted increasingly. L-Arg and its in vivo metabolite NO can efficiently reduce the content of TNF- α and OFR in blood; Ca²⁺ antagonist can inhibit the generation and release of some inflammatory cytokines and oxygen free radicals. Zhang QH *et al.*^[26] found that somatostatin and somatropin can inhibit the excessive release of inflammation mediators and hyper expression of hepatic TNF- α mRNA transcription in SAP, reducing the secretion of pancreatin and its activity, all of these assist protection for the liver. Ueda *et al.*^[27] found that, when SAP complicate with hepatic injury, the level of vascular endothelial cell growth factor(VEGF) increase, and that giving recombinant VEGF to the SAP rat model can efficiently improve hepatic function and significantly inhibit hepatic apoptosis. In addition, continuous hemofiltration can remove massive mediators of inflammation in blood^[28], stabilize hemodynamics, increase oxygen uptake, improve microcirculation, efficiently protect the liver and prevent hepatic injury. Wang *et al.*^[29] after observing the effect of continuous venous hemofiltration on hemodynamics and oxygen metabolism in SAP pig model, found that CVVH stabilizes hemodynamics, and promote oxygen uptake of tissues.

Tiopronin has the function of reducing serum ALT, ASF can inhibit the formation of oxidation ester, regulate in vivo glutathione balance, increase mitochondrial energy, improve protein compensation and remove free radicals^[30], thus promote the recovery of hepatic function. The literature reported that hyperlipemia is one of factors inducing AP^[31], Tiopronin can inhibit triglyceride accumulation induced by chronic hepatic injury, and inhibit cholesterol increase, which is benefit to prevent AP provocation. The main therapeutic principles^[32] are: the patient should be treated by fasting, gastrointestinal

decompression, antiacid, Somatostatin, promoting blood flow, anti-infection and supportive treatment. Based on these measures, Tiopronin 0.2 g/d is administrated by intravenous drip infusion, 7 d is a course of treatment.

Ulinastatin is a kind of polypeptide extracted from human urine, which can inhibit the activity of many enzymes, remove OFR, and inhibit the release of inflammatory mediators. Intabashi *et al.*^[33] found that ulinastatin can inhibit the expression of hepatic ICAM-1 and CNC1, and reduce the concentration of TNF- α in blood plasma. Aosasa *et al.*^[34] proved that ulinastatin can inhibit NF- κ B activation and down regulate TNF- α expression. In addition, anti-inflammatory agent Aspirin(ASP) and calcium channel antagonist Tetrandrine(Tet) can significantly improve pancreatic and hepatic tissue and function damaged in AP^[35].

Tu Y *et al.*^[36] found that lipo prostaglandin E₁(PGE₁) can protect hepatic cells. ALT, AST and TBIL in treated groups were significant lower than that in control group after 7 d of treatment($P < 0.05$ for all). This suggested that it was significantly effective for acute pancreatitis induced hepatic damage. Our empirical study found that intravenous injected dexamethasone can reduce the damage of the pancreas, lung, kidney and liver in SAP rat, and prevent multiple organ damage in the SAP rat model^[6]. In addition, Ding TG *et al.*^[37] found that regional arterial infusion can relieve SAP complicated with hepatic injury.

Chinese traditional medicine therapy

The roles of traditional Chinese medicine in this field have been generally acknowledged. The research found that^[38] Triptolide is a purified preparation of Tripter-ygium wilfordii, which has a better anti-inflammatory and immunosuppressive action in inhibiting; NF- κ B activity, the generation of inflammatory mediators such as TNF, IL-1, IL-6 and IL-8, and phagocytic function of phagocyte, thus relieving hepatic pathological change.

In AP, the intestinal mucosa barrier becomes damaged, bacteria and endotoxin in the intestinal tract migrates into the blood, and then activates NF- κ B to promote the transcription of downstream gene, thus inflammatory cytokines can induce SIRS and MODS. The traditional Chinese medicine Rhubarb can protect the intestinal mucosa barrier, preventing endotoxemia, avoid aggravating AP by stimulating excessive transcription of NF- κ B, ICAM-1 and inflammatory cytokines, relieve the damages of organs out of the pancreas such as the liver, and thus prevent the development of MOF. Another study^[39] proved that: Herbs of Huo-Xue-Hua-Yu such as rhubarb and Danshen Root can inhibit excessive release of NO in serum and hepatic tissue, and thus relieve hepatic damage in SD rat and

inhibit excessive systemic inflammatory reaction. The effect of effective constituent of rhubarb on the expression of NF- κ B, ICAM-1 and cytokines is worth further research.

Combined therapy

SAP induced hepatic injury is a local organ lesion occurring in systemic inflammatory reaction status, however simple hepatic protection therapy can not completely prevent the progression of this disease. Therefore, we should follow the 'individualized' combined therapy principle when protecting the liver, to radically control the invasive foundation of hepatic injury. Usually non-surgery therapy should be the first choice, including fasting, gastrointestinal decompression, fluid replacement, broad-spectrum antibiotic administration, inhibiting pancreatin activity, and active nutritional supportive treatment, to correct electrolyte disturbances. Once the signs of systemic infection have occurred, active surgery therapy should be performed, to prevent the development of multiple organ damage induced by inflammatory stimulation.

One report showed that, based on applying Sandostatin to inhibit pancreatin secretion, (combined with colon cleaning to treat SAP) the efficacy was good, because colon clearing can efficiently remove OFR in blood, thus relieving SAP induced hepatic injury. The mechanism may include: ① efficiently remove enterogenic bacteria/endotoxin; ② irrigating solution infused by pressure, which can promote enteric peristalsis, improve intestinal mucosa microcirculation, strengthen defense ability of mucosa barrier, and efficiently prevent enteric bacteria translocation, thus reduce blood OFR; ③ irrigating solution of this experiment contain mannitol and glucose. Mannitol can bind with OH \cdot , to cause OH \cdot transformed into H₂O, thus relieving OH \cdot hepatotoxicity. Mannitol can also absorb excessive water in vessel wall tissue of digestive tract, relieve inflammatory edema, improve microcirculation, and relieve enteroplegia and abdominal distension in AP^[40].

Wang G et al.^[41] found that, earlier enteral nutrition (EEN) combined with Rhubarb, can efficiently reduce the degree of SAP induced hepatic injury. The mechanism might associate with protecting intestinal mucosa barrier, improving hepatic microcirculation disturbance, and inhibiting hepatic acute inflammatory reaction, oxidizing reaction and hepatic apoptosis. Another study^[42] found that IL-2 and Ligustrazine have certain value in treating AP complicated with hepatic injury: combination of two drugs has synergism in protecting pancreatic and hepatic cells, and the effect of two drug combination is better than single use.

Prospects

Many factors including inflammatory cytokines, endotoxin, NF- κ B and OFR participate in the pathophysiology process of AP complicated with hepatic injury, while their reticular signal conduction pathway and regulation network should be further studied. Investigating intracellular earlier events in AP to block inflammation activation and magnification effect will become the new direction for clinically intervention of AP. Proper protection to the structure of the liver and improving its function should be beneficial to prevent and treat MODS of AP, and provide new strategy for AP treatment. In addition, traditional Chinese medicine has good research value, from a clinic application perspective, and provides hope for a contribution in treating AP, complicated with hepatic injury.

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