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Review:

Study progress on mechanism of severe acute pancreatitis complicated with hepatic injury*

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Abstract: Study on the action mechanism of inflammatory mediators generated by the severe acute pancreatitis (SAP) in multiple organ injury is a hotspot in the surgical field. In clinical practice, the main complicated organ dysfunctions are shock, respiratory failure, renal failure, encephalopathy, with the rate of hepatic diseases being closely next to them. The hepatic injury caused by SAP cannot only aggravate the state of pancreatitis, but also develop into hepatic failure and cause patient death. Its complicated pathogenic mechanism is an obstacle in clinical treatment. Among many pathogenic factors, the changes of vasoactive substances, participation of inflammatory mediators as well as OFR (oxygen free radical), endotoxin, etc. may play important roles in its progression.

Key words: Severe acute pancreatitis, Hepatic injury, Inflammatory mediators, Cytokines, Endotoxin, Nuclear factor-κB
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INTRODUCTION

The pathogenic mechanism of severe acute pancreatitis (SAP) is still not completely clear now (Wu, 2001; He *et al*., 2003; Wang *et al*., 2001; Xia *et al*., 2001; Li *et al*., 2000). Its onset process is hazardous with high mortality, the illness state evolves rapidly accompanied by multiple complications, which is extremely harmful (Yousaf *et al*., 2003; Hartwig *et al*., 2002a; 2002b; Abu-Zidan and Windsor, 2002). Although the modern medicine develops at very fast speed and extensive studies have been directed on SAP pathogenic mechanism, pathological process and prevention and treatment measures, the morbidity and incidence of serious complications of SAP haven't been reduced till now (Ge and Wang, 1994). The main cause of early death is multiple organ failure and liver is one of the most involved (Shen *et al*., 1997). Studies prove there is a positive correlation between the incidence and level of hepatic injury and the state of pancreatitis (Wang, 2003), indicating the high clinical value of its pathogenic mechanism study. We hereunder have summarized the main pathogenic mechanism of SAP complicated with hepatic injury after collecting domestic and international research materials.

CHANGES OF VASOACTIVE SUBSTANCES

Trapnell (1981) believed the microcirculation disturbance is an extremely important cause of SAP complicated with hepatic injury. In SAP the hepatic injury is related with hypovolemia and insufficient hepatic blood circulation due to the release of vasoactive substances. The decline of hepatic blood flow can cause dyssynthesis of mitochondria ATP and meanwhile the phosphorization rate of cytochrome A and B also drops. The results from the

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dynamic observation of the changes of endothelin (ET) and nitrogen monoxidum (NO) secreted by the vascular endothelial cells; arachidonic acid metabolite thromboxane (TXA_2) and prostacyclin (PGI_2) indicate there is certain relation between ET/NO and TXA_2/PGI_2 and SAP hepatic injury.

ET/NO

ET and NO are the organ regional flow modulating factors only discovered recently. The vascular endothelial cells can contract the blood vessels by releasing ET and relax vascular endothelial cells by releasing NO. Under normal conditions, ET and NO, the two vasoactive substances with opposite effects remain in dynamic balance, adjusting blood vessel elasticity to maintain the vascular peripheral resistance and local vasodilatation and vasoconstriction. Under pathological conditions, the elevation of ET and decline of NO has resulted in the unbalance between ET and NO, maladjustment of vasodilatation and vasoconstriction, increase of vasoconstriction and finally disturbance of blood circulation. Rockey and Chung (1996) found through experiment that in AP (acute pancreatitis) the endotoxin and TNF (tumor necrosis factor) stimulates the liver tissues, mainly the NO synthetase on the hepatic cells, cell Kupffer and hepatic sinusoid endothelial cell to synthesize NO. IL-I relies on the endogenous INF-γ to mediate the NO synthesis of hepatic cells (Schroeder *et al*., 1998). The results of sampling and analysis of the plasma of SAP patients and healthy adults show that both ET and NO are elevated in SAP patients ($P<0.05$) and that the elevation of the plasma ET is markedly higher than that of NO. The markedly increased ET/NO ratio increases markedly the unbalance of ET/NO (Wu *et al*., 2000). And the change rules of ALT (alanine aminotransferase) and LDH (lactate dehydrogenase) are consistent with ET/NO ratio, indicating the increase of ET/NO ratio is related with hepatic injury.

TXA_2/PGI_2

The metabolite of arachidonic acid in serum also increases mainly markedly the elevation of TXA_2 and TXA_2/PGI_2 ratio (Wu *et al*., 1999). TXA_2 plays an important role in ischemia hepatic injury. TXA_2 as a potent capillary vasoconstrictor substance and platelet aggregation promoter, can induce platelet deformation, release, secretion, and cause local and/or systemic disturbance of hemorrhage blood coagulation, destroy the cell protecting mechanism (Mao *et al*., 1997; Wang *et al*., 1998), and can also promote neutrophilic granulocyte activation, release OFR (oxygen free radical), and cause blood vessel endothelium injury (Zhou *et al*., 2000). PGI_2 with extremely potent TXA_2 antagonist function can greatly inhibit platelet aggregation and activation, inhibit leukocyte activation, protect lysosome, and prevent the release of lysosome inside tissue (Gong *et al*., 1995; Sun *et al*., 1998). PGI_2 can markedly alleviate hepatic injury secondary to SAP; indicating certain relation between the metabolic disturbance of arachidonic acid and SAP hepatic injury. Therefore, TXA_2 in SAP patient plasma is elevated markedly and so does PGI_2 but with limited degree and soon dropping to the normal level, which has led to the rise of TXA_2/PGI_2 ratio. As a couple of angiotasis regulatory substances, the proportion unbalance of TXA_2/PGI_2 can cause vasomotion disturbance, formation of microthrombus, vascular occlusion and other pathological changes (Gu *et al*., 1999; Shen *et al*., 1991), which also could be closely related to hepatic injury. The vaso-excitor effect of TXA_2 is only next to that of ET, which is by far the most potent vaso-excitor material. When both TXA_2 and ET after increase have exceeded the value of their main antagonists, they cause vasoconstriction, blood circulation disturbance and further organ injury. There could be one of the common mechanisms of SAP causing injury of pancreas and other organs including liver.

PARTICIPATION OF INFLAMMATORY MEDIATORS

The excessive release of inflammatory transmitters is an important cause of SAP onset and progression besides autodigestion of pancreatin. Current studies found some inflammatory mediators play important roles in SAP complicated with multiple organ injury (Makhija and Kingsnorth, 2002; Keck *et al*., 2002). Due to co-action of manifold inflammation transmitters, AP rapidly develops into SAP from local pathological changes and systemic multiple organ dysfunction occurs together with massive necrosis of pancreatic tissues (Shimada *et al*., 2002; Rau *et al*., 2001; Foitzik *et al*., 2000; Lundberg *et al*., 2000).

Platelet activating factor (PAF)

Recently PAF is deemed to be the key inflammatory mediator in SAP external secretion and local, systemic inflammatory reactions (Bhatia *et al*., 2000). Main actions of PAF (Kingsnorth, 1996; Wang *et al*., 1997; Roudebush *et al*., 2000; Reinhardt *et al*., 1999) include activation of platelet, promotion of platelet adhesion and aggregation, formation of thrombus; elevation of adhesion factor β_2-integrin, change of endothelial cell skelemin, increase of capillary permeability, massive effusion of plasma, blood viscosity increase, slow down of blood flow, participation of ischemia-reperfusion injury; stimulation of vasoactive substances, generation of cytokine and inflammatory mediators, and so on.

The unbalance between PAF and vasoactive substances can cause a vicious cycle, leading to a series of chain reactions and amplifying reactions such as cascade reaction. It can increase tissue and organ injury, cause systemic inflammatory reaction syndrome (SIRS), and further multiple organ dysfunction syndromes (MODS) and/or multiple organ failure (MOF), or even death (Lei and Zhang, 2000; Ji *et al*., 1997). PAF can cause rapid rise of Ca^{2+} within hepatic cells that is relevant to hepatic cell injury and apoptosis. Therefore, the rise of PAF plays an important role in the occurrence and progression of SAP (Xia *et al*., 2001).

Neutrophilic infiltration and generation of cytokines

Many studies show that injury of the over activated neutrocyte on self tissue is an important cause of systemic complications due to AP (Chen *et al*., 2001; de Dios *et al*., 2002; Descamps *et al*., 2003; Ammori, 2003; Shields *et al*., 2001; 2002; Demols and Deviere, 2003; Zhao *et al*., 2003; Zhou *et al*., 2002; Song *et al*., 2002; Brady *et al*., 2002; Clemons *et al*., 2002; Hartwig *et al*., 2002c; Mikami *et al*., 2002). The neutrophilic granulocyte stimulated by pancreatitis can release inflammatory cytokines such as TNF-α (Cassatella, 1995; Ni *et al*., 1998; Ogawa, 1998). The inflammatory cytokines especially TNF-α as one of the important cytokines in the SAP pathological mechanism participates in the occurrence and progression of SAP. It has extensive bioactivities. Lipsett (2001) and Hirota *et al*.(2000) proved that the occurrence of AP is always accompanied with the rise of inflammatory cytokine, with the extent of rise having close relationship with the disease severity. On the contrary, decreasing TNF-α promotes tissue repair and immune response, and then weakens the chemotaxis of neutrophils. It will inhibit the adhesion of neutrophils to vascular endothelial cells as well as degranulation of neutrophils that generate free radicals, and thus can prevent local tissue damage and increase of capillary permeability, and reduce hemorrhage and necrosis of pancreatic tissue. The endoxemia at the early stage of SAP can induce TNF-α and when the quantity of produced TNF-α exceeds that of tissue TNF receptor, the excessive TNF-α enters blood circulation, activates neutrophilic granulocyte, causes aggregation of neutrophilic granulocyte, then stimulates the release of cytokines such as IL-1β, IL-8 and IL-6 (Zhang *et al*., 1997). In addition, TNF-α in serious injury and shock can cause extensive autoimmune pathological reactions which also demonstrates it is an important initiator in inducing SAP complicated with hepatic injury.

IL-1β and TNF-α have many similar biological activities: for example, pyrogen functions, promoting cell catabolism, producing protein in acute reaction period, and making endothelial cell secrete PGI_2 and platelet activating factor, etc., which will cause the expansion of inflammation area and increase of inflammatory mediators, destructive enzymes, OFR secretion. It can cooperate with TNF-α to aggravate and induce organ injury. It has chemotaxis and activating effects on granulocyte, also can stimulate the production of other inflammatory mediators such as IL-8, IL-6 and other inflammatory cytokines through autocrine or paracrine. IL-8 is a kind of potent neutrophilic granulocyte chemotatic factor and activating factor mainly generated by neutrophilic granulocyte. Generated by mononuclear/macrophages and endothelial cells, it can activate and induce T, B cell differentiation, enhance NK (nature killer) cell for killing target cell, and promote phagocytosis, and play an important role in tissue injury mediated by neutrophilic granulocyte. The most direct proof of IL-8 mediating granulocyte chemotaxis and participating in tissue injury is that the neutrophil chemoattractant (CINC) induced by the cytokine excessively expressed by the hepatic cells infected by adenovirus is closely related to the level of inflammatory cell infiltration, ALT and AST (aspartate aminotransferase) (Maher *et al*., 1997). Currently it is believed that most

inflammatory reactions induced by TNF-α, IL-1 and IL-6 are realized by inducing the generation of chemotatic factors, mainly IL-8.

IL-6 mainly generated by mononuclear macrophage has extensive inflammation promoting effects such as promoting B cell activation, proliferation, and its final differentiation into plasmocyte, increasing immunoglobulin synthesis, promoting T cell differentiation and proliferation, promoting acute period reaction, and causing tissue injury. Carried by blood to the liver, IL-6 can make the liver secrete the mannose-bonding protein to bind bacteria and endotoxin, trigger a series of complementary reactions and lead to hepatic injury. IL-6 also can lead to leukocyte adhesion to the surface of endothelial cells of hepatic vasculature. The leukocytes adhered to the endothelial cells can release toxic substances such as elastic protease, OFR, etc., to injure the surface of vascular endothelial cell (Sun *et al*., 2003).

Many endogenous inflammatory mediators invade the hepatic tissues, destroy the Na^+-K^+ pump on hepatic cell membrane, cause hepatic cellar edema and then induce neutrophil infiltration within the liver. The inflammatory reactions inside the liver may further aggravate hepatic injury. Most mild pancreatitis can recover itself after expectant treatment while serious pancreatitis with hepatic injury takes longer healing time with poor prognosis (Zhang, 2003). During SAP, there is a marked decline of liver capacity in eliminating toxic and bioactive substances. The liver has been inhibited and lost its barrier function to prevent endotoxemia, which then has led to the excessive release of the endogenous inflammatory mediators, forming a vicious cycle. Numerous endogenous inflammatory mediators enter the systemic circulation, cause continuous systemic inflammatory reactions as well as the injury of systemic tissues and organ dysfunction. The resulted chain reactions and amplifying reactions are namely the cascade reactions, leading to SIRS and MODS (Mayer *et al*., 2000; Brivet *et al*., 1999). MODS are the main cause of severe pancreatitis (Yang *et al*., 2003).

ROLE OF ENDOTOXIN

Endotoxin mainly produced by Gram-negative bacteria is a component of lipopolysaccharide in cell wall. Clinical studies show that there is endotoxemia in AP especially SAP, and that it is closely related to the onset, progression and complication of multiple organ failure of SAP. Windsor *et al*.(1993)'s study proved SAP's relation with the state of pancreatitis. Some domestic scholars who study the relation between plasma endotoxin levels of AP patient with multiple organ injury have proven the important promoting effect of endotoxin during the progression of multiple organ injury. Kazantsev *et al*.(1994) proved that in SAP the blood endotoxin mainly originates from the intestinal tract. Pancreatitis injures the intestinal tract function, reduces intestinal barrier function, disturbs the microenvironment and normal bacteria colony, and induces translocation of intestinal bacteria and endotoxin to nearby tissues and tissues outside intestinal tracts. The endotoxin enters blood to invade the liver, activates the phospholipase A_2 (PLA_2) to mediate membrane phospholipids degradation, and induces the free radicals to mediate the lipid peroxidation of hepatic cells. In addition, it also causes hepatic injury by interfering in energy metabolism. Its hepatic injury action mainly shows that the ALT, AST and BIL (Bilirubin) values are all elevated with the increase of endotoxin mass concentration. The scope of elevation is related to the endotoxin concentration, positive correlation in certain range (Wang *et al*., 1996).

The cytokines and inflammatory mediators released by the activated cell Kupffer are more important than the direct effect of endotoxin in the hepatic injury (Fujita *et al*., 1995; Suzuki *et al*., 1996). Liver is the main endotoxin-eliminating organ while cell Kupffer is the hepatic component with that function. Cell Kupffer can both eliminate endotoxin and be activated by endotoxin to generate a great quantity of cytokines (Luster *et al*., 1994). The study result of Eguchi *et al*.(1991) proved there is a close relation between endotoxin and hepatic injury since the cell Kupffer activated by endotoxin can generate a series of chemical mediators such as active OFR, TNF-α, IL-1 and IL-6 which all can affect the functions of leukocytes, platelets, sinusoid endothelial cells and parenchymal cell to further influence hepatic microcirculation and functions (Zhou and Liang, 1999a; 1999b; Han, 1996).

ROLE OF OFR

OFR is an oxygen contained group with great chemical reaction activities mainly including peroxide anion free radical (O_2^-) and hydroxy radical (OH·) which during causing lipid oxidation can increase mucosa permeability, further enhance phagocyte activity, generate more OFR, and finally cause histiocyte injury. Scott *et al*.(1993) proved that in pathologic state, excessive OFR could cause tissue and cell injury. OFR can participate in the formation of AP pancreatic edema and possibly pancreatic necrosis, mediating leukocyte and platelet activated by TNF-α in all organs to release lysosome, OFR and lipid inflammatory mediators. OFR can react with protein and enzyme to lead to protein denaturation and enzyme inactivation. OFR peroxidation product LPO (lactoperoxidase) can cause inactivation of membrane-bound enzyme, cell membrane injury, and vascular permeability increase. The OFR generation rate has greatly exceeded the body anti-oxidation capacity or body anti-oxidation capacity is over exhausted to eliminate OFR in time, which causes a series of oxidations resulting in lipid peroxidation of cell and organelle plasma membrane, directly injuring cells, damaging the lysosome and mitochondria in hepatic cells, even lytic necrosis and lymphocyte infiltration of hepatic cells (Luo and Ye, 1995). The changes of inflammatory mediators can generate OFR, stimulate and increase the auto-secretion, cause cascade reactions, enhance systemic inflammatory reactions, and then increase capillary permeability, cause local ischemia aggravating the progression of SAP.

ROLE OF NF-κB AND ITS REGULATION OF ICAM-1 EXPRESSION IN SAP COMPLICATED WITH HEPATIC INJURY

Nuclear factor-κB (NF-κB) is a kind of transcription factor mainly participating in the regulation of inflammatory molecule expression (Li and Gao, 2001; Suk *et al*., 2001). As a protein capable of bonding κB sequence of some genetic initiator and enhancer region, it can start or enhance genetic transcription (Izumi *et al*., 2001; Antonelli *et al*., 2001; Ginis *et al*., 2002; Wright *et al*., 2002). In silent cells, NF-κB inactively exists in cytoplasm, and can be activated by stimulation with nuclear translocation. It can bond the kb site of target gene initiator or enhanser to start or enhance genetic transcription (Lakshminarayanan *et al*., 2001; Moine *et al*., 2000; Valen *et al*., 2001; Omoya *et al*., 2001), and further participate in the injury process of tissue (Shames *et al*., 2002; Wang *et al*., 2002; Theuer *et al*., 2002). During occurrence of AP hepatic injury, the activation of hepatic NF-κB also plays an important role. When SAP occurs, NF-κB activation increases markedly. The time dependence NF-κB activation will increases with time. The abnormal NF-κB activation can promote the genetic transcription pre-inflammatory factors (TNF-α, IL-1, IL-6), and TNF-α, IL-1 as extracellular stimulation signal can also activate NF-κB, and further enhance the inflammatory reactions. The participation of NF-κB during AP in regulating body inflammatory reactions as well as genetic transcription of cytokines and inflammation transmitters related immunization, stress, etc. has been recognized (Li and Gao, 2001).

There is an NF-κB bonding site on intercellular adhesion molecule (ICAM-1) initiator. ICAM-1 as a member of cell adhesion molecule immunoglobulin superfamily, mainly mediates the adhesion between polymorphonuclear granulocyte (PMN) and vascular endothelial cells, playing an important role in the aggregation process of PMN toward tissue. The aggregated PMN in tissue can cause cell and organ injury. Because of the NF-κB binding site on ICAM-1 initiator, hepatic NF-κB activation in SAP has promoted the expression of ICAM-1, further causes PMN aggregation in hepatic tissues and results in hepatic injury. This again proves the NF-κB can cause tissue injury effect by regulating the expression of hepatic ICAM-1 expression.

ROLE OF LYSOSOME

Extensively distributed in body cells, most lysosomes exist in macrophage, neutrophilic granulocyte, etc. with phagocytosis function. There are over 50 kinds of known enzymes in lysosome such as β-glycuronidase, cathepsin, TRAP (thrombospondin related anonymous protein) and collagenase which can decompose exogenous harmful substances as well as intracellular injured or effete organelles, partici-

pate in cell physiological and pathological processes, cell differentiation and aging, and also play an important role in cytophylaxis (Hirano and Hirano, 1999; Dlugosz *et al*., 1993). Among various enzymes, the level of PLA_2 is consistent with the state of SAP and also related to prognosis. PLA_2 is widely distributed at plasma and organelle membrane of various cells. Usually the PLA_2 inside plasma is mainly secreted by pancreas and little by salivary gland, prostate, etc. Serum PLA_2 mainly comes from neutrophilic granulocyte, macrophage and platelet of pancreatic acinus and other positions outside the pancreas. After SAP occurs, polymorphonuclear leukocyte and mononuclear macrophage stimulated by endotoxin can release numerous PLA_2 into blood to attack and decompose the phospholipids ingredient of membrane, destroying cell membrane stability and causing massive outleakage of lysosome enzymes on one hand; and on the other hand generating bioactive free fatty acid and soluble lecithin, and destroying the function and structure of systemic cell and organ system. The conclusion could be: PLA_2 is an important mediator for mediating viscera injury of pancreatic and other tissues after pancreatitis (Wereszczynska *et al*., 1986; 2000).

HEPATIC APOPTOSIS

Hepatic apoptosis could be one of the factors leading to hepatic failure. Studies showed that hepatic Bax and Bcl-2 participates in the regulation of hepatic cell apoptosis during hepatic injury of SAP. The ascites accompanying SAP can induce hepatic apoptosis; IL-1 converting enzyme inhibitor can relieve hepatic apoptosis and hepatic cell injury, and partial apoptosis could be prevented by neutralizing the transforming growth factor-β (TGF-β). Researchers believe the occurrence of hepatic apoptosis in SAP is related to TGF-β in ascites (Ueda *et al*., 1999; 2000; 2002).

In short, there are manifold causes of SAP complicated with hepatic injury. During the progression of SAP, these factors cause cascade reactions and the synergism among them causes the hepatic injury.

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