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REVIEW

Specific aspects of acute pancreatitis

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Abstract: Acute pancreatitis (AP) is still a disease with a significant mortality rate, mainly concerning the severe forms of this disease. Mortality in acute pancreatitis has 2 peaks. The first peak is caused by systemic inflammatory response syndrome (SIRS), which takes place in the first week of the disease. Sepsis is responsible for a second peak. It begins 1 to 3 weeks after the onset of acute pancreatitis and is caused by pancreatic superinfection. Sepsis as a result of infected pancreatic necrosis is the most serious complication in late phase of severe acute pancreatitis (SAP) and contributes to the high mortality rate of this disease. This complication is thought to be a result of the bacterial translocation from the gastrointestinal tract. The damage of the microvessels and the subsequent onset of systemic cascade reactions plays also an important role during acute pancreatitis. Recent experimental data suggest also the role of nervous system in etiopathogenesis of acute pancreatitis. We assume that the diagnostic and treatment strategy can not improve without a thorough knowledge of the physiology and patophysiology of acute pancreatitis. Therefore the aim of this paper is to highlight certain specific situations of high importance that are activated in the human organism during acute pancreatitis *(Ref. 100)*. Full Text (Free, PDF) *www.bmj.sk.*
Key words: specific aspects, acute pancreatitis, organ dysfunction syndrome.

Acute pancreatitis (AP) has an annual incidence of 5–40 per 100 000 population (1) with an overall mortality approaching 1–5 per 100 000 population (1). Approximately one-third of patients develop pancreatic necrosis, which has an associated mortality rate approaching 30 % (3). This severe form of the disease is characterized by pancreatic necrosis, cytokine activation, systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) (4). Necrotic pancreatic and peripancreatic tissue may become infected, further increasing morbidity and mortality (4). Pancreatic perfusion and hypoxia have a significant impact on the early stages of the disease and play an important role in the pathogenesis of pancreatic necrosis (5). There is accumulating evidence in human and animal studies that changes of perfusion, particularly to the microvasculature, are significant events in the progression of AP. Microvascular compromise has been suggested as the critical event in the development of severe pancreatitis, and treatment aimed at the microvasculature may decrease necrosis and disease severity (6). Interestingly, recently accumulated data indicate that also innervation of pancreas may play an important role in the initiation and maintenance of the pancreatic inflammation (97).

AP is described to have a wide range of severity from a mild, self-limiting condition to a fulminant illness resulting in death within a few days of onset. Mortality in AP has 2 peaks. The first peak is caused by SIRS, which takes place in the first week. Sepsis accounts for a second peak. It begins 1 to 3 weeks after the onset of pancreatitis and is caused by pancreatic superinfection. The origin of this infection arises from translocation of intestinal bacteria. The disruption of gut mucosal barrier during AP contributes to the genesis of infection (74). Severe acute pancreatitis (SAP) is a difficult clinical condition, the prognosis of which has not been significantly improved till present. One of the reasons may be that the treatments do not fully aim at the key event of AP (47).

The aim of this article is to describe the complexity of biological interactions and point out some specific situations occurring during AP. The role of pancreatic microcirculation as well as innervation in the pathogenesis and progression of AP are described.

Pathophysiology and diagnostics

In the last two decades many studies have shown that severe AP is characterized by the increase in serum levels of numerous inflammatory mediators, which are thought to be directly related to tissue damage. Several cytokines and acute-phase proteins have been studied for prediction of severity in AP. Among them, the pro-inflammatory IL-6 and CRP have demonstrated to be effective predictors, even more accurate than APACHE II score. However, time elapsed from AP onset must be considered when using these markers, given that IL-6 attains its peak concentration 24–48h before CRP. Another cytokine, the anti-inflammatory IL-10 has also been described as a useful marker of severity. The

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pancreatitis associated protein (PAP) is an acute-phase protein secreted by the exocrine pancreas in response to tissue damage. In normal subjects the circulating level of PAP is almost undetectable, althought it significantly increases during AP. Experimental models have demonstrated that PAP has a rapid and strong induction during AP in response to circulating cytokines, and it has been postulated an early and specific acute-phase protein to establish the presence and degree of pancreatic injury (57).

Biliary calculi and alcohol abuse are the most common causes of AP. Other causes such as iatrogenic factors, sphincter of Oddi dysfunction (SOD) and eating disorders also cannot be omitted. Blockage of duodenal papilla or ampulla of Vater is common characteristics of AP. Once the blockage appears, the occurrence of pancreatic duct obstruction and bile reflux is inevitable. Obstruction of the pancreatic duct leads to increased intraductal pressure, which results in damage to the integrity of the duct system to a certain extent. Bile reflux can activate trypsin and once trypsin is activated, it activates a variety of injurious pancreatic digestive enzymes with subsequent release of a series of inflammatory mediators. Pancreatic duct obstruction and bile reflux probably are the key events of AP induced by a variety of other upstream causes. Whenever pancreatic duct obstruction and bile reflux are triggered simultaneously, activated digestive enzymes and inflammatory mediators can infiltrate into the parenchyma of the pancreas through impaired pancreatic barrier and induce AP. Blocking the key event of AP is of a great interest with potential therapeutic implications. Endoscopic sphincterotomy (EST) and nasobiliary drainage, which target the cause of AP, may prevent the transformation from AP to SAP and this may be adopted as an sesential treatment strategy (47).

Inflammation

One recent study has focused on the neuropeptide, substance P and its role in pancreatic inflammation. Ramnath et al (2008) reported that expression of the substance P gene (preprotychykinin-A, PPT-A) and neurokinin-1 receptor (NK-1R), the primary receptor for substance P, were increased in caerulein-treated mouse pancreatic acinar cells. Ramnath et al also showed that substance P stimulated early protein kinase C (PKC)-α activation, followed by increases in mitogen-activated protein kinase kinase (MAPKK), mitogen extracellular response kinase kinase (MEKK1), MAP kinases, extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) activities as well as activating nuclear factor kappa B (NFκB) and activator protein-1. This led to production of the inflammatory protein (MIP)-19 and MIP-2. This study highlights the importance of the substance P pathway in pancreatic inflammation (17).

Tumor necrosis factor (TNF)-α, a key regulator of proinflammatory genes, may be a target for the treatment of AP. In caerulein-induced AP, the TNF-α inhibitor thalidomide was found to reduce disease by Malleo et al (2008) (8). *N*-acetylcysteine (NAC), a potent antioxidant, has been demonstrated to be able to inhibic tumor necrosis factor (TNF)-α production in acinar cells and circulating monocytes at early stages of bile-pancreatic duct obstruction-induced AP (16).

The proto-oncogene Tpl2 (tumor progression locus-2) can modulate some inflammatory processes. Van Acker et al (2007) showed that Tpl2 ablation markedly reduced pancreatic and lung inflammation in secretagogue-induced or bile salt-induced pancreatitis but did not alter pancreatic injury/necrosis in either model (62).

Animal models of SAP and chronic pancreatitis have recently been developed. Several unexpected protective mechanisms, mediated by the protease activated receptor 2 and heat shock protein 70, have been described. A genetic study suggested that polymorphisms in toll-like receptor-4 might affect the risk of developing infections in AP (43).

The study of Malleo et al (2008) undercors the fact that there are changes in multiple inflammatory cytokines/chemokines during AP and these have distict mechanisms for causing injury. One implication of such findigs is that clinical therapies may need to target multiple inflammatory mediators (43).

Procalcitonin (PCT) is the inactive 116 amino acid pro-peptide of the biologically active hormone calcitonin. In 1993, Assicot et al (61) first described significantly increased concentrations of PCT in patients with bacterial and fungal infections and sepsis.Hence, it has been largely confirmed that PCT is the only one among a large array of biochemical parameters, which closely correlates with the inflammatory host response to microbial infections. In acute pancreatitis, PCT has been shown to predict the development of infected necrosis accurately. In other series, PCT was found to be an excellent predictor of severity and organ silure within the first 24 hours after hospital admission or onset of symptoms. However, a number of subsequent studies have shown opposite results, and the clinical usefulness of this parameter in acute pancreatitis still remains controversial. In the absence of representative studies, we addressed this isme by conducting the first prospective international multicenter trial in patients with severe acute pankreatitis (67).

Apoptosis

The severity of pancreatitis may depend on the mechanism of cell death; greater levels of apoptosis over necrosis favor milder disease. To examine the mechanisms of apoptosis, Baumgartner et al (33) used the oxidative stressor menadione and identified two independent apoptotic pathways in pancreatic acinar cells. The first is the classical caspase-9-mediated pathway that is Ca^{2+}--dependent, mediated by mitochondria and is rapidly initiated. The second is much slower, mediated by caspase-8, depends on the lysosomal activities of cathepsins and is used when the caspase-9 pathway is disabled. This information might be used to develop strategies for lifting cell death pathways to favor apoptosis during AP.

Genetic factors

Two studies have highlighted the importance of genetic factors in predisposing patients to acute pancreatitis (22, 37). Gao et al (37) investigated why some patients are more prone to pancreatic infection during AP. LPS or endotoxin may cross leaky paracellular barriers in the colon or be released into the blood

stream by circulating Gram-negative bakteria during AP. LPS can then bind to toll-like receptors (TLRs) on the surface of the acinar cell, producing a host defense response. However, in some patients, a polymorphism in TLR-4 led to impaired signaling and lack of a defensive response, rendering them more prone to infection. In another genetic study, Chang et al (22) found that mutations on the cystic fibrosis transmembrane conductance regulator (CFTR) predisposed patients with elevated lipids to developing hypertriglyceridemic pancreatitis. Further studies that use newer genome-wide analysis will likely reveal additional genetic factors that affect the risk of developing acute pancreatitis or its severity.

Arteficial neural networks

Arteficial neural networks (ANNs) are a family of data analysis algorithms. They are designed to resemble biological nervous system. They differ in structure and function from conventional data analysis models, as ANNs are able to learn from the data presented to them, thereby improving their predictive ability. ANNs have been used in medicine in a wide variety of clinical situations as decision support aids to analyse complex clinical problems (48). Several authors have used ANNs to develop predictive models for the assessment of patients with AP, with varying degrees of success (89).

Keogan et al used an ANN to identify patients with AP whose hospital stay exceeded the mean of 8.4 days. They did not find any difference between the predictive ability of the ANN and stepwise linear discriminate analysis. This study was limited by small cohort size and the retrospective nature of the study design (66). ANNs can predict mortality in the early phase of predicted SAP. They appear to be more accurate than the APACHE II and Ranson systems (26). One recent study suggest that ANNs are significantly more accurate than conventional scoring systems (APACHE II and Glasgow outcome scores) at predicting the development of SAP, multiorgan dysfunction and death (89).More complex predictive models, such as genetic algorithms, are also accurate predictors of outcome (21).

Vascular effects

Both major vessel and microvascular pathology are present in acute pancreatitis in humans. Haemodynamic dysfunction is often a feature of severe disease at the onset of AP (43), which is secondary to reduced circulating volume, due to increased capillary permeability (44). As a result, splanchnic perfusion falls (45), with subsequent impairment in renal blood flow, leading to renal failure and acute tubular necrosis. Other vascular complications include intestinal ischaemia (46), hepatic hyperaemia, subcutaneous fat necrosis and vascular retinopathy (50). Coagulopathy is common and there is documented incidence of splenic vein thrombosis and thrombotic microangiopathies leading to haemolytic uraemic syndrome and thrombocytopenic purpura (51). Complications related to large vessel in acute pancreatitis tend to occur late in the course of disease (52), and range from arterial spasm to pseudoaneurysm (53). Angiographic changes correlate with the severity of disease (54). Animal models of pancreatitis, both mild and severe, can be used to characterize further the large vessel and microvascular derangement in acute pancreatitis. Haemodynamic changes as haemoconcentration, tachycardia, and decreased mean arterial pressure, cardiac index and central venous pressure are common (57). Despite improved cardiac function and splanchnic blood flow with aggressive fluid resuscitation, the pancreatic perfusion remains altered, owing to independent microvascular changes (60). In fact, pancreatic perfusion decreases disproportionately to the reduction in cardiac output (63). Reduced tissue blood flow in pancreatitis is related to its severity (64). Severe pancreatitis is associated with reduction of tissue perfusion, pancreatic oxygen tension, oxygen saturation of haemoglobin and reduction of pancreatic oxygen consumption (68). Mild pancreatitis, on the other hand, may be associated with a relative hyperaemia, increased tissue oxygen tension and increased oxygen saturation of haemoglobin (70). Other studies suggest that pancreatic blood flow in severe pancreatitis is inadequate to flush the tissue of enzyme breakdown products, possibly leading to increased disease severity (71).

Capillaries in the pancreas are richly fenestrated, and have much greater permeability than those in other tissues such as heart or skeletal muscle. Physiological shunts divert approximately 10 % of blood flow from the acini (18). Regulation by hormonal and neural mechanisms allows perfusion of the normal pancreas to be maintained through a range of systemic conditions (20) to a lower limit of 40 ml per minute per 100 g tissue. In health, the whole gland is perfused evenly (19). Blood flow is tightly linked to exocrine secretion, and is modulated by somatostatin, secretin and cholecystokinin (23). The structural and functional anatomy of the pancreas renders it extreme susceptible to ischaemia. Autopsy studies often demonstrate subclinical pancreatitis in patients subjected to hypovolaemia and shock (24). Vascular and perfusion derangements leading to pancreatic ischaemia may promote the development of pancreatitis. These include vasculitis, cardiac surgery and pancreatic transplantation (30). In addition, vascular insufficiency is likely to be a factor in AP associated with diabetes and increasing age (31). Experimental evidence supports a role for ischaemia in the development of acute pancreatitis. Temporary vascular occlusion causes a transient rise in serum amylase (32) and prolonged ischaemia can induce histological pancreatitis (34), albeit relatively inconsistently owing to the abundant collateral supply of the organ. Ischaemia and hypoperfusion (38) can convert oedematous pancreatitis into haemorrhagic and necrotic pancreatitis. Phenylephrine infusion and water immersion both cause vasoconstriction, and can increase the severity of inflammation (40).

Acute intestinal ischaemia itself is well known to be critical, and experimental investigation of ischaemic injury of the intestinal mucosa has been performed to study pathophysiology of necrotizing enterocolitis or nonoclusive mesenteric ischaemia (91).

The major obstacle to the development of effective therapies is our limited understanding of the pathogenesis of AP. Despite a number of theories have been proposed to explain the patho-

genesis from various aspects, but there are still controversies about the mechanism of the disorder (90).

Microvascular impairment during AP

Microcirculation disturbance is one of the main causes of injuries of the pancreas and other organs during AP. The gastrointestinal tract is one of the most frequently affected organs (93).

Little is known of the microvascular derangements in the patients, because it can be studied only indirectly. Histological patterns of necrosis occur in a specific model, which is characterized by ischaemic damage (72). Vessel wall necrosis, infiltration of leucocytes, local haemorrhage and intravascular microthrombi are also seen. Microangiographic studies of pathological specimens show large areas of poor filling, as well as extravasation of contrast medium, which correlate with disease severity (73). Functional microcirculatory dysfunction is proportional to disease severity. It occurs later and with lesser severity in oedematous pancreatitis than in severe disease (75). Vasoconstriction appears to be an early event in pancreatic inflammation (78), leading to ischaemia and blood stasis. Pancreatic blood flow, red cell density and red cell velocity decrease within 8 hours of the onset of pancreatitis (79), although some changes may be seen as early as 6 minutes of initial phase of disease (80). Changes of the microvascular circulation are not confined to the pancreas but may affect the gastrointestinal tract and liver (86).

As a systemic pathological change, abnormal hemorheology can not only influence pancreatic microcirculation, but also cause microcirculation disturbance of extra-pancreas organs, especially the intestine. On the other hand, microcirculation disturbance may be directly or indirectly caused by a number of cytokines and vasoactive substances induced by activation of elastinase and excessive inflammatory reactions. Microcirculation disturbance includes decreases of regional blood flow and blood flow rate, increases of leukocyte adhesion and capillary permeability, and a functional decrease of capillary density (93). Clinical manifestation of septicemia and septic shock during severe acute pancreatitis (SAP) resides in mutual interaction of invading microbes and immune mechanisms of the body. A vicious circle develops on the level of microcirculation, namely between the decreasing tissue perfusion and progressive deterioration of capillary endothelium. This process incurs damage to the tissues. If the vitious circle is not interrupted, the state has a lethal outcome (95).

In SAP, microcirculatory disturbances and ischeamic changes of the gut have been reported to play important roles for the development of bacterial translocation (91).

Bacterial translocation and intestinal mucosal barrier

Sepsis due to infected pancreatic necrosis is the most serious complication in late phase of SAP and contributes to the high mortality rate of this disease. This complication is thought to be a result of the bacterial translocation (BT) from the gastrointestinal tract (91).

Bacterial translocation plays an important role for infectious complications in SAP. Alteration of intestinal mucosal integrity may increase intestinal permeability and may be implicated in BT. It is suggested that increase in intestinal permeability is correlated with the changes of tight junction and/or apoptosis in intestinal epithelial cells (90).

Despite advances in intensive medical management, the mortality rate in SAP is still high, and death from SAP occurs mainly from two different causes. During the first week of hospitalization, patients with SAP tend to have the complication of multiple organ failure as a consequence of SIRS. Thereafter, infectious complication such as infected pancreatic necrosis or sepsis is the problem in the management for patients with SAP (2). This complication is thought to be a result of BT and endotoxin translocation from the gastrointestinal tract (7). Such translocation is induced by the gastrointestinal derangements that may disrupt mucosal integrity, accompanied by increase in permeability of gastrointestinal tract (30). However, detail of the mechanism of increasing intestinal permeability during SAP is still unknown.

The intestinal epithelium forms a relatively impermeable barrier between the lumen and the submucosa. This barrier function is maintained by a complex of proteins composing the tight junction that is located at the subapical aspect of the lateral membranes of cells. Tight junction consists of numerous proteins, in which zonula occludens and occludin are well characterized (9). These proteins are considered to be involved in the regulation of paracellular permeability. Recently, it has been reported that disruption of the intestinal epithelial barrier as a consequence of a disorganization of the tight junction leads to an increase in paracellular permeability in inflammatory bowel disease and intestinal infections (10).

In SAP, since apoptosis-inducing activity for kidney cells in pancreatitis-associated ascitic fluid (PAAF) in 1995 was identified (11), authors have demonstrated that apoptosis occurred in renal tubular cells, hepatocytes, thymocytes (15), peripheral lymphocytes and intestinal epithelial cells (25, 35) and that apoptotic cell injury may be involved in the mechanism of multiple organ failure and infectious complications in this disease (28). Therefore, it is possible that apoptosis of intestinal epithelial cells is implicated in the mechanism of increasing intestinal permeability in SAP.

The intestinal mucosa forms an effective barrier to the intraluminal bacteria and toxins, as well as absorbs the nutrient. The mechanisms underlying gut barrier dysfunction in AP are complex and still not fully elucidated. In early phase of AP, gut mucosa hypoperfusion resulting from hypovolemia and systemic inflammatory response causes intestinal muscosal damage and is the possible reason of high intestinal permeability and absorptive capacity disruption. Early intestinal mucosal damage may play an important role in the pathophysiology of SAP, and it has long been involved in the development of sepsis and multiple organ failure as a major cause of death in AP (74).

Studies have also found that mast cells, endotoxin, cytokines, and other inflammatory mediators such as platelet-activating fac-

tor (PAF) contribute to early pancreatitis induced systemic epithelial barrier dysfunction. Endotoxin is an important product of gram-negative bacteria, which often originates from the gut and goes through the epithelial mucosa. So endotoxemia is one of the evidences of mucosal damage. Production of a wide array of cytokines was found in SAP. TNF-α is one kind of main proinflammatory cytokines in disruption of epithelial barrier function. The relationship between TNF-α and gut barrier dysfunction is not clear yet. The normal intestinal mucosa forms an effective barrier to the intraluminal bacteria and toxins, as well as absorbs nutrients. Gastrointestinal mucosal damage takes place in early phase of AP resulting from local or systemic inflammation response, hypovolemic shock, and gut ischaemia. Intestinal flora enters into circulation following dysfunction of the gut barrier, which was considered to be the main mechanism resulting in secondary infection in pancreatitis patients (74).

The intestinal mucosa forms an effective barrier to the intraluminal microorganisms and toxins. In AP, splanchnic hypoperfusion has been found to be caused by early hypovolemia (36). Splanchnic hypoperfusion causes ischaemic reperfusion injury, which along with gut mucosal damage represents one of the possible mechanisms of increased gut permeability. Disruption of this protective mechanism with increased intestinal permeability may allow the excess shifting of intestinal bacteria and toxin into local tissues and distant organs (39). Translocation of potentially harmful bacteria and toxins has been shown to occur in patients with burns, shock, and bowel obstruction and in patients after major surgery (41). Complications like sepsis and organ failure derived from infected pancreatic necrosis have been incriminated as a major cause of death in AP. Normal intestinal flora represents the most common microbes found in infected necrosis (42). Reduction of pancreatic infection by selective digestive decontamination (49) suggests that BT does occur from the bowel during AP. In experimental pancreatitis, the bacterial translocation has been shown to occur via different routes, such as transmurally through large bowel, transperitoneally through lymphatic ducts, or haematogenously (55). In human pancreatitis, the proof of BT is based on indirect evidence of intestinal permeability, and there are only few direct studies to support this fact.

Under stringent states, such as SAP, trauma, operation, radiotherapy, chemotherapy and severe infection, the structure and function of intestinal mucosa is damaged. Electron-microscopically manifested exuviations in microvillus of the intestinal mucosa, significantly reduced height, width and area of microvillus, damaged cell tight junction and increased apoptotic cells and other pathologic alternations are found during condition related to gut mucosa damage. Therefore, it will lead to an increase of intestinal permeability, causing translocation of bacteria and endotoxin, activation of endothelial cells, release of inflammatory mediators and cytokines, and initiation of SIRS and multiple organ dysfunction syndrome (MODS) (93).

The actual route of migration of microorganisms from intestinal lumen to the pancreatic and/or peripancreatic necrosis is not clearly understood. Breakdown of intestinal integrity is considered to be implicated in the mechanism of BT (91). Yasuda et al (2006) demonstrated that breakdown of intestinal mucosa via accelerated apoptosis increases intestinal permeability in rat SAP (92). Therefore, it is presumed that acceleration of apoptosis in intestinal epithelium causes the increase of intestinal permeability and subsequent BT (91).

Bifidobacteria may play a protective role against bacterial translocation via immunologic mechanisms. When bifidobacteria administered orally to germ-free (GF) mice, they colonize the intestinal tract and reach a concentration of 10^9–10^{10} x g^{-1} of intestinal content in 2–3 days. Translocation of bifidobacteria to mesenteric lymphatic nodes, liver, lungs, kidneys, spleen occurs for short but then disappears. In contrast, bifidobacterial translocation persist in nude mice is stopped by inoculation of T-cells from bifidobacteria-associated mice. Bifidobacterial translocation could be regulated through the T-lymphocyte mediated immunity. Moreover, experimental gut colonistian of ex-GF mice with human bifidobacteria inhibits E.coli translocation. All gram-positive enteric bacteria are not capable of such effect. Peptococcus induces the inhibition of E. coli translocation, whereas Lactobacillus acidophilus is ineffective. As for the regulation of the bifidobacterial translocation, T-cell mediated mechanism is implicated in the regulation of E. coli passage from the gut as shown by the disappearance of E. coli in internal organs of T--cell depleted mice following transfer of T-lymphocytes (13).

Taken together, the studies carried out in gnotobiotic animals strongly suggest the elicitation of an immune response by bifidobacteria allowing the host to control bacterial translocation from the gut. In infants, breast-feeding, known to favour the bifidobacterial population, is also associated with the absence of bacterial translocation during the two first weeks after birth (13).

Vascular endothelial growth factor and endothelial dysfunction

A MODS is the most serious complication in the early phase of SAP, and it remains the main contributing factor to the high mortality of this disease (56). Evidence has accumulated of the significance of apoptotic cell death in the systemic manifestations associated with SAP (58). Since the authors identified apoptosis-inducing activity in pancreatitis-associated ascitic fluid (59), a number of investigators, have reported, through animal experiments, that apoptosis occurred in the parenchymal cells constituting organs, such as alveolar epithelial cells in the lung, renal tubular cells in the kidney, and hepatocytes in the liver, and that apoptotic cell injury was involved in the mechanism of MODS in AP (65).

Vascular endothelial growth factor (VEGF), also known as vascular permeability factor (69), is a heparinbinding glycoprotein with potent angiogenic, mitogenic, and vascular permeability-enhancing activities specific for endothelial cells (91). VEGF can also stimulate cell migration and inhibit apoptosis (14, 91). VEGF has been suggested to be important mediator for inflammation during normal and pathological angiogenesis, a process that is associated with wound healing, embryonic development, and growth and metastasis of solid tumours (77). Elevated levels of VEGF have been reported in synovial fluids of rheumatoid

arthritis (81) and in sera from cancer patients (82, 83). Several studies have shown that high serum levels of VEGF are associated with poor prognosis in cancer patients. Shinzeki et al reported that serum VEGF concentrations significantly increased in patients with AP (84), but relationships with severity indexes or prognosis were not analyzed. In this study, serum VEGF levels increased in AP, but are not related to its severity or prognosis. Thus, serum VEGF levels are not as useful as a clinical marker for disease severity or prognosis. Increased vascular permeability and development of tissue oedema are pathognomonic features of AP. Although VEGF can increase vascular permeability, administration of VEGF did not affect the water content of lung, volume of ascitic fluid or hematocrit in this experimental study. It is unlikely that systemic release of VEGF plays a major role in alterations of vascular permeability.

In normal tissues, VEGF expression has been found in activated macrophages (85), keratinocytes (87), renal glomerular visceral epithelium and mesangial cells (88), hepatocytes, smooth muscle cells, Leydig cells, embryonic fibroblasts and bronchial and choroids plexus epithelium (29).

Endothelial dysfunction plays an important role in all stages of atherosclerosis, and is characterized by an increased activity of vasoconstricting factors, proinflammatory and prothrombotic mediators. Ang II with AT(1) receptor are through several mechanisms implicated in the progression of atherosclerosis. Stimulation of AT(1) receptor increases oxidative stress especially through activation of NADH/NADPH oxidase in the vascular cells. Oxidative stress is associated with activation of the inflammatory processes. Ang II via AT(1) receptor increases expression of adhesion molecules and stimulates the induction of monocyte chemoattractant protein-1 (MCP-1). AT(1) receptor enhances the activation of nuclear factor NF-kappaB, which stimulates the production of proinflammatory cytokines. Proinflammatory cytokines on the other side may induce acute-phase response in the liver. Activation of AT(1) receptor via inducible cyclooxygenase (COX)-2 promotes biosynthesis of matrix metalloproteinases (MMPs). Ang II is implicated in the process of angiogenesis. Via AT(1) receptor takes part in the regulation of VEGF, which is one of the most angiogenic factors and stimulates the activity of endothelial progenitor cells. Recently some patents were reported discussing role of different compounds for the treatment of cardiovascular disease, renovascular disease nephropathy, peripheral vascular disease, portal hypertension and ophthalmic disorders, are cyclooxygenase-2 inhibitors (94).

The role of the nervous system in etiopathogenesis of acute pancreatitis

The vagus nerve constitutes highly complex system that modulates various activity of an organism (99). Experimental data showed that efferent pathway of the vagus nerve exert strong inhibitory influence on immune system activity (cholinergic anti-inflammatory pathway) (98). Activation of vagal anti-inflammatory pathway might influence progression of wide spectrum of diseases with inflammatory components. It was found that inhibition of vagal anti-inflammatory pathway results in enhanced severity of experimental pancreatitis. Conversely, increased activity of peripheral component of vagal anti-inflammatory pathway attenuated severity of experimental pancreatitis. These data suggest that cholinergic anti-inflammatory pathway plays important role in regulation of inflammation during experimental pancreatitis (100). Importance of modulation of immune function by the nervous system in pancreatitis supports the idea of neurobiological view of etiopathogenesis of peripheral tissues diseases (96).

Conclusion

It is necessary to point out some very specific aspects of AP. Especially the severe form of acute pancreatitis (SAP) that could be described as “a very intricate and complicated disease”, involves many of the depicted processes.

Haemodynamic dysfunction during AP is secondary to reduced circulating volume, due to increased capillary permeability. The damage of splanchnic perfusion causes subsequent impairment of renal blood flow, leading to renal failure and acute tubular necrosis. Reduced tissue blood flow during AP is related to its severity.

Microcirculation disturbance is one of the major causes of pancreatic damage and other organs durig AP. Functional microcirculatory dysfunction is proportional to disease severity. It occurs later and with lesser severity in oedematous pancreatitis than in severe form of disease. Abnormal hemorheology can not only influence pancreatic microcirculation, but also causes microcirculation disturbance of extrapancreatic organs, espetially the intestine. Splanchnic hypoperfusion causes ischemic reperfusion injury, which along with gut mucosal damage represents one of the possible mechanisms of increased gut permeability.

During SAP microcirculatory disturbances and ischemic changes of the gut play important roles for the development of bacterial translocation. Sepsis due to infected pancreatic necrosis is the most serious complication in the late phase of SAP and contributes to the high mortality rate of AP. This complication is thought to be a result of the bacterial translocation from the gastrointestinal tract. Alteration of intestinal mucosal integrity may increase intestinal permeability and may be implicated in bacterial translocaion.

Increase of intestinal permeability is correlated with the changes of tight junctions and/or apoptosis of intestinal epithelial cells. VEGF has been suggested to be important mediator for inflammation during normal and pathological situations.

Activation of vagal anti-inflammatory pathway might influence progression of a wide spectrum of diseases with inflammatory components. Inhibition of vagal anti-inflammatory pathway results in enhanced severity of experimental pancreatitis. The cholinergic anti-inflammatory pathway plays an important role in regulation of inflammation during experimental pancreatitis.

References

1. Toouli J et al. Guidelines for the management of acute pancreatitis. J Gastroenterol Hepatol 2002; 17 (Suppl): S15—S39.

2. Isenmann R et al. Early severe acute pancreatitis: Characteristics of a new subgroup. Pancreas 2001; 22: 274.

3. Mitchell RM et al. Pancreatitis. Lancet 2003; 361: 1447—1455.

4. Perez A et al. Is severity of necrotizing pancreatitis increased in extended necrosis and infected necrosis? Pancreas 2002; 25: 229—233.

5. Kinnala PJ et al. Pancreatic tissue perfusion in experimental acute pancreatitis. Eur J Surg 2001; 167: 689—694.

6. Plusczyk T et al. ETA and ETB receptor function in pancreatitis-associated microcirculatory failure, inflammation, and parenchymal injury. Am J Physiol Gastrointest Liver Physiol 2003; 285: G145—G153.

7. Takeyama Y et al. Apoptotic cell death of hepatocytes in rat experimental severe acute pancreatitis. Surgery 2000; 127: 55.

8. Malleo G et al. Effects of thalidomide in a mouse

model of cerulein-induced acute pancreatitis. Shock 2008; 29: 89—97.

9. Alon T et al. Vascular endothelial growth factor acts as a survival factor for newly formed retinal vessels and has implications for retinopathy of prematurity. Nat Med 1995; 1: 1024.

10. Ueda T et al. Hematin is one of the cytotoxic factors in pancreatitis-associated ascitic fluid that causes hepatocellular injury. Surgery 2002; 131: 66.

11. Saitoh Y, Yamamoto M. Evaluation of severity of acute pancreatitis. According to a report of the cooperative national survey in Japan. Int J Pancreatol 1991; 9: 51.

12. Ranson JH et al. Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet 1974; 139: 69.

13. Romond MB et al. Does the intestinal bifidobacterial colonisation affect bacterial translocation? Anaerobe 2008;14: 43—48.

14. Munshi N et al. Lipopolysaccharide-induced apoptosis of endothelial cells and its inhibition by vascular endothelial growt facotr. J Immunol 2002; 168: 5860—5866.

15. Ueda T et al. Hepatocyte growth factor increases in injured organs and functions as an organotrophic factor in rats with experimental acute pancreatitis. Pancreas 2000; 20: 84.

16. Tubero S et al. Targeting peripheral immune response reduces the severity of necrotizing acute pankreatitis. Crit Care Med. 2009 Vol. 37, No 1.

17. Ramnath RD et al. Role of PKC-delta on substance

P-induced chemokine synthesis in pancreatic acinar cells. Am J Physiol Cell Physiol 2008; 294: C683—C692.

18. Menger MD, Vollmar B. In vivo documentation of an arteriovenous shunt in rat pancreatic acinar tissue. Pancreas. 1996; 13: 125—129.

19. Plusczyk T et al. Comparative effects of secretin (SEC) and cholecystokinin-octapeptide (CCK-8) on pancreatic microcirculation. Dig Dis Sci. 1995; 40: 1199—1206.

20. Wilmore DW et al. Effect of injury and infection on visceral metabolism and circulation. Ann Surg 1980; 192: 491—504.

21. Mofidi R et al. Can a genetic algorithm improve prediction of severity in patiens with acute pancreatitis? Br J Surf 2007; 94 (Suppl 2): 5.

22. Chang YT et al. Association of cystic fibrosis transmembrane

conductance regulator (CFTR) mutation/variant/haplotype and tumor necrosis factor (TNF) promoter polymorphism in hyperlipidemic pancreatitis. Clin Chem 2008; 54: 131—138.

23. Lo SK et al. Endoscopic measurement of pancreatic blood flow. Gastrointest Endosc Clin N Am 1998; 8: 249—266.

24. Warshaw AL, O'Hara PJ. Susceptibility of the pancreas to ischemic injury in shock. Ann Surg 1978; 188: 197—201.

25. Mentula P et al. Serum levels of mast cell tryptase, vascular endothelial growth factor and basic fibroblast growth factor in patients with acute pancreatitis. Pancreas 2003; 27: E29.

26. Halonen KI et al. Predicting fatal outcome in the early phase of severe acute pancreatitis by using novel prognostic models. Pancreatology 2003; 3: 309—315.

27. Benz S et al. Effect of nitric oxide in ischemia/reperfusion of the pancreas. J Surg Res 2002; 106: 46—53.

28. Fava RA et al. Vascular permeability factor/endothelial growth factor (VPF/VEGF): Accumulation and expression in human synovial fluids and rheumatoid synovial tissue. J Exp Med 1994; 180: 341.

29. Miyamoto K et al. Protective efect of vascular endothelial growt factor/vascular permeability factor 165 and 121 on glomerular endothelial cell injury in the rat. Lab Invest 2004; 84: 1126—1136.

30. De Waele JJ et al. Intra-abdominal hypertension in patients with severe acute pancreatitis. Crit Care 2005; 9: 452—457.

31. Blackstone MO. Hypothesis: vascular compromise is the central pathogenic mechanism for acute hemorrhagic pancreatitis. Perspect Biol Med 1995; 39: 56—63.

32. al-Mufti RA, Williamson RC. Experimental models of pancreatitis. Ann Acad Med Sing 1999; 28: 133—140.

33. Baumgartner HK et al. Caspase-8-mediated apoptosis induced by oxidative stress is independent of the intrinsic pathway and dependent on cathepsins. Amer J Physiol Gastrointest Liver Physiol 2007; 293: G296—G307.

34. Broe PJ et al. The role of ischemia in acute pancreatitis: studies with an isolated perfused canine pancreas. Surgery 1982; 91: 377—382.

35. Windsor JA. Search for prognostic markers for acute pancreatitis. Lancet 2000; 355: 1924—1925.

36. Andersson R et al. Effect of a platelet-activating factor antagonist on pancreatitis-associated gut barrier dysfunction in rats. Pancreas 1998; 17: 107—119.

37. Gao HK et al. Toll-like receptor 4 Asp299Gly polymorphism is associated with an increased risk of pancreatic necrotic infection in acute pancreatitis: a study in the Chinese population. Pancreas 2007; 34: 295—298.

38. Kusterer K et al. Microcirculatory changes in sodium taurocholate-induced pancreatitis in rats. Amer J Physiol 1991; 260: G346—G351.

39. Chao W, Olson MS. Platelet-activating factor: receptors and signal transduction. Biochem J 1993; 292: 617—27.

40. Furukawa M et al. Role of local pancreatic blood flow in development of hemorrhagic pancreatitis induced by stress in rats. Pancreas 1993; 8: 499—505.

41. Juvonen PO et al. Gut permeability in patients with acute pancreatitis. Scand J Gastroenterol 2000; 35: 1314—1318.

42. Kingsnorth AN et al. Randomized, doubleblind phase II trial of lexipafant, a platelet-activating factor antagonist, in human acute pancreatitis. Brit J Surg 1995; 82: 1414—1420.

43. Thrower E et al. Molecular basis for pancreatitis. Curr Opinion Gastroenterol 2008, 24: 580—585.

44. Steinberg W, Tenner S. Acute pancreatitis. New Engl J Med 1994; 330: 1198—1210.

45. Juvonen PO et al. Gastric tonometry in assessing splanchnic tissue perfusion in acute pancreatitis. Scand J Gastroenterol 2000; 35: 318—321.

46. Inoue K et al. Further evidence for endothelin as an important mediator of pancreatic and intestinal ischemia in severe acute pancreatitis. Pancreas 2003; 26: 218—223.

47. Siqin D et al. The key event of acute pancreatitis: Pancreatic duct obstruction and bile reflux, not a single one can be omitted. Med Hypotheses 2009; doi: 10.1016/j.hehy.2008.12.009.

48. Modifi R et al. Risk assessment in acute pankreatitis. Brit J Surg 2009; 96: 137—150.

49. Leveau P et al. Alterations in intestinal motility and microflora in experimental acute pancreatitis. Int J Pancreatol 1996; 20: 119—125.

50. Hollo G et al. Retinopathy of pancreatitis indicates multiple-organ failure and poor prognosis in severe acute pancreatitis. Acta Ophthalmol 1994; 72: 114—117.

51. Bong JJ et al. Thrombotic microangiopathy in acute pancreatitis. Pancreas 2002; 25: 107—109.

52. Beattie GC et al. Evidence for a central role for selective mesentericangiography in the management of the major vascular complications of pancreatitis. Amer J Surg 2003; 185: 96—102.

53. Bergert H et al. Management and outcome of hemorrhage due to arterial pseudoaneurysms in pancreatitis. Surgery 2005; 137: 323—328.

54. Inoue K et al. Angiographic features in acute pancreatitis: the severity of abdominal vessel ischemic change reflects the severity of acute pancreatitis. JOP 2003; 4: 207—213.

55. Wang XD et al. Carbon dioxide transport in rats with acute pancreatitis. Int J Pancreatol 1996; 19: 103—112.

56. Beger HG et al. Bacterial contamination of pancreatic necrosis. A prospective clinical study. Gastroenterology 1986; 91: 433.

57. Duarte-Rojo A et al. Time Frames for Analysis of Inflammatory Mediators in Acute Pancreatitis: Improving Admission Triage. Dig Dis Sci 2008. DOI 10.1007/s10620-008-0615-1

58. Runkel NS et al. The role of the gut in the development of sepsis in acute pancreatitis. J Surg Res 1991; 51: 18.

59. Medich DS et al. Pathogenesis of pancreatic sepsis. Amer J Surg 1993; 165: 46.

60. Kerner T et al. Determinants of pancreatic microcirculation in acute pancreatitis in rats. J Surg Res 1996; 62: 165—171.

61. Assicot M et al. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993; 341: 515—518.

62. Van Acker GJ et al. Tumor progression locus-2 is a critical regulator of pancreatic and lung inflammation during acute pancreatitis. J Biol Chem 2007; 282: 22140—22149.

63. Juvonen PO et al. Splanchnic tissue perfusion in acute experimental pancreatitis. Scand J Gastroenterol 1999; 34: 308—314.

64. Liu X et al. Measurement of pancreatic blood flow with the intraductal electrode method of the hydrogen clearance technique in acute pancreatitis in rats. Pancreas 1996; 13: 289—294.

65. Wang XD et al. Alterations in intestinal function in acute pancreatitis in an experimental model. Brit J Surg 1996; 83: 1537.

66. Keogan MT et al. Outcome analysis of patients with acute pancreatitis by using an artificial neural network. Acad Radiol 2002; 9: 410—419.

67. Rau BM et al. Early Assessment of Pancreatic Infections and Overall Prognosis in Severe Acute Pancreatitis by Procalcitonin (PCT). Ann Surg 2007; 245: 745—754.

68. Donaldson LA, Schenk WG Jr. Experimental acute pancreatitis: the changes in pancreatic oxygen consumption and the effect of Dextran 40. Ann Surg 1979; 190: 728—731.

69. Ammori BJ et al. Early increase in intestinal permeability in patients with severe acute pancreatitis: Correlation with endotoxemia, organ failure, and mortality. J Gastrointest Surg 1999; 3: 252.

70. Kinnala PJ et al. Splanchnic and pancreatic tissue perfusion in experimental acute pancreatitis. Scand J Gastroenterol 2002; 37: 845—849.

71. Foitzik T et al. Effect of microcirculatory perfusion on distribution of trypsinogen activation peptides in acute experimental pancreatitis. Dig Dis Sci 1995; 40: 2184—2188.

72. Aho HJ et al. Human acute pancreatitis: a light and electron microscopic study. Acta Pathol Microbiol Immunol Scand 1982; 90: 367—373.

73. Pitkaranta P et al. Vascular changes of pancreatic ducts and vessels in acute necrotizing, and in chronic pancreatitis in humans. Int J Pancreatol 1991; 8: 13—22.

74. Haiyan Liu et al. Early gut mucosal dysfuntion in patients with acute pancreatitis. Pancreas 2008; 36 (2).

75. Chen HM et al. Early microcirculatory derangement in mild and severe pancreatitis models in mice. Surg Today 2001; 31: 634—642.

76. Sonnenburg JL et al. Glycan foraging in vivo by an intestine-adapted bacterial symbiont. Science 2005; 307: 1955—1959.

77. Balda MS, Matter K. Tight junctions. J Cell Sci 1998; 111 (5): 541.

78. Bloechle C et al. Inhibition of bradykinin B2 receptor preserves microcirculation in experimental pancreatitis in rats. Amer J Physiol 1998; 274: G42—G51.

79. Hackert T et al. Effects of heparin in experimental models of acute pancreatitis and post-ERCP pancreatitis. Surgery 2004; 135: 131—138.

80. Plusczyk T et al. Somatostatin attenuates microcirculatory impairment in acute sodium taurocholate-induced pancreatitis. Dig Dis Sci 1998; 43: 575—585.

81. Kucharzik T et al. Neutrophil transmigration in inflammatory bowel disease is associated with differential expression of epithelial intercellular junction proteins. Amer J Pathol 2001; 159: 2001.

82. Nusrat A et al. Clostridium difficile toxins disrupt epithelial barrier function by altering membrane microdomain localization of tight junction proteins. Infect Immun 2001; 69: 1329.

83. Chen ML et al. Protein kinase C signalling regulates ZO-1 translocation and increased paracellular flux of T84 colonocytes exposed to Clostridium difficile toxin A. J Biol Chem 2002; 277: 4247.

84. Shinzeki M et al. Intraperitoneal administration of oxygenated perfluorochemical inhibits bacterial translocation associated with severe acute pancreatitis. Kobe J Med Sci 2003; 49: 17.

85. Takeyama Y. Significance of apoptotic cell death in systemic complications with severe acute pancreatitis. J Gastroenterol 2005; 40: 1.

86. Kelly DM et al. Microvasculature of the pancreas, liver, and kidney in cerulein-induced pancreatitis. Arch Surg 1993; 128: 293—295.

87. Hori Y et al. Macrophage-derived transforming growth factor-beta1 induces hepatocellular injury via apoptosis in rat severe acute pancreatitis. Surgery 2000; 127: 641.

88. Rahman SH et al. Intestinal hypoperfusion contributes to gut barrier failure in severe acute pancreatitis. J Gastrointest Surg 2003; 7: 26.

89. Mofidi R et al. Identification of severe acute pancreatitis using an artificial neural network. Sumery 2007; 141: 59—66.

90. Xue P et al. Effect of Chaiqinchengqi decoction on sarco/endoplasmic reticulum Ca2+-ATPase mRNA expression of pancreatic tissues in acute pancreatitis rats. World J Gastroenterol 2008; 14 (15): 2343—2348.

91. Nakajima T et al. Pancreas 2007; 34: 410—416.

92. Yasuda T et al. Breakdown of intestinal mucosa via accelerated apoptosis increases intestinal permeability in experimental severe acute pancreatitis. J Surg Res 2006; 135: 18—26.

93. Zhang X et al. Mechanism of acute pancreatitis complicated with injury of intestinal mucosa barrier. J Zhejiang Univ Sci B 2007; 8 (12): 888—895.

94. Skultetyova D et al. The role of angiotensin type 1 receptor in inflammation and endothelial dysfunction. Rec Pat Cardiovasc Drug Discov 2007; 2 (1): 23—27.

95. Mifkovic A, Pindak D et al. Septic complications of acute pancreatitis. Bratisl Lek Listy 2006; 107 (8): 296—313.

96. Mravec B et al. Neurobiological principles in the etiopathogenesis of disease: when diseases have a head. Med Sci Monit 2008 (accepted).

97. Liddle RA. The role of Transient Receptor Potential Vanilloid 1 (TRPV1) channels in pancreatitis. Biochim Biophys Acta 2007; 1772 (8): 869—878.

98. Czura CJ et al. Neural inhibition of inflammation: the cholinergic anti-inflammatory pathway. J Endotoxin Res 2003; 9 (6): 409—413.

99. Mravec B, Hulin I. Does vagus nerve constitute a self-organization complexity or a "hidden network"? Bratisl Lek Listy 2006; 107 (1—2): 3—8.

100. van Westerloo DJ et al. The vagus nerve and nicotinic receptors modulate experimental pancreatitis severity in mice. Gastroenterology 2006; 130 (6): 1822—1830.

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