A mouse model of severe acute pancreatitis induced with caerulein and lipopolysaccharide

Shi-Ping Ding, Ji-Cheng Li, Chang Jin

ABSTRACT

AIM: To establish a non-traumatic, easy to induce and reproducible mouse model of severe acute pancreatitis (SAP) induced with caerulein and lipopolysaccharide (LPS).

METHODS: Thirty-two healthy mature NIH female mice were selected and divided at random into four groups (each of 8 mice), i.e., the control group (NS group), the caerulein group (Cn group), the lipopolysaccharide group (LPS group), and the caerulein+LPS group (CN+LPS group). Mice were injected intraperitoneally with caerulein only, or LPS only, and caerulein and LPS in combination. All the animals were then killed by neck dislocation three hours after the last intraperitoneal injection. The pancreas and exo-pancreatic organs were then carefully removed for microscopic examination. The pancreatic acinus was further observed by transmission electron microscope (TEM). Pancreatic weight, serum amylase, serum nitric oxide (NO) concentration, superoxide dismutase (SOD) and malondialdehyde (MDA) concentration of the pancreas were assayed respectively.

RESULTS: (1) NS animals displayed normal pancreatic structure both in the exocrine and endocrine. In the LPS group, the pancreas was slightly edematous, with the infiltration of a few inflammatory cells and the necrosis of the adjacent fat tissues. All the animals of the Cn group showed distinct signs of a mild edematous pancreatitis characterized by interstitial edema, infiltration of neutrophil and mononuclear cells, but without obvious parenchyma necrosis and hemorrhage. In contrast, the CN+LPS group showed more diffuse focal areas of nonviable pancreatic and hemorrhage as well as systemic organ dysfunction. According to Schmidt’s criteria, the pancreatic histologic score showed that there existed significant difference in the Cn+LPS group in the interstitial edema, inflammatory infiltration, parenchyma necrosis and parenchyma hemorrhage in comparison with those of the Cn group, LPS group and NS group (P<0.01 or P<0.05). (2) The ultrastructure of acinar cells was seriously damaged in the Cn+LPS group. Chromatin margination of nuclei was present, the number and volume of vacuoles greatly increased. Zymogen granules (ZGs) were greatly decreased in number and endoplasmic reticulum exhibited whors. The swollen mitochondria appeared, the crista of which was decreased in number or disappeared. (3) Pancreatic weight and serum amylase levels in the Cn+LPS was significantly higher than those of the NS group and the LPS group respectively (P<0.01 or P<0.05). However, the pancreatic weight and serum amylase concentration showed no significant difference between the CN+LPS group and the Cn group. (4) NO concentration in the CN+LPS group was significantly higher than that of NS group, LPS group and Cn group (P<0.05 or P<0.01). (5) The SOD and MDA concentration of the pancreas in the CN+LPS group were significantly higher than those of NS, LPS and Cn groups (P<0.05 or P<0.01). CONCLUSION: The mouse model of severe acute pancreatitis could be induced with caerulein and LPS, which could be non-traumatic and easy to induce, reproducible with the same pathological characteristics as those of SAP in human, and could be used in the research on the mechanism of human SAP.

Ding SP, Li JC, Jin C. A mouse model of severe acute pancreatitis induced with caerulein and lipopolysaccharide. World J Gastroenterol 2003; 9(3): 584-589

http://www.wjgnet.com/1007-9327/9/584.htm

INTRODUCTION

Severe acute pancreatitis (SAP) is characterized by local pancreatic necrosis as well as systemic organ failure and is still associated with a higher morbidity and mortality despite continuing improvements in critical care[1-9]. Several animal models have been developed for studying the mechanism, recovery, prognosis and treatment of human SAP[10-12]. However, these methods such as retrograde pancreatic duct injection, intraductal infusion of sodium taurocholate, closed duodenal loop, pancreatic duct obstruction are so invasive and complex in operation that the mortality of the animals was high[10-12]. The aim of this study is to establish a SAP animal model induced with caerulein and lipopolysaccharide (LPS), which is non-traumatic, convenient and easy to practise, and reproducible and with the same histopathologic characteristics as those of SAP in human.

MATERIALS AND METHODS

Chemicals

Cerulein and LPS (Escherichia coli 0111:B4) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Assay kits for serum amylase, NO, SOD and MDA concentration were from Nanjing Jiancheng Biological Products Institute (Nanjing, China). Other reagents used were of analytic grade.

Animal and grouping

Thirty-two healthy mature NIH female mice, weighing 22.0-28.0 g, provided by Experimental Animal Center of Zhejiang Academy of Medical Sciences, were selected and divided at random into four groups (each of 8 mice), i.e. the control group (NS group), the caerulein group (Cn group), the lipopolysaccharide group (LPS group), and the caerulein+LPS group (CN+LPS group). Mice were injected intraperitoneally with caerulein only, or LPS only, and caerulein and LPS in combination. All the animals were then killed by neck dislocation three hours after the last intraperitoneal injection. The pancreas and exo-pancreatic organs were then carefully removed for microscopic examination. The pancreatic acinus was further observed by transmission electron microscope (TEM). Pancreatic weight, serum amylase, serum nitric oxide (NO) concentration, superoxide dismutase (SOD) and malondialdehyde (MDA) concentration of the pancreas were assayed respectively.
lipopolysaccharides group (LPS group), the caerulein + lipopolysaccharides group (Cn+LPS group).

Establishment of the model of severe acute pancreatitis
All the female NIH mice were fed with a standard diet and fasted for 18 hours before induction of pancreatitis. They received water ad libitum during the experiments. In the NS group, the animals were injected intraperitoneally by normal saline at a dose of 50 ml/kg at a 1 h interval six times. In the Cn group, acute pancreatitis was induced by six intraperitoneal injections of caerulein administered at a dose of 50 µg/kg at a 1 h interval. This pancreatitis was mild, and all animals survived. In the LPS group, the animals were injected intraperitoneally with normal saline (50 ml/kg) six times every one hour prior to the intraperitoneal infusion of LPS (10 mg/kg). In the Cn + LPS group, the mice were induced by LPS challenge after induction of mild pancreatitis, i.e., the mice received intraperitoneal injections of 10 mg/kg LPS immediately after the sixth caerulein injection. Three hours later, all the animals were killed by neck dislocation and the pancreas was carefully dissected from its attachment to the stomach, duodenum and spleen. Fat and tissue excess were trimmed away. The pancreas was rinsed with saline, blotted on paper and weighed. And then, one part was fixed and embedded in paraffin wax for histological analysis; the other part was immediately frozen in liquid nitrogen and stored at -78 °C until the measurement of SOD and MDA concentration. And the liver, kidney and lung were also carefully removed. Blood samples were obtained from femoral artery and were stored at -78 °C until use.

Histological examination
For histological examination, the pancreas was fixed in 10 % formaldehyde for 24 hours, embedded in paraffin, and stained with haematoxylin and eosin. According to Schmidt’s standard[13], a pathologist who was blinded to the treatment protocol scored the tissues for edema, inflammatory infiltration, parenchymal necrosis, and hemorrhage in 20 fields. Grading for edema was scaled as: 0, absent or rare; 1, edema in the interlobular space; 2, edema in the intralobular space; and 3, the isolated-island shape of pancreatic acinus. Inflammation was scored as: 0, absent; 1, mild; 2, moderate; and 3, severe. The parenchyma necrosis was as follows: 0, absent; 1, focal (<5 %); 2, and/or sublobular (<20 %); 3, and/or lobular (>20 %). The parenchyma hemorrhage was scored as: 0, absent; 1, mild; 2, moderate and 3, severe. Liver, kidney and lung sections were similarly stained and assessed for histological changes.

Separate experiment was performed to observe the changes of the pancreas. Pancreatic tissues were double fixed in 2.5 % glutaraldehyde and 1 % osmic acid for 2 hours, then stained with 2 % acetic acid U rapidly, dehydrated in a graded series of alcohol and acetone, embedded in Epon 812 and cut with Leica Ultracut UCT ultramicrotome. Specimens were double stained by acetic acid U and lead citrate fluid and examined with Philips Tecnai 10 TEM operated at 80Kv.

Measurement of serum amylase, NO concentration, SOD and MDA concentration of the pancreas
Serum amylase and NO concentration were assayed according to I-starch chromatometry and a copper-coated cadmium reduction method respectively. The pancreas was isolated and was made homogenate. SOD and MDA concentration of the pancreas were measured by the xanthine oxidase method and the sulfo-barbituric acid method respectively.

Statistical analyse
Data were expressed as means ± SD and analyzed by two-tailed Student’s t test.

RESULTS
Histological examination
Microscopic examination NS animals displayed normal pancreatic histology both in the exocrine and endocrine. In the LPS group, the pancreas was slightly edemalous (Figure 1), with the infiltration of a few inflammatory cells and the necrosis of the adjacent fat tissues. The animals of the Cn group treated with caerulein, showed distinct signs of a mild edematous pancreatitis characterized by interstitial edema (Figure 2), infiltration of neutrophil and mononuclear cells, but without obvious parenchyma necrosis and hemorrhage. The organs, except for the pancreas, showed normal histological characteristics. However, the animals of the Cn+LPS group, which was induced with caerulein and aggravated by subsequent LPS injection, showed the features of a severe form of acute pancreatitis characterized by expansion of interlobular and intralobular spaces caused by moderate to severe interstitial edema, extensive infiltration with inflammatory cells, more diffuse focal areas of nonviable pancreatic parenchyma (Figure 3). Necrosis of peripancreatic fat was also a distinct feature in these animals. In addition, renal cells were swollen (Figure 4A); the lobules of liver was disorganized, with the vacuolization of liver cells (Figure 4B) and a lot of erythrocyte and inflammatory cells also infiltrated in the cavity of pulmonary alveolus (Figure 4C).

According to Schmidt’s criteria, the histological score showed that there existed significant difference in the Cn+LPS group in the interstitial edema, inflammatory infiltration, parenchyma necrosis and parenchyma homorrage as compared with those of the Cn group, the LPS group and the NS group (P<0.01 or P<0.05) (Table 1).

| Groups          | Interstitial edema | Inflammatory infiltration | Parenchyma necrosis | Parenchyma hemorrhage |
|-----------------|--------------------|---------------------------|--------------------|-----------------------|
| NS              | 0.0                | 0.0                       | 0.0                | 0.0                   |
| Cn              | 1.95±0.26          | 1.12±0.22                 | 0.63±0.09          | 0                     |
| LPS             | 0.25±0.03          | 0.25±0.43                 | 0.33±0.03          | 0                     |
| Cn+LPS          | 2.75±0.47          | 2.88±0.33                 | 2.75±0.33          | 1.25±0.26             |

*P<0.05, **P<0.01, vs NS group; †P<0.05, ‡P<0.01, vs Cn group.

Electron microscope examination of the pancreatic acinus
The ultrastructure of acinar cells was normal in the NS group. In the cytoplasm of the acinar cells, a plenty of rough endoplasmic reticulum (RER) and ribosome and a great deal of ZGs appeared. After LPS stimulation, a few cytoplasmic vacuoles formed in acinar cells (Figure 5). In the Cn group, a few cytoplasmic vacuoles in acinar cells also appeared, and ZGs were decreased in number. The RER and the mitochondria was slightly swollen (Figure 6). However, in the Cn+LPS group, the morphological alterations of mouse pancreatic acinar cells were observed under transmission electron microscope. Chromatin margination of nuclei was present (Figure 7A), the number of vacuoles greatly increased and their volume also greatly increased (Figure 7B). ZGs were greatly decreased in number and endoplasmic reticulum exhibited whorls (Figure 7C). The swollen mitochondria appeared, the crista of which was decreased or disappeared (Figure 7D).

Comparison of pancreatic weight and serum amylase
Subsequent experiment showed that pancreatic weight and serum amylase in the Cn +LPS and the Cn group were significantly higher than those in the NS group and the LPS group respectively (P<0.01 or P<0.05). However, the pancreatic wet weight and serum amylase showed no significant difference between the Cn+LPS and the Cn groups (Table 2).
Figure 1 In the LPS group, the pancreas was slightly edemalous. ×100.

Figure 2 Microscopic section of the pancreas from the Cn group, showing the features of acute edematous pancreatitis notably interstitial edema. ×100.

Figure 3 In the Cn+LPS group, more diffuse focal areas of nonviable pancreatic parenchyma appeared obviously. ×100.

Figure 4 The histological change of the exo-pancreatic organs in the Cn+LPS group. A: Renal cells were swollen; ×100; B: The vacuolization of liver cells; ×400; C: A lot of erythrocyte and inflammatory cells also infiltrated in the cavity of pulmonary alveolus. ×100.

Figure 5 A few cytoplastic vacuoles formed in acinar cells in the LPS group. ×10 000.

Figure 6 In the Cn group, a few cytoplastic vacuoles in acinar cell appeared, and ZGs were decreased in number. The RER and the mitochondria was slightly swollen. ×10 000.

Figure 7 The ultrastructure change of the pancreatic acinus in the Cn+LPS group. A: Chromatin margination of nuclei was present, the swollen mitochondria appeared; ×7 000; B: the number of vacuoles greatly increased and their volume also greatly increased; ×7 000; C: the endoplasmic reticulum exhibited whorls; ×14 000; D: The crista of mitochondria was decreased or disappeared. ×20 000.


**DISCUSSION**

Acute pancreatitis may be classified histologically as interstitial edematous or necrotizing according to the inflammatory changes in the pancreatic parenchyma. As for a mild edematous form, the pancreas observed under light microscope showed interstitial edema, interstitial hyperemia and inflammatory cell infiltration and occasionally punctate fat necrosis, but without obvious parenchyma necrosis and hemorrhage. However, a severe necrotizing form is characterized by extensively coagulative necrosis and hemorrhage as well as systemic organ dysfunction. In the present study, the results showed that the animals of the Cn group, which was treated with caerulein only, showed distinct signs of a mild edematous pancreatitis, indicating that the pancreatic weight and serum amylase became gradually higher than those of the NS group and the LPS group. The microscopic examination showed interstitial edema and inflammatory cell infiltration in the pancreas, and slight parenchyma necrosis and hemorrhage. And the organs except the pancreas, had a normal histological feature. Furthermore, transmission electron microscopic observation of the acinus cells displayed a few cytoplasmic vacuoles in acinar cell, and ZGs were found decreased in number and the RER and the mitochondrion were slightly swollen. In the LPS group which was treated with LPS only, serum amylase and pancreatic weight had an increasing tendency, but the pancreas showed interstitial edema and the formation of a few vacuoles in the cytoplasm of the acinar cells. LPS could not induce acute pancreatitis, which further confirmed Jaworek’s findings. In the Cn+LPS group, which was induced by caerulein and aggravated by subsequent LPS injection, the level of serum amylase and pancreatic weight increased and the pancreas became edematous and the inflammatory cells infiltrated and necrosis and hemorrhage appeared obviously in the pancreas, the ultrastructure of the acinus was destroyed, the organs except the pancreas was lesioned to a different extent. Moreover, in the histological score, there existed significant difference in the Cn+LPS group in the interstitial edema (2.75±0.43), inflammatory infiltration (2.88±0.33), parenchyma necrosis (2.75±0.33) and parenchyma hemorrhage (1.25±0.26) in comparison with those of caerulein only (1.95±0.26; 1.12±0.22; 0.63±0.09; 0), those of LPS only (0.25±0.03; 0.25±0.43; 0; 0) and the NS group (0; 0; 0; 0) (P<0.01 or P<0.05). It is thus clear that, when induced with caerulein and LPS in combination, the pancreas was destroyed so severely as to result in inflammatory reaction in the body and systemic organ dysfunction. Moreover, the model induced with caerulein and LPS was almost stable under the condition of duplications. Therefore, the mouse model induced with caerulein and LPS was non-traumatic, convenient, easily replicating and bearing the same histological changes as those of human SAP.

Caerulein is a kind of ten-peptide substances, the analog of cholecystokinin, and possesses different biological activities. Caerulein can stimulate the acinar cells to excrete a large amount of digestive enzyme and pancreatic fluid, resulting in a mild edematous pancreatitis characterized by a higher serum amylase level, interstitial edema, leukocyte infiltration and the vacuolation of acinar cells. LPS is a kind of endotoxin, which could activate the mononuclear cell system to release cytokines to switch on systemic inflammation reaction. Clinically, the endotoxin level was related to the severity of the illness. Therefore, the mechanism to develop severe acute pancreatitis and organ failure with caerulein and LPS might be that caerulein could activate the pancreatin to destroy the pancreas, and activate inflammatory cells to release inflammation mediators and subsequently LPS challenged the reaction of inflammation medium, thus developing local pancreatitis into severe inflammation reaction in the body.

Recent evidence indicated that these cytokines from the inflamed pancreas can activate the production of the inducible nitric oxide (NO) synthase, resulting in overproduction of NO, which acts as a key final cellular and intercellular mediator. In this study, the concentration of NO was significantly higher in the Cn+LPS group, as compared with that of caerulein alone or LPS alone (P<0.01). NO as an endothelium-derived relaxing factor (EDRF) and a highly reactive free radical, is produced from the amino acid L-arginine by a family of isoenzymes, the nitric oxide synthases (NOS). Two broad groups can be

### Table 2 Comparison of pancreatic wet weight and serum amylase between groups (x±s)

| Groups | Pancreatic weight (mg) | Serum amylase (U/L) |
|--------|------------------------|---------------------|
| NS     | 247.70±30.20           | 1861.35±303.36      |
| Cn     | 337.20±50.90<sup>c</sup> | 11042.32±528.03<sup>d</sup> |
| LPS    | 290.10±39.70           | 2385.50±73.60<sup>c</sup> |
| Cn+LPS | 380.00±32.00<sup>c</sup> | 10031.70±906.19<sup>d</sup> |

<sup>a</sup> P<0.05, <sup>b</sup> P<0.01, vs NS group; <sup>c</sup> P<0.05, <sup>d</sup> P<0.01, vs LPS group.

### Comparison of NO concentration

There was significant difference in the concentration of NO among the groups (Figure 8). The results showed that the concentration of NO in the Cn+LPS group was significantly higher than that in the NS, LPS and Cn groups (P<0.01).

![Figure 8](image-url)

**Figure 8** Comparison of NO concentration between groups (x±s) (n=8). <sup>a</sup> P<0.01, vs NS group; <sup>b</sup> P<0.01, vs LPS group; <sup>c</sup> P<0.05, vs Cn group.

### SOD and MDA concentration of the pancreas

The concentration of SOD and MDA in the pancreas showed significant difference between groups (Table 3). SOD concentration of the pancreas in the Cn+LPS group decreased significantly as compared with that of the NS, LPS and Cn groups. However, MDA concentration of the pancreas in the Cn+LPS group increased significantly compared with that of the NS, LPS and Cn groups.

### Table 3 Comparison of SOD and MDA concentration between groups (x±s) (n=8)

| Groups   | SOD concentration (U/mgprot) | MDA concentration (nmol/mgprot) |
|----------|------------------------------|---------------------------------|
| NS       | 151.67±10.74                 | 0.74±0.34                       |
| Cn       | 135.73±10.87                 | 0.79±0.31                       |
| LPS      | 136.05±17.25                 | 0.97±0.29                       |
| Cn+LPS   | 85.13±17.19<sup>d</sup>      | 1.22±0.24<sup>d</sup>           |

<sup>a</sup> P<0.05, <sup>b</sup> P<0.01, vs NS group; <sup>c</sup> P<0.01, vs LPS group; <sup>d</sup> P<0.01, vs Cn group.
identified: constitutive (cNOS) and inducible (iNOS). cNOS is present predominantly as a normal constituent of healthy endothelial cells (endothelial isoform, eNOS) and synthesizes NO in small amounts in response to physical or receptor stimulation. iNOS is not a normal cellular constituent, but can be expressed in a wide variety of cells and generates large amounts of NO in a sustained and largely uncontrolled manner. Excessive production of NO causes vasodilatation and hypotension that is refractory to vasoconstriction, together with increased microvascular permeability and extravascular third spacing. The physiological inability to correct these adverse responses results in end organ hypoperfusion, oedema, initiation of anaerobic metabolism, and end organ dysfunction. Moreover, the reaction of NO with superoxide causes the formation of peroxynitrite, which is a powerful oxidant and cytotoxic agent and may play an important role in the cellular damage associated with the overproduction of NO. The spontaneous reaction of peroxynitrite with proteins makes the nitration of tyrosine residues to form nitrotyrosine, which is a specific nitrination product of peroxynitrite and a marker for peroxynitrite induced oxidative tissue damage. It is thus evident that the increase of NO concentration is related to the lesion of pancreas and other organs. In addition, the concentration of SOD as an antioxidant significantly lowered and that of MDA as the lipid peroxide significantly increased, which further indicated that the free radical reaction and oxidation response could be intensified with caerulein and LPS so that a mild edematous form could change subsequently into a severe necrotizing form.

REFERENCES
1. Baron TH, Morgan DE. Acute necrotizing pancreatitis. N Engl J Med 1999; 340: 1412-1417
2. Pastor CM, Frossard JL. Are genetically modified mice useful for the understanding of acute pancreatitis. FASEB J 2001; 15: 893-897
3. Lecesne R, Taoureil P, Blet PM, Atri M, Reinhold C. Acute pancreatitis: Interobserver agreement and correlation of CT and MR cholangiopancreatography with outcome. Radiology 1999; 213: 727-735
4. Slavin J, Ghaneh P, Sutton R, Hartley M, Rowlands P, Garvey C, Hughes M, Neoptolemos J. Management of necrotizing pancreatitis. World J Gastroenterol 2001; 7: 476-481
5. Wu XN. Treatment revised and factors affecting prognosis of severe acute pancreatitis. World J Gastroenterol 2000; 6: 633-635
6. Qi QH, Guo LM. Acute pancreatitis: Interobserver agreement and correlation of CT and MR cholangiopancreatography with outcome. World J Gastroenterol 2000; 6: 329-332
7. Zhao M, Chen RF. Pathogenesis of acute lung injury induced by acute necrotizing pancreatitis. Shijie Huanren Xiuhaoxia Zazhi 2001; 9: 954-957
8. Chen QP. Enteral nutrition and acute pancreatitis. World J Gastroenterol 2001; 7: 185-192
9. Shang ZM, Wang BE, Zhang SW, Ci XL. The establishment of the rat model of severe acute pancreatitis. Shijie Huanren Xiuhaoxia Zazhi 2000; 8: 921
10. Tashiro M, Saka M, Yamauchi T, Yoshida T, Ueda T, Takeuchi K. Early diagnosis of severe acute pancreatitis. Gastroenterol Jpn 1998; 33: 115-118
11. Shimizu T, Shiratori K, Sawada T, Kobayashi M, Hayashi N, Satome H, Keith JC. Recombinant human interleukin-11 decreases severity of acute necrotizing pancreatitis in mice. Pancreas 2000; 21: 134-140
12. Li JC. Discussion on the conception of severe acute pancreatitis. Shijie Huanren Xiuhaoxia Zazhi 1999; 7: 1072-1073
13. Wu XN. Current concept of pathogenesis of severe acute pancreatitis. World J Gastroenterol 2000; 6: 32-36
14. Pezzilli R, Mancini F. Assessment of severity of acute pancreatitis: a comparison between old and most recent modalities used to evaluate this peripheral problem. World J Gastroenterol 1999; 5: 283-285
15. Uhl W, Buchler MW, Malfertheiner P, Beger HG, Adler G, Gaus W. German pancreatitis study group. A randomized, double blind, multicentrical of octreotide in moderate to severe acute pancreatitis. Gut 1999; 45: 57-104
16. Hartwig W, Carster EA, Jimenez RE, Werner J, Fischman AJ, Castillo CF, Warshaw AL. Chymotatic peptide uptake in acute pancreatitis: correlation with tissue accumulation of leukocytes. J Appl Physiol 1999; 87: 743-749
17. Pezzilli R, Morselli- labate AM, Miniero R, Barakat B, Fiocchi M, Cappelletti O. Simultaneous serum assays of lipase and interleukin-6 for early diagnosis and prognosis of acute pancreatitis. Clin Chim Acta 1999; 34: 1762-1767
18. Zhou ZG, Chen YD. Influencing factors of pancreatic microcirculatory impairment in acute pancreatitis. World J Gastroenterol 2002; 8: 406-412
19. Chen DL, Wang WZ, Wang JY. Epidermal growth factor prevents gut atrophy and maintains intestinal integrity in rats with acute pancreatitis. World J Gastroenterol 2000; 6: 762-765
20. Kohut M, Nowak A, Nowakowska-Dulawa E, Marek T. Presence and density of common bile duct microthlas in acute biliary pancreatitis. World J Gastroenterol 2002; 8: 558-561
21. Fleischer F, Davin R, Gobe K, Wagner AC. Stress kinase inhibition modulates acute experimental pancreatitis. World J Gastroenterol 2001; 7: 259-265
22. Tiscomia OM, Hanamura S, de Leman ES, Otero G, Waisn H, Tissomia-Wasserlman P, Bant S. Biliary acute pancreatitis: a review. World J Gastroenterol 2000; 6: 157-168
23. Frossard JL, Hadengue A, Pastor CM. New serum markers for the detection of severe acute pancreatitis in humans. Am J Respir Crit Care Med 2001; 164: 162-170
24. Hamsuna A, Kawiwa D, Hiroiuchi A, Unno H, Furuya N, Amasaki M, Fujikshima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K. High serum IgG concentrations in patients with sclerosing pancreatitis. N Engl J Med 2001; 344: 732-738
25. Kyrriakides C, Jasleen J, Wang Y, Moore FD, Ashley SW, Hechtman HB. Neutrophils, not complement, mediate the mortality of experimental hemorrhagic pancreatitis. Pancces 2001; 22: 40-46
26. Luo Y, Yuan CX, Peng YL, Wei PL, Zhang ZD, Jiang JM, Dai L, Hu YK. Can ultrasound predict the severity of acute pancreatitis earlier by observing acute fluid collection. World J Gastroenterol 2001; 7: 293-295
27. Wu JX, Xu JY, Yuan YZ. Effect of emodin and sandostatin on metabolism of eicosanoids in acute necrotizing pancreatitis. World J Gastroenterol 2000; 6: 293-294
28. Qin RY, Zou SQ, Wu ZD, Qiu FZ. Influence of splanchic vascular infuion on the content of endotoxins in plasma and the transplantation of intestinal bacteria in rats with acute hemorrhage necrosis pancreatitis. World J Gastroenterol 2000; 6: 577-580
29. Yuan YZ, Gong ZH, Lou XK, Tu SP, Zhai ZX, Xu JY. Involvement of apoptosis of alveolar epithelial cells in acute pancreatitis-associated lung injury. World J Gastroenterol 2000; 6: 920-924
30. Sun QX, Fu XB, Zhang R, Lu Y, Deng Q, Jiang XG, Sheng ZY. Relationship between plasma D(-) lactate and intestinal damage after severe injuries in rats. World J Gastroenterol 2001; 7: 555-558
31. Zhang WZ, Han TQ, Tang YQ, Zhang SD. Rapid detection of sepsis complicating acute necrotizing pancreatitis using polymerase chain reaction. World J Gastroenterol 2001; 7: 289-292
32. Xie Q, Jiang JM, Gong X, Chen GY, Li L, Huang ZW. Experimental study of Tung Xia purgative method in ameliorating lung injury in acute necrotizing pancreatitis. World J Gastroenterol 2000; 6: 115-118
33. Jaworek J, Jaworek J, Tomaszewska R, Konturek PC, Pawlik T. High serum IgG concentrations in patients with sclerosing pancreatitis. World J Gastroenterol 2001; 7: 293-295
34. Pastor CM, Frossard JL. Are genetically modified mice useful for the understanding of acute pancreatitis. FASEB J 2001; 15: 893-897
35. Slavin J, Ghaneh P, Sutton R, Hartley M, Rowlands P, Garvey C, Hughes M, Neoptolemos J. Management of necrotizing pancreatitis. World J Gastroenterol 2001; 7: 476-481
Frossard JL, Bhagat L, Lee HS, Hietaranta AJ, Singh VP, Song AM, Steer ML, Saluja AK. Both thermal and non-thermal stress protect against caerulein induced pancreatitis and prevent trypsinogen activation in the pancreas. Gut 2002; 50: 78-83

Vaccaro MI, Calvo EL, Suburo AM, Sordelli DO, Lanosa G, Iovanna JL. Lipopolysaccharide directly affects pancreatic acinar cell: implications on acute pancreatitis pathophysiology. Dig Dis Sci 2000; 45: 915-926

Xia SH, Zhao XY, Guo P, Da SP. Hemocirculatory disorder in dogs with severe acute pancreatitis and intervention of platelet activating factor antagonist. Shijie Huaren Xaohua Zazhi 2001; 9: 550-554

Yin Y, Gao NR, Li ZL. Protective effects of ulinostatin on acute lung injury induced by acute necrotizing pancreatitis in rats. Shijie Huaren Xaohua Zazhi 2002; 10: 558-561

Chen H, Li F, Cheng YF, Sun JB. Pathogenic role of neutrophils in evolution of acute pancreatitis in rats. Shijie Huaren Xaohua Zazhi 2001; 9: 776-779

Yuan YZ, Lou KX, Gong ZH, Tu SP, Zhai ZK, Xu YJ. Effects and mechanisms of emodin on pancreatic tissue EGF expression in acute pancreatitis in rats. Shijie Huaren Xaohua Zazhi 2001; 9: 127-130

Wu K, Wang BX, Wang XP. Effects of clostridium butyricum on bacterial translocation in rats with acute necrotizing pancreatitis. Shijie Huaren Xaohua Zazhi 2000; 8: 883-886

Gong ZH, Yuan YZ, Lou KX, Tu SP, Zhai ZK, Xu YJ. Effects and mechanisms of somatostatin analogues on apoptosis of pancreatic acinar cells in acute pancreatitis in mice. Shijie Huaren Xaohua Zazhi 1999; 7: 964-966

Wang CH, Qian KD, Zhu YL, Tang XQ. The significance of TNF and IL-6 level in the patients with acute pancreatitis. Shijie Huaren Xaohua Zazhi 2001; 9: 1434

Okabe A, Hirota M, Ozawa F, Shibata M, Nakano S, Ogawa M. Altered cytokine response in rat acute pancreatitis complicated with endotoxemia. Pancreas 2001; 22: 32-39

Vaquero E, Gukovsky I, Zaninovic V, Gukovskaya AS, Pandol SJ. Localized pancreatic NF-kB activation and inflammatory response to taurocholate-induced pancreatitis. Am J Physiol Gastrointest Liver Physiol 2001; 280: G1197-G1208

Mayer J, Rau B, Gansauge F, Beger HG. Inflammatory mediators in human acute pancreatitis: clinical and pathophysiologic implications. Gut 2000; 47: 546-552

Sahuja AK, Bhagat L, Lee HS, Bhatia M, Frossard JL, Steer ML. Secretagogue-induced digestive enzyme activation and cell injury in rat pancreatic acini. Am J Physiol 1999; 276: G835-G842

Matsumura N, Ochi K, Ichimura M, Mizushima T, Harada H, Harada M. Study on free radicals and pancreatic fibrosis-pancreatic fibrosis induced by repeated injections of superoxide dismutase inhibitor. Pancreas 2001; 22: 53-57

Simsek I, Refik M, Yasar M, Ozyurt M, Saglamkaya U, Deveci S, Comert B, Basustaoglu A, Kocabalkan F. Inhibition of inducible nitric oxide synthase reduces bacterial translocation in a rat model of acute pancreatitis. Pancreas 2001; 23: 296-301

Gomez-Cambronero L, Camps B, de La Asuncion JG, Corda M, Pellin A, Palardio FV, Calvetj J, Sweiry JH, Mann GE, Vina J, Sadrej. Pentoxifylline ameliorates cerulein-induced pancreatitis in rats: role of glutathione and nitric oxide. J Pharmacol Exp Ther 2000; 293: 670-676

Schulz HU, Niederau C, Klonowski Stumpe H, Halangk W, Luthen R, Lippert H. Oxidative stress in acute pancreatitis. Hepatogastroenterology 1999; 46: 2736-2750

Edited by MajY