Review Article

Experimental Animal Models of Acute Pancreatitis

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ABSTRACT

Acute pancreatitis is an inflammatory disease characterized by interstitial edema, inflammatory cell infiltration, hemorrhages, vacuolization and necrosis of acinar cell necrosis, depending on its severity. Its pathogenic mechanism to closely associate with tissue injury related to intracellular digestive enzyme activation. Due to these difficulties, most of our knowledge on pancreatitis is based on research conducted using experimental models of pancreatitis and have many studies of experimental model of acute pancreatitis. In this review tried to gather the basic, easy to construct acute pancreatitis models in animals.

Key words : Animal models, acute pancreatitis

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INTRODUCTION

Acute pancreatitis is an inflammatory disease of the pancreas characterized by acute abdominal pain. Severity of acute pancreatitis ranging from mild (found 70 -80%) caused low mortality to severe (found 15-25%) with high mortality from complication pathogenesis[1]. Acute pancreatitis can present in a wide spectrum ranging from edema of the organ to necrosis and hemorrhage.

Acute pancreatitis is a multi-etiology disease with controversial physiopathology. Thus, it has an unpredictable course without a targeted treatment[2] which results in high morbidity and mortality. In the clinical find gallstone obstruction is the most common cause of acute pancreatitis and alcoholism is the second most common cause leads to chronic pancreatitis[3]. There are many experimental studies identify the pathogenesis and treatment options for pancreatitis.

However, because of the anatomical location of the pancreas and the difficulty in procuring tissue at different stages of the inflammatory process in humans, our understanding of the pathogenesis of pancreatitis mainly relies on data from experimental animal models. In this review tried to evaluate the differences between models and the particular methodologies of each experimental model with outline of each technique.

Closed Duodenal Loop (CDL)

Experimental acute pancreatitis in animals may be produced by creating a closed duodenal loop (CDL).

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This technique involves surgically closing above and below the duodenal papilla while bile is diverted into the jejunum via an implanted cannula. The model was first developed by Pfeffer et al.[4]. CDL, increases intraduodenal luminal pressure causing reflux of duodenal fluid to pancreatic duct (PD) causing pancreatitis. Closed loop is constructed with duodenum surrounding the opening of the PD.

Nevalainen and Seppa[5] also conducted a modification of CDL in rats. An intraduodenal tube was placed prior to ligating the duodenal loop in order to restore the continuity of the gastrointestinal tract. Within 24 h, acute hemorrhagic pancreatitis was visible in the animals. The findings support the view that refluxes of the duodenal contents into the pancreatic duct is an important early pathogenesis mechanism in the development of acute pancreatitis.

Chetty et al.[6] performed another modification of the technique by instilling infected bile into the closed loop under pressure, at a known time, in the rat. This resulted in the production of a lethal hemorrhage, periductal abscess formation and fat necrosis. The model of Chetty et al.[6] produces a consistently severe acute pancreatitis in comparison with the model produced by Nevalainen and Seppa[5].

Duct Infusion Pancreatitis

Cannulation of the pancreatic duct provides another way of inducing an experimental AP model. Several substances have been used as inducers of pancreatitis in this method. These have included stimulating factors and toxic substances such as bile acids (taurocholate or glycodeoxycholic acid), ethyl alcohol, peracetate and tert-butyl hydroperoxide. The most common of all these substances are bile acids[7,8].

In rats biliopancreatic duct is catheterized with 24 G polyethylene tube and ligated[9]. Main hepatic duct is clamped under liver and intraductal infusion is started. Glycodeoxycholic acid prepared in glycylglycine buffer (pH = 8) is recommended as infusate. Infusion should be in 1.5 minutes, with 30 mmHg pressure and 0.1-0.5 ml volume. Acute edematous pancreatitis develops if activated pancreatic enzymes are perfused following early induced changes in ductal permeability[10].

The severity of the disease can be manipulated by changing either the pressure or the concentration of bile salt used. Acute severe pancreatitis develops within 2-24 h and is characterized by edema, necrosis and hemorrhage. Almost any form of detergent injected into the pancreatic duct under pressure will cause acute pancreatitis in laboratory animals in rats[11-13]. One of the best standardized compounds to use to develop acute pancreatitis is sodium taurocholate. Infusion of 0.2 mL/kg of 3%, 4.5% or 5% solution induced acute hemorrhagic pancreatitis with 72-h mortality rates of 24%, 71%, and 100% respectively[11-13].

Duct Obstruction Induced Pancreatitis

Acute pancreatitis may be induced by ligating the distal bile duct at the level of the duodenum[14]. The surgical manipulation is simple, requiring either ligation of the common biliopancreatic duct or obstruction of the pancreatic duct by vertical cannulation. The point of obstruction is close to the entry to duodenum, much like gallstone obstruction at the ampulla of Vater[15, 16]. It is postulated that bile reflux by triggering intrapancreatic digestive enzyme activation accounts for the major pathological factor in this model. After 24 hours the equilibrium between secretion and PD obstruction is maintained which stops further PD pressure rise and parenchymal water content[17, 18]. One week after PD ligation acinar cell zymogen content was found to be decreased, rough endoplasmic reticulum is fragmented, golgi apparatus function is lost, autophagic vacuoles appear and exocrine pancreas is replaced with fibrous tissue[19].

In rats, main bile duct passes through pancreas and many small pancreatic ducts join with it. In order to prevent flow of only pancreatic secretions, duodenum is separated from transverse colon and a polyethylene tube inserted in to the proximal part of main bile duct[20].

Occlusion of the common bilipancreatic duct causes acute hemorrhagic pancreatitis and results in 100% mortality in 14 days[21]. When it is sutured adjacent to duodenum, pancreatic edema forms in 6 hours and peaks in 12 hours. At this stage fatty necrosis and parenchymal hemorrhage start to appear and infiltration by inflammatory cells occurs[21,22].

Vascular Induced Pancreatitis

Acute pancreatitis is encountered after cardiopulmonary bypass[23]. Changes in vascular perfusion of pancreas leads to pancreatitis in many animals including dogs, rats, and cats[24,25]. Vascular perfusion can be changed by altering either of inflow, outflow or microcirculation of the organ. In 1962, Pfeffer et al. used

8-20 μgr polyetyhlene microspheres to occlude superior pancreaticoduodenal arteries. With this technique irreversible occlusion of terminal arterioles is achieved impeding microcirculation[26] causing hemorrhagic pancreatitis in 11 hours. Using larger particles only result in pancreatic edema, elevated serum pancreatic enzymes and necrosis.

Ischaemia/Reperfusion Model

Studies have shown that there is correlation between the impairment of microcirculation in human pancreas with the degree of ischaemic injury[27], and microvasculature presents the primar target of reperfusion injury after ischaemia[28].

In 1995, Hoffman et al.[29] developed a model to study the microcirculation of the pancreas in the rat after complete (interruption of arterial blood supply to the pancreas) and reversible ischaemia of the pancreas using intravital fluorescence microscopy. Blood supply for complete ischaemia of the pancreas was impaired by isolating arteries from surrounding tissue of gastroduodenal artery. Complete but reversible ischaemia of the pancreas was induced by occluding the four vessels using microvascular clips. The clips were taken out 30 min, 1 h or 2 h after ischaemia to produce reperfusion.

The duration of ischaemia and of reperfusion is responsible for the severity of post-ischaemic inflammatory reaction. In addition, there was a rise in the concentration of serum amylase after 1 and 2 h of ischaemia[29]. Redha et al.[30] reported even higher serum amylase concentration after ischaemia-induced acute pancreatitis. This may occur because of the extended time (27 h) of reperfusion.

Diet Induced Pancreatitis

Ethionine is toxic to pancreatic acinar cells[31]. It inhibits phospholipid metabolism intracellularly[32,33]. Lombardi et al induced acute hemorrhagic pancreatitis in female mice with 0.5% ethionine enriched diet[35]. Widespread intra-abdominal fatty necrosis follows pancreatitis. If feeding is limited to 24 hours mortality is 55-60%. If fed ad libitum this diet is 100% lethal in 5 days[34]. Histopathologic and gross examination of pancreas between 48-72 hours after 24 hours feed did not show any pancreatic damage[36].

When animals are fed with choline, pancreatitis does not develop[37]. Choline takes up the ethyl groups liberated during breakdown of ethionine. Female sex steroids seem to promote development of pancreatitis so either young female mice or estrogen treated male mice are preferred[38]. Diet without choline exerts synergistic effect to ethionine causing intraparenchymal activation of zymogens leading to massive hemorrhagic necrosis. The subcellular mechanism underlying this is the inhibition of membrane lipid synthesis resulting in breakdown of endoplasmic reticulum and release of autophagic vacuoles. The end result is autolysis[39,40].

Table 1. Induction of acute pancreatitis[46].

Dose of L-Arginine	Reference
Single dose	
500 mg/100 g bm ip.	Mizinuma et al. 1984, Kishino et al. 1984, Tani et al. 1990, Shields et al. 2000, Kihara et al. 2001, Tachibana et al. 1997, Tashiro et al. 2001
450 mg/100 g bm ip.	Tashiro et al. 2001
400 mg/100 g bm ip.	Tashiro et al. 2001, Rakonczay et al. 2002
300 mg/100 g bm ip.	Tashiro et al. 2001, Rakonczay et al. 2002
250 mg/100 g bm ip.	Pozsar et al. 1997
200 mg/100 g bm ip.	Tashiro et al. 2001
Double dose	
2x250 mg/100g bm ip.	Takacs et al. 1996, Varga I, et al. 1997, Toma et al. 2000, Czako et al. 2000, Czako et al. 2000, Czako et al. 2000, Takacs et al. 2002, Toma et al. 20002
2x230 mg/100 g bm ip.	Takacs et al. 2002
2x200 mg/100 g bm ip.	Hegyi et al. 1997, Hegyi et al., 1999, Hegyi et al. 2000, Takacs et al. 2001
Multiple dose	
350 mg/100 g bm ip. Daily from 1 to 4 wk	Weaver et al. 1994
a single 500 mg/100 g bm ip. and triple 250 mg/100 gbm ip. (d 4, 7, 10)	Delaney et al. 1993

Arginine Induced Pancreatitis

L-arginine is an essential amino acid that has been used to induce severe necrotizing acute pancreatitis in rats[41]. High dose intraperitoneal injection of 500 mg/100 gr arginine can cause acute necrotizing pancreatitis in rats and mice[42-45]. All in all, the dose- and time-dependency of the effects of arginine gives an excellent opportunity to study the different phases of pancreatitis. Long-term administration of arginine is suggested to study chronic pancreatitis (Table 1)[46]. The mechanisms underlying the effect of arginine are via excessive nitric oxide production, lipid peroxidation and inhibition of protein synthesis[47-49]. The changes range between interstitial edema, inflammatory infiltration, acinar degranulation to massive necrosis (Figure 1)[51]. After 250 mg/kg and 450 mg/100 kg of injections respectively[50,51]. Details of the points assigned to the different degrees of inflammation and edema/fat necrosis in acute pancreatitis are explained in (Table 2)[52]. The sum of the points for each criterion in acute pancreatitis was calculated with a maximal score of 6 for acute pancreatitis. A total point score of 0 was considered normal pancreatic histopathology. A score of 1-2 total points was considered mild acute pancreatitis; 3-4, moderate; and 5-6, severe acute pancreatitis.

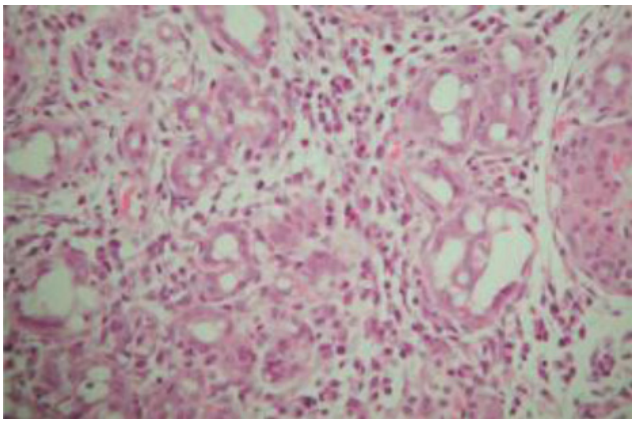

Figure 1. Pancreatic injury in L-arginine-induced experimental acute pancreatitis (H & E × 40).
Note the presence of edema, inflammatory cell infiltration, acinar cell degranulation[51].

Cerulein Induced Pancreatitis

Cerulein is a decapeptide analogue of cholecystokinin (CCK), has been used to successfully cause acute pancreatitis in rats[51,52] and mice[53]. Acute pancreatitis can be induced by an intravenous or intraperitoneal injection of an overdose of cerulein 5 µg/kg/hr in rats and 50 µg/kg several times at hourly intervals in mice. When given either 1-5 ng/kg intravenous (iv) bolus or 0.25-1 ng/kg/min iv infusion or 50-100 ng/kg subcutaneously this substance increases pancreatic secretions[54]. If administered in supramaximal doses it causes edematous pancreatitis by increasing pancreatic protein secretions[55]. According to previous studies, cerulein is known to induce pancreatic enzyme activation within 30 minutes of intravenous administration.

The usual way of administration is by a catheter inserted in internal jugular vein of the rat at a rate of 1-2 ml/hour[56]. Cerulein can be diluted in normal saline and infused iv in 3-5 hours[57]. Cerulein can also be administered intraperitoneally[58-60]. Multiple injections can be done in one hour intervals with 5-200 µg/kg doses. Subcutaneous delivery can be achieved in multiple injections with 25-50 µg /kg dose[53].

Cerulein interferes with packaging of zymogens and lysosomal hydrolases after synthesis in endoplasmic reticulum leading to intracellular activation of trypsinogen[61]. In 48 hours after infusion zymogen granules start fusion with lysosomes resulting in in-

Table 2. Scoring system for characterized severity of acute pancreatitis[52].

Score	Inflammation	Edema and Fat Necrosis
0	No neutrophils present	Not present
1	Mild neutrophilic inflammatory infiltrate affecting maximum 25% of the pancreatic parenchyma	Mild, < 25% of the parenchyma involved
2	Moderate neutrophilic inflammation affecting 25-50% of the parenchyma	Moderate, present in 25-50% of the parenchyma
3	Severe neutrophilic inflammation affecting > 50% of the pancreatic parenchyma	Severe, > 50% of the parenchyma involved

flammation and acute pancreatitis[52,62].

CONCLUSION

We have reviewed several experimental models of pancreatitis. Each models have their own advantages or disadvantages. Investigators, who want to explore some aspects of pancreatitis, should be aware the characteristics of experimental model of pancreatitis and carefully choose suitable animal model for get reliable answer. Therefore, comparison between the existing models is complex and interpretations of results from various studies are consequently difficult.

REFERENCES

1. Steer LM. Etiology and pathogenesis of acute pancreatitis. Ann Ital Chir 1995;66:159-63.
2. Wilson C, Imrie CW. Experimental models of acute pancreatitis. In: Johnson CD, Imrie CW, Eds., Pancreatic Disease: Progress and Prospects, Springer-Verlag London Limited, Great Britain 1991;227-39.
3. Chetty U, Gilmour HM, Taylor TV. Experimental acute panereatitis in the rat-A new Mmodel. Gut 1980; 21:115-7.
4. Pfeffer RB, Stasior O, Hinton JW. The clinical picture of the sequential development of acute hemorrhagic pancreatitis in the dog. Surg Forum 1957;8:248-51.
5. Nevalainen TJ, Seppa A. Acute pancreatitis caused by closed duodenal loop in the rat. Scand J Gastroenterol 1975;10:52-17.
6. Chetty U, Gilmour HM, Taylor TV. Experimental acute pancreatitis in the rat a new model. Gut 1980;21:11-57.
7. Sledzinski Z, Wozniak M, Brunelli A, et al. Experimental pancreatitis induced by synthetic prooxidant tert-Butyl hydroperoxide. Pancreas 2000;20:146-51.
8. Jankowski K, Kubasik-Juraniec J, Sledzinski Z, *et al*. The morphology of acinar cells during acute pancreatitis in rats induced by intraductal infusion of peracetate. Folia Microbiologica 2004;63:179-81.
9. Schmidt J, Lewandrowsky K, Warshaw AL, *et al*. Morphometric charachteristics and homogeneity of a new model of acute pancreatitis in the rat. Int J Pancreatol 1992;12:41-51.
10. Farmer RC, Maslin SC, Reber HA. Acute pancreatitis: the role of duct permeability. Surg Forum 1983;34:22-47.
11. Aho HJ, Koskensalo SM, Nevalainen TJ. Experimental pancreatitis in the rat. Sodium taurocholate-induced acute haemorrhagic pancreatitis. Scand J Gastroenterol 1980;15:41-16.
12. Aho HJ, Nevalainen TJ. Experimental pancreatitis in the rat. Ultrastructure of sodium taurocholate-induced pancreatic lesions. Scand J Gastroenterol 1980;15:417-24.
13. Aho HJ, Nevalainen TJ, Aho AJ. Experimental pancreatitis in the rat. Development of pancreatic necrosis, ischemia and edema after intraductal sodium taurocholate injection. Eur Surg Res 1983;15: 28-36.
14. Baxter JN, Jenkins SA, Day DW, *et al*. Effects of somatostatin and a long-acting somatostatin analogue on the prevention and treatment of experimentally induced acute pancreatitis in the rat. Br J Surg 1985;72:38-25.
15. Ohshio G, Saluja A, Steer ML. Effects of short-term pancreatic duct obstruction in rats. Gastroenterology 1991;100:196-202.
16. Lerch MM, Saluja AK, Runzi M, *et al*. Pancreatic duct obstruction triggers acute necrotizing pancreatitis in the opossum. Gastroenterology 1993;104:853-61.
17. Elliot DW, Williams RD, Zollinger RM. Alterations in the pancreatic resistance to bile in the pathogenesis of acute pancreatitis. Ann Surg 1975;146:669-82.
18. Dumont AE, Martelli AB. Pathogenesis of pancreatic edema following exocrine duct obstruction. Ann Surg 1968; 168:302-9.
19. Churg A, Richter WR. Early changes in the exocrine pancreas of the dog and rat after ligation of the pancreatic duct. A light and electron microscopy study. Am J Pathol 1971;63:521-6.
20. Tsuzuki T, Watanabe N, Thal AP. The effect of obstruction of the pancreatic duct and acute alcoholism on pancreatic protein synthesis. Surgery 1965;57:724-9.
21. Senninger N, Moody FG, Van Buren DH, *et al*. Effect of biliary obstruction on pancreatic exocrine secretion in conscious opossums. Surgery Forum 1984;35:226-8.
22. Lerch MM, Saluja AK, Runzi M, et al. Pancreatic duct obstruction triggers acute necrotizing pancreatitis in the opossum. Gastroenterology 1993;104:853-61.
23. Haas GS, Warshaw AL, Dagget WM, *et al*. Acute pancreatitis after cardiopulmonary bypass. Am J Surg 1985;149:508-15.
24. Friess H, Weber A, Buchler M. Standards in monitoring acute experimental pancreatitis. Eur Surg Res 1992;24(Suppl.1):1-13.
25. Waldner H. Vascular mechanisms to induce acute pancreatitis. Eur Surg Res 1992;24(Suppl. 1):62-7.
26. Pfeffer RB, Lazzarini-Robertson A, Safadi D, *et al*. Gradation of pancreatitis: edermatous through hemorrhagic, experimentally produced by controlled injection of microspheres into blood vessels in dogs. Surgery 1962;51:564-9.
27. Takahasi T, Yaginuma N. Ischemic injury of the human pancreas. Its basic patterns correlated with the pancreatic microvasculature. Pathol Res Pract 1985;179:645-51.
28. Menger MD, Vollmar B, Glasz J, *et al*. Microcirculatory manifestations of hepatic ischemia/reperfusion injury. Prog Appl Microcirc 1993;19:106-24.
29. Hoffmann TF, Leiderer R, Waldner H, *et al*. Ischemia reperfusion of the pancreas: a new in vivo model for acute pancreatitis in rats. Res Exp Med (Berl) 1995;195:125-44.
30. Redha F, Uhlschmid G, Ammann RW, *et al*. Injection of microspheres into pancreatic arteries causes acute hemorrhagic pancreatitis in the rat: a new animal model. Pancreas 1990; 5:188-93
31. Loring EW, Hanley LJ. The destructive effects of Dl-Ethionine on the pancreas. Stomach and submaxillary glands. Am J Pathol 1955;31:521-33.
32. Gordon FB, Farbel E. Selective effects of adenine triphosphate upon the hepatic biochemical lesionsinduced by Ethion-

ine. Arch Biochem Biophys 1965;112:233-7.
33. Ariyoshi T, Takabatake E. Effects of phenobarbital ethanol and ethionine on the content and fatty acid composition of hepatic microsomal phospholipids. Chem Pharm Bull (Tokyo) 1972;20:170-4.
34. Lombardi B, Estes LW, Longnecker DS. Acute hemorrhagic pancreatisis (Massive Necrosis) with fat necrosis induced in mice by DL-Ethionine fed with a choline defficient diet. Am J Pathol 1975;79:465-80.
35. Steer ML, Meldoresi J. The cell biology of experimental pancreatitis. N Engl J Med 1987;316:144-50.
36. Steer M. How and where does acute pancreatitis begin. Arch Surg 1992;127:1350-3.
37. Gilliland L, Steer ML. Effects of Ethionine on digestive enzyme synthesis and discharge by mouse pancreas. Am J Physiol 1980;239:418-26.
38. Rao KN, Eagon PK, Okamura K. Acute hemorrhagic pancreatic necrosis in mice. Induction in male mice treated with estradiol. Am J Pathol 1982;109:8-14.
39. Leevathi DE, Katyal SL, Lombardi B. Lecithin depletion in liver mitochondria of rats fed with choline- deficint diet. Effect of β-hydroxybutyrate dehydrogenase. Life Sci 1974; 14:1203-10.
40. Rao KN, Zuretti MF, Bacchino FM, *et al*. Acute hemorrhagic pancreatitis in mice. The activity of lysosomal enzymes in the pancreas and the liver. Am J Pathol 1980;98:45-60.
41. Tani S, Itoh H, Okabayashi Y, *et al*. New model of acute necrotizing pancreatitis induced by excessive doses of arginine in rats. Dig Dis Sci 1990;35:367-74.
42. Mizunuma T, Kawamura S, Kishino Y. Effects of injecting excess arginine on rat pancreas. J Nutr 1984;114:467-1.
43. Kishino Y, Kawamura S. Pancreatic damage induced by injecting a large dose of arginine. Virchows Arch B Cell Pathol Incl Mol Pathol 1984;47:147-55.
44. Tani S, Itoh H, Okabayashi Y, *et al*. New model of acute necrotizing pancreatitis induced by excessive doses of arginine in rats. Dig Dis Sci 1990;35:367-74.
45. Bulbuller N, Dogru O, Umac H, *et al*. The effects of melatonin and pentoxiphylline on L-arginine induced acute pancreatitis. Ulus Travma Acil Cerrahi Derg 2005;11:108-14.
46. Zhao QL, Huang CY, Huang Y, *et al*. Study on acute pancreatitis-associated lung injury induced by L-arginine in mice. Sichuan Da Xue Xue Bao Yi Xue Ban 2004;35:839-42.
47. Kishino Y, Takama S, Kitajima S. Ultracytochemistry of pancreatic damage induced by excess lysine. Virchows Arch B Cell Pathol Incl Mol Pathol 1986;52:153-67.
48. Takacs T, Czako L, Morschl E, *et al*. The role of nitric oxide in edema formation in L-arginine-induced acute pancreatitis. Pancreas 2002;25:277-82.
49. Czako L, Takacs T, Varga IS, *et al*. Involvement of oxygen-derived free radicals in L-arginine-induced a cute pancreatitis. Dig Dis Sci 1998;4:1770-7.
50. Hardman J, Jamdar S, Shields C, *et al*. Intravenous selenium modulates L-arginine-induced experimental acute pancreatitis. JOP 2005;6:431-7.
51. Lampel M, Kern HF. Acute interstitial pancreatitis in the rat induced by excessive doses of a pancreatic secretagogue. Virchows Arch A Pathol Anat Histol 1977;373:971-17.
52. Watanabe O, Baccino FM, Steer ML, *et al*. Supramaximal caerulein stimulation and ultrastructure of rat pancreatic acinar cell: early morphological changes during development of experimental pancreatitis. Am J Physiol 1984;246:457-67.
53. Niederau C, Ferrell LD, Grendell JH. Caerulein-induced acute necrotizing pancreatitis in mice: protective effects of proglumide, benzotript, and secretin. Gastroenterology 1985;88(5 Pt 1):1192-204.
54. Rao KN, Zuretti MF, Bacchino FM, *et al*. Acute hemorrhagic pancreatitis in mice. The activity of lysosomal enzymes in the pancreas and the liver. Am J Pathol 1980;98:45-60.
55. Bertaccini G, de Caro G, Endean R, *et al*. The action of caerulein on pancreatic secretion of the dog and biliary secretion of the dog and rat. Br J Pharmacol 1969;37:185-97.
56. Adler G, Hahn C, Kem HF, *et al*. Cerulein-induced panereatitis in rats: increased lysosomal enzyme activity and autophagocytosis. Digestion 1985;32:10-18.
57. Dabrowski A, Gabryelewicz A, Wereszynska Siemiatkowska U, *et al*. Oxygen-derived free radicals in cerulein-induced acute pancreatitis. Scand J Gastroenterol 1988;23:1245-9.
58. Dabrowsky A, Chwiecko M. Oxygen radicals mediat depletion of pancreatic sulfnydryl compounds in rats with cerulein-induced acute pancreatitis. Digestion 1990;47:15-9.
59. Wisner JR, Renner IG. Allopurinol attenuates caerulein induced acute pancreatitis in the rat. Gut 1988;29:926-9.
60. Devenyl Z, Orchard JL, Powers RE. Xanthine oxidase activitiy in mouse pancreas: effects of caerulein- induced acute pancreatitis. Biochem Biophys Res Commun 1987;149:841-5.
61. Tardini A, Anversa P, Bordi C, *et al*. Ultrastructural and biochemical changes after marked caerulein stimulation of the exocrine pancreas in the dog. Am J Pathol 1971;62:35-47.
62. Lampel M, Kem H. Acute interstitial pancreatitis in the rat induced by excessive doses of a pancreatic secretagogue. Virchows Archiv A Patholo Anat Histopathol 1977;373:107-17.