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Endothelin Receptor Blockade Improves Fluid Sequestration, Pancreatic Capillary Blood Flow, and Survival in Severe Experimental Pancreatitis

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Objective
To evaluate the effect of a new endothelin receptor antagonist (ET-RA) on the course of severe experimental pancreatitis.

Background
Endothelin-1 has been shown to reduce regional blood flow in various organs, including the pancreas, and to aggravate cerulein-induced mild pancreatitis.

Methods
Acute necrotizing pancreatitis (ANP) was induced in rats by standardized intraductal bile acid infusion and cerulein hyperstimulation. Serum trypsinogen activation peptides (TAP) were measured to verify comparable disease severity. Starting 6 hours after the onset of ANP, animals randomly received either saline or the new ET-RA LU-135252. Monitoring included cardiorespiratory parameters, urine output, hematocrit, and TAP levels. After 24 hours, animals were relaparotomized to determine pancreatic capillary blood flow and to assess the amount of free intraabdominal fluid and acinar cell necrosis. Survival was determined in a second set of experiments on 24 animals observed for 48 hours after pancreatitis induction and treatment with either normal saline or ET-RA.

Results
Comparable TAP increases confirmed equally severe ANP in both groups before treatment. Treatment with ET-RA significantly reduced the mortality rate, from 50% in untreated animals to 8%. Improved survival was associated with significantly decreased hematocrit, improved urinary output, decreased ascites, and increased pancreatic capillary blood flow. There were no significant differences in plasma TAP and acinar cell injury in the surviving animals of the two treatment groups.

Conclusion
Therapy with the new ET-RA reduces the early mortality rate in experimental ANP, probably by reducing fluid sequestration and improving microcirculation.

The severity of acute pancreatitis is determined by the extent of pancreatic necrosis, the presence of secondary infection of pancreatic necrosis, and the systemic inflammatory response to pancreatic injury and infection. Thus, the aim is to limit the progression of necrosis, to prevent pancreatic infection, and to eliminate or block the inflammatory mediators responsible for the systemic inflammatory response. Using an improved model of acute necrotizing pancreatitis (ANP) in the rat, we and others have previously shown the beneficial effect of reducing pancreatic necrosis and infection on survival.[1–4] The clinical relevance of the experimental concepts used in this model (*e.g.*, hemodilution, antibiotic administration, selective gut decontamination) has been confirmed by clinical studies in which the same measures proved effective in severe pancreatitis in humans.[4–7]

The present study reports our first experience with a new endothelin receptor antagonist (ET-RA) in this model of ANP. Based on experimental and clinical data suggesting that endothelin plays a major role in triggering the multiorgan dysfunction syndrome in low-flow states and sepsis,[8,9]

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we assumed that endothelin receptor blockade would affect the systemic rather than the local sequelae of acute pancreatitis. Therefore, we evaluated the effect of the new specific endothelin-1 (ET-1) antagonist LU-135252 on intrapancreatic protease activation, pancreatic capillary blood flow, acinar cell injury, systemic cardiorespiratory parameters, renal function, fluid sequestration, and mortality rate. Our data provide strong evidence that endothelin is a major contributor to death and complications in acute pancreatitis and that endothelin receptor blockers may become a new therapeutic tool in this disease.

METHODS

All experiments were conducted in accordance with national guidelines for the use and care of laboratory animals and were approved by the local ethics committee. After overnight fasting, male Sprague-Dawley rats (330 ± 20 kg) were anesthetized with intraperitoneal pentobarbital (20 mg/kg) and ketamine (40 mg/kg). Polyethylene catheters (ID 0.5 mm) were inserted into the right jugular vein and the left carotid artery and subcutaneously tunneled to the neck and advanced through a steel tether that allowed blood sampling and intravenous access in the unrestrained animals. An additional catheter was placed in the bladder for continuous urine collection, as described previously.[10] ANP was induced by a standardized retrograde infusion of 0.5 ml of 10 mM glycodeoxycholic acid (Sigma, St. Louis, MO) into the biliopancreatic duct for 10 minutes, followed by a continuous intravenous infusion of 5 μg/kg/hour cerulein (CAE; Farmitalia Freiburg, Germany) over 6 hour. As an improvement on the original technique first described in 1992,[11] a special infusion pump (IVAC 770; Lilly Medizintechnik, Giessen, Germany) was used for a pressure-controlled (30 mmHg), volume-controlled (0.5 cc), and time-controlled (10 minutes) intraductal glycodeoxycholic acid infusion.

Experiment 1

Six hours after induction of pancreatitis, 24 animals were randomized for intravenous injection of either 100 mg/kg of LU-135252 (provided by Knoll AG, Ludwigshafen, Germany) or the volume equivalent (0.5 cc) of normal saline. Ten healthy sham-operated animals (intraductal and intravenous saline infusion) given ET-RA or normal saline served as additional controls. Mean arterial pressure, heart rate, arterial blood gases, hematocrit, urine production, trypsinogen activation peptides (TAP) in plasma, and plasma ET-1 levels were determined before the start of therapy, 6 hours thereafter, and at the end of the experiment at 24 hours. At 24 hours, animals were reanesthetized and laparotomized to determine ascites, pancreatic capillary blood flow, and acinar cell necrosis.

Experiment 2 (Survival Study)

After pancreatitis induction, 24 animals were randomized to receive either 100 mg/kg ET-RA (n = 12) or the volume equivalent of normal saline (n = 12). The animals had free access to water and (after 24 hours) dry food. The mortality rate was assessed at 48 hours, after which surviving animals were killed. Measurements included arterial pressure, urinary output, hematocrit, and TAP in plasma at 6 and 48 hours, as well as ascites and acinar cell necrosis in animals that survived the 48-hour observation period. To measure ET-1 levels, plasma withdrawn from the carotid artery was immediately placed on ice, centrifuged at 4°C, and stored at −70°C until it was assayed by a commercially available enzyme-linked immunosorbent assay kit (Biomedica, Vienna, Austria).

Pancreatic capillary blood flow was determined by intravital microscopy using the equipment and technique described previously.[12,13] The animals were reanesthetized 24 hours after pancreatitis induction and therapy with ET-RA or saline. The abdomen was opened through a small midline incision; the duodenum and the head of the pancreas were mobilized and exteriorized, placed in an immersion chamber with Ringer's lactate maintained at 37°C, and positioned under a fluorescence microscope (Leitz, Wetzlar, Germany) with a heat-protection and excitation filter (450 to 490 nm). At that point, the animals received an intravenous injection of 0.5 ml/kg erythrocytes labeled with fluorescein isothiocyanate (FITC; Sigma, Deisenhofen, Germany). After a stabilization period of 5 to 10 minutes, three randomly chosen regions in the head of the pancreas (400 to 325 μm) were recorded for off-line analysis. In each animal, blood flow was calculated in 30 to 40 consecutively recorded capillaries from the concentration of fluorescent erythrocytes per unit of arterial blood at the time of the recording, the capillary hematocrit, and the number of FITC-labeled erythrocytes passing through the respective vessel.[12,13]

Cardiorespiratory monitoring included repeated measurements of mean arterial pressure, heart rate, and arterial blood gases. Because systemic circulatory derangement may influence regional perfusion, intravital micro-

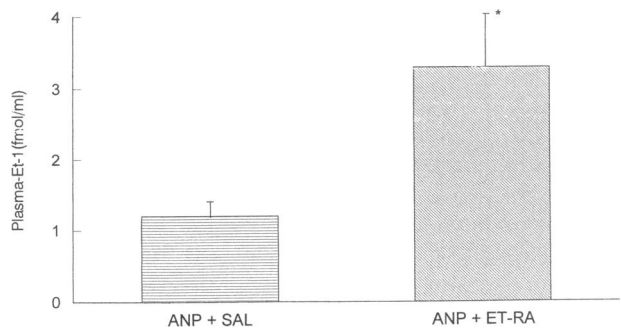

Figure 1. Endothelin plasma levels in animals with severe acute pancreatitis treated with endothelin receptor antagonist and saline.

Table 1. TARGET PARAMETERS BEFORE THERAPY*

		Sham-OP		Pancreatitis	
		SAL	ET-RA	SAL	ET-RA
MAP	(mm Hg)	126 ± 4	124 ± 3	125 ± 5	126 ± 5
HR	(min−1)	350 ± 6	358 ± 5	430 ± 12†	440 ± 10†
pO2	(mm Hg)	101 ± 4	98 ± 6	105 ± 8	108 ± 9
pCO2	(mm Hg)	38 ± 2	40 ± 3	40 ± 3	40 ± 4
pH		7.40 ± 0.04	7.44 ± 0.22	7.43 ± 0.02	7.46 ± 0.02
TAP	(nmol/l)	<1.5 ± 0.5	<1.5 ± 0.5	5.4 ± 0.4†	5.9 ± 1.3†
Hct	(%)	46 ± 1	46 ± 1	54.0 ± 2*	54 ± 2†
Urine	(ml/h)	0.6 ± 0.1	0.7 ± 0.1	0.3 ± 0.1†	0.3 ± 0.1†

* 6 hours after pancreatitis induction or sham-operation and randomization for administration of ET-RA or saline.
† $p < 0.05$ pancreatitis *vs.* sham-OP.
SAL = normal saline; ET-RA = endothelin receptor antagonist; MAP = mean arterial pressure; HR = heart rate; TAP = trypsinogen activation peptides; Hct = hematocrit.

scopic evaluation of pancreatic capillary blood flow was measured only in animals with stable cardiorespiratory function (mean arterial pressure > 90 mmHg; Po_2 > 90 mmHg; pco_2 < 50 mmHg; pH 7.3 to 7.5). According to these criteria, one animal treated with ET-RA and two animals given normal saline had to be excluded. In addition, three animals treated with normal saline died before the end of the 24-hour observation period (experiment 1).

Urine output was measured cumulatively at 6, 12, 24, and 48 hours.

TAP levels were determined by an enzyme-linked immunosorbent assay using affinity-purified rabbit anti-TAP antibodies, as described by Hurley et al.[14] Samples were coded, stored at −20°C, and assayed in a blinded fashion.

Pancreatic necrosis was evaluated and scored according to previously described criteria[11] by a pathologist blinded to treatment.

Statistical Analysis

All results are expressed as mean ± SEM. Variables were tested for group differences with the Student's t test. A probability value < 0.05 was considered significant.

RESULTS

ET-1 plasma levels in animals treated with ET-RA were about threefold higher than in animals given saline, indicating that LU-135252 expelled ET-1 from its receptors (Fig. 1). In sham-operated healthy controls, plasma ET-1 levels were beyond the reliable lower detection limit of the test.

Mean arterial pressure, respiratory parameters, urine production, hematocrit, and TAP levels in plasma before ET-RA administration are shown in Table 1. Compared with healthy controls, animals with ANP developed a significant decrease in urine production and an increase in hematocrit and plasma TAP levels. However, these param-

Table 2. TARGET PARAMETERS 24 HOURS AFTER THERAPY WITH ET-RA OR SALINE

		Sham-OP		Pancreatitis	
		SAL	ET-RA	SAL	ET-RA
MAP	(mm Hg)	122 ± 4	126 ± 5	120 ± 2	125 ± 6
HR	(min^{-1})	376 ± 5	380 ± 8	447 ± 10	442 ± 9
pO2	(mm Hg)	101 ± 4	98 ± 6	105 ± 8	110 ± 9
pCO2	(mm Hg)	36 ± 1	37 ± 3	36 ± 2	35 ± 2
pH		7.41 ± 0.02	7.43 ± 0.02	7.45 ± 0.04	7.41 ± 0.02
TAP	(nmol/l)	<1.5 ± 0.5	<1.5 ± 0.5	6.1 ± 1.3	6.3 ± 1.9
Hct	(%)	46 ± 1	45 ± 1	53 ± 2	48 ± 1*
Urine	(ml/h)	0.5 ± 0.1	0.5 ± 0.1	0.2 ± 0.1	0.4 ± 0.1*
Ascites	(ml)	-	-	0.6 ± 0.1	0.3 ± 0.1*

* $p < 0.05$ ET-RA *vs.* SAL.
SAL = normal saline; ET-RA = endothelin receptor antagonist; MAP = mean arterial pressure; HR = heart rate; TAP = trypsinogen activation peptides; HCT = hematocrit.

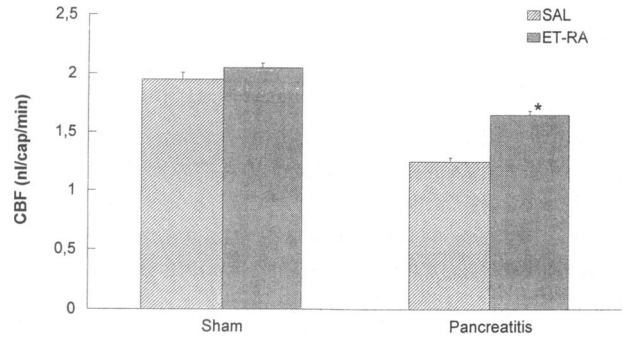

Figure 2. Pancreatic capillary blood flow after therapy with endothelin receptor antagonist or normal saline.

eters (including plasma TAP) did not differ at the time of randomization, indicating that the severity of pancreatitis was comparable in all animals before administration of the test compounds (ET-RA or saline). Six and 24 hours after the start of therapy, ANP animals treated with ET-RA had a higher urine output, lower hematocrit values, and less ascites than those given normal saline (Table 2). Measurements obtained at 48 hours revealed analogous results (data not shown), indicating that the decrease in urine production and hemoconcentration was less severe in animals with endothelin receptor blockade. Comparison of the other parameters (including TAP) showed no significant differences. Ascites collected in animals killed at 24 hours (experiment 1) was less than 0.3 cc in animals treated with ET-RA and 0.6 cc in those given normal saline ($p < 0.05$). Animals that survived 48 hours (experiment 2) had no significant amounts of ascites, indicating that free abdominal fluid was reabsorbed. In healthy controls, all parameters remained stable, with no differences between animals treated with ET-RA or saline (see Table 2).

Histologic examination revealed acinar cell necrosis scores of 2.8 ± 0.1 (24 hours) and 3 ± 0.2 (48 hours) for the saline-treated animals and 2.6 ± 0.1 (24 and 48 hours) for those given ET-RA (not significant).

Compared with healthy controls, pancreatic capillary blood flow was significantly decreased 24 hours after pancreatitis induction (Fig. 2). ET-RA therapy enhanced pancreatic capillary blood flow by 25% in ANP animals but had no effect in healthy controls.

The mortality rate at 48 hours (experiment 2) was 8% in animals with severe pancreatitis treated with ET-RA and 50% in saline-treated controls ($p < 0.05$) (Fig. 3).

DISCUSSION

Death from acute pancreatitis occurs biphasically from two different causes. Early death (within the first 2 weeks) results from acute consequences of the pancreatic inflammatory process and the systemic inflammatory response, with subsequent multiorgan dysfunction; late death (after several weeks) is mainly caused by sepsis.[15] Factors contributing to early multiorgan dysfunction in acute pancreatitis are believed to involve proinflammatory cytokines and other still unknown immunomodulators and vasoactive substances.[16]

The hypothesis that ET-1, first described in 1988 as a vasoconstrictor,[17] may play a significant role in triggering the multiorgan dysfunction syndrome is supported by the fact that elevated plasma levels of ET-1 are found in critically ill patients with hypoxemia, low-flow states, and sepsis, and by its broad spectrum of action as an ubiquitous polyfunctional cytokine that involves not only the vascular system but also other organs by not yet completely understood mechanisms.[8,9]

The role of ET-1 in acute pancreatitis has not yet been systematically studied, but findings suggest that the pancreas is particularly susceptible to ET-1. For example, exogeneous endothelin given in a dose not affecting systemic hemodynamics has been shown to reduce pancreatic perfusion and aggravate mild cerulein-induced pancreatitis.[18,19] To our knowledge, our study is the first to investigate the effect of endothelin receptor blockade in a model of severe pancreatitis that closely resembles severe human pancreatitis. The ET-RA used in the present experiment (LU-135252) is a new, specific agent. Depending on the dose, LU-135252 first blocks endothelin A receptors mainly found on vascular smooth muscle cells, which selectively bind ET-1 over ET-3 to mediate contraction. It also blocks ET-B receptors, which mediate contraction by releasing mediators such as prostacyclin and nitric oxide.[20,21] The properties of LU-1352525 have been described elsewhere.[22–25]

Because doses as high as 100 mg/kg of LU-1352525 are well tolerated in rats and do not cause significant changes in systemic hemodynamic parameters (as shown in previous experiments[26,27] and the healthy controls in the present experiment), we chose this dose for our experiments to achieve complete ET-A receptor blockade. Depending on the type and dose, endothelin antagonists can block ET-A or ET-B receptors or both. This and the different degree of cytokine activation, endogeneous endothelin release, and microcirculatory disorders in the various models used may

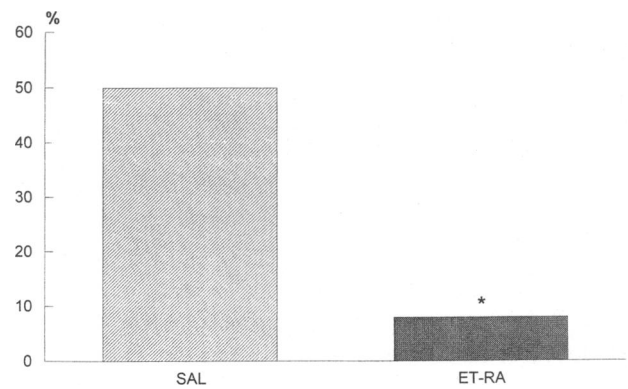

Figure 3. Mortality rate after 48 hours in animals with acute necrotizing pancreatitis treated with endothelin receptor antagonist or normal saline.

explain different (even contrary) results[28] after administration of ET-1 and ET-RA in experimental pancreatitis.

To test the therapeutic effect of endothelin receptor blockade, ET-RA was given 6 hours after disease onset, when the first acinar cell necroses have developed and systemic cardiorespiratory parameters and pancreatic capillary perfusion are already reduced.[11] The manifold increase of plasma ET-1 measured in ET-RA-treated animals compared with saline-treated controls indicated effective receptor blockade by LU-1352525.

The most striking finding of this study was a significant reduction in the death rate, from 50% in untreated animals to 8% in ET-RA-treated rats. The 50% mortality rate in untreated animals exceeded the 30% to 40% mortality rate in this model observed in previous experiments.[29] In those experiments, the observation time was limited to 24 hours (here it was 48 hours) and the animals were given vigorous fluid resuscitation. Fluid resuscitation was not given in the present experiment so that the effect of ET-RA could be tested selectively.

Improved survival was not associated with significantly decreased TAP levels and acinar cell necrosis, suggesting that intrapancreatic protease activation and the evolution of acinar cell injury are not affected when ET-RA therapy is delayed. However, some data indicate that ET-RA prevents pancreatic injury when given prophylactically.[30]

Clinical experience has demonstrated that pancreatic necrosis is only one factor determining the severity of pancreatitis.[31] Just like patients, animals with severe acute pancreatitis do not die of intrapancreatic protease activation or pancreatic necrosis but of the systemic inflammatory response to pancreatic injury, which can lead to multiorgan failure. The interrelation between local injury and systemic response is not completely understood and is believed to involve the release and activation of enzymes, cytokines, and other yet unknown factors, including vasoactive substances.[32,33] The significance of vasoactive substances (*e.g.*, platelet-activating factor or ET-1) for both the progression of local tissue injury and the development of multiorgan dysfunction syndrome has recently been addressed by experts in the field.[34,35] There is increasing evidence that microcirculatory derangement is not confined to the pancreas but may be a systemic phenomenon in severe pancreatitis. We have recently demonstrated that capillary blood flow in the colon is likewise decreased in this model of acute pancreatitis,[36] whereas others have shown microcirculatory changes in the liver and capillary leakage in the lung.[37] Our study, as well as the findings of other groups,[38] suggests that ET-1 contributes to the development of these systemic sequelae in acute pancreatitis and that these systemic complications can be prevented by the use of ET-RA. In the present experiment, this is demonstrated by decreased fluid loss into the third space (as indicated by lower hematocrit levels, increased urine output, and less ascites) and increased pancreatic capillary blood flow with endothelin receptor blockade. In other studies, we could demonstrate that ET-RA also increases capillary blood flow in the colon,[36] underlining its systemic rather than local action.

Despite the differences in capillary blood flow and fluid homeostasis between animals treated with ET-RA and saline, we found no significant differences in systemic cardiorespiratory parameters. There may be several reasons for this. A selection bias may exist because we obtained our results from the surviving animals; thus, animals with less severe disease may be overrepresented in the control group. Also, ET-1 may affect the microcirculation rather than the macrohemodynamics, and fluid loss at the capillary level may be sufficiently compensated by decreased urine production.

Although we could not conclusively resolve the ET-RA mechanisms, the present study clearly demonstrates that endothelin receptor blockade significantly reduces fluid sequestration and hemoconcentration and improves pancreatic capillary blood flow and survival in this model of ANP. This model was previously shown to mimic many aspects of severe human pancreatitis and to be most suited for evaluating novel therapies for this disease. Thus, we conclude that endothelin is a major contributor to the systemic sequelae of severe acute pancreatitis and that endothelin antagonists, which will presently be available for clinical use, may become a new therapeutic tool in the treatment of this disease.

References

1. Schmidt J, Fernandez del Castillo C, Rattner DW, Lewandrowski KB, Messmer K, Warshaw AL. Hyperoncotic ultrahigh molecular weight dextran solutions reduce trypsinogen activation, prevent acinar necrosis, and lower mortality in rodent pancreatitis. Am J Surg 1993; 165:40–45.
2. Mithöfer K, Fernandez-del Castillo C, Ferraro MJ, Lewandrowski KB, Rattner DW, Warshaw AL. Antibiotic treatment improves survival in experimental acute necrotizing pancreatitis. Gastroenterology 1996; 110:232–240.
3. Werner J, Schmidt J, Langer C, Gebhard MM, Herfarth C, Klar E. Superiority of dextran compared to crystalloids and other colloids in the treatment of acute necrotizing pancreatitis [abstract]. Pancreas 1995; 11:452.
4. Foitzik T, Fernandez-del Castillo C, Rattner DW, Ferraro MJ, Warshaw AL. Pathogenesis and prevention of early pancreatic infection in experimental acute necrotizing pancreatitis. Ann Surg 1995; 222:179–185.
5. Klar E, Foitzik T, Buhr HJ, Messmer K, Herfarth C. Isovolemic hemodilution with dextran 60 as treatment of pancreatic ischemia in acute pancreatitis. Ann Surg 1993; 217:369–374.
6. Pederzoli P, Bassi C, Vesentini S, Campedelli A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg Gynecol Obstet 1993; 176:480–483.
7. Luiten EJT, Hop WCJ, Lange JF, Briuning HA. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. Ann Surg 1995; 222:57–65.
8. McMillen MA, Sumpio BE. Endothelins: polyfunctional cytokines. J Am Coll Surg 1995; 180:621–637.
9. Epstein FH. Mechanism of disease. N Engl J Med 1995; 10:356–363.

10. Mandavilli U, Schmid J, Rattner DW, Watson WT, Warshaw AL. Continuous complete collection of uncontaminated urine in conscious rodents. Laboratory Animal Science 1991; 41:258–261.
11. Schmidt J, Rattner DW, Lewandrowski K, et al. A better model of acute pancreatitis for evaluating therapy. Ann Surg 1992; 215:44–56.
12. Mithöfer K, Schmidt J, Gebhard MM, Buhr HJ, Herfarth C, Klar E. Measurement of blood flow in pancreatic exchange capillaries with FITC-labelled erythrocytes. Microvasc Res 1995; 49:33–48.
13. Hotz HG, Schmidt J, Ryschich EW, et al. Isovolemic hemodilution with dextran prevents contrast medium-induced impairment of pancreatic microcirculation in necrotizing pancreatitis in the rat. Am J Surg 1995; 169:161–166.
14. Hurley PR, Cook A, Jehanli A, et al. Development of radioimmunoassays for free tetra-l-aspartyl-L-lysine-trypsinogen activation peptides (TAP). J Immunol Methods 1988; 111:195–203.
15. Mann DV, Hershman MJ, Hittinger R, Glazer G. Multicentre audit of death from acute pancreatitis. Br J Surg 1994; 81:890–893.
16. De Beaux AC, Goldie AS, Ross JA, Carter DC, Fearon KCH. Serum concentrations of inflammatory mediators related to organ failure in patients with acute pancreatitis. Br J Surg 1996; 83:349–353.
17. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 1988; 332:411–415.
18. Takaori K, Inoue K, Kogire M, et al. Effects of endothelin on microcirculation of the pancreas. Life Sci 1992; 51:615–622.
19. Liu XH, Kimura T, Ishikawa H, et al. Effect of endothelin-1 on the development of hemorrhagic pancreatitis in rats. Scand J Gastroenterol 1995; 30:276–282.
20. Arai H, Hori S, Aramori I, Ohkubo H, Nakanashi S. Cloning and expression of a cDNA encoding an endothelin receptor. Nature (London) 1990; 348:730–732.
21. Sakurai T, Yanagisawa M, Takuwa Y, et al. Cloning of a cDNA encoding a non-isopeptide-selective subtype of the endothelin receptor. Nature (London) 1990; 348:732–735.
22. Knoll: Investigator's brochure, LU 135252, 2d ed. Ludwigshafen, 1997:14–32.
23. Riechers H, Albrecht H-P, Amberg W, et al. Discovery and optimization of a novel class of orally active nonpeptidic endothelin-A receptor antagonists. J Med Chem 1996; 39:2123–2128.
24. Mμnter K, Hergenröder S, Unger L, Kirchengast M. Oral treatment with an ETA-receptor antagonist inhibits neointima formation induced by endothelial injury. Pharm Pharmacol Lett 1996; 2:90–92.
25. Raschack M, Unger L, Riechers H, Klinge D. Receptor selectivity of endothelin antagonists and prevention of vasoconstriction and endothelin-induced sudden death. J Cardiovasc Pharmacol 1995; 26 (Suppl 3):S397–S399.
26. D'Uscio LV, Moreau P, Shaw S, Takase H, Barton M, Lμscher TF. Effects of chronic ETA-receptor blockade in angiotensin II-induced hypertension. Hypertension 1997; 29:435–441.
27. Birck R, Knoll T, Kränzlin B, et al. Improvement of acute renal failure in rats with oral endothelin receptor antagonist LU 135252 [abstract]. J Am Soc Nephrol 1996; 7:A2876.
28. Kogire M, Inoue K, Higashide SI, et al. Protective effects of endothelin-1 on acute pancreatitis in rats. Digest Dis Sci 1995; 40:1207–1212.
29. Foitzik T, Bassi DG, Schmidt J, et al. Intravenous contrast medium accentuates the severity of acute necrotizing pancreatitis in the rat. Gastroenterology 1994; 106:207–214.
30. Foitzik T, Faulhaber J, Hotz HG, Kirchengast M, Buhr HJ. Endothelin-1 triggert die Ausbildung der schweren akuten Pankreatitis. Langenbecks Arch 1997(Suppl 1); 749–753.
31. Banks PA, Tenner S, Noordhoek EC, Sica G, Feng S, Zinner M. Does pancreatic necrosis predict severity in patients with acute pancreatitis? [abstract]. Digestion 1996; 57:218.
32. Weidenbach H, Lerch MM, Gress TM, Pfaff D, Turi S, Adler G. Vasoactive mediators and the progression from edematous to necrotizing experimental acute pancreatitis. Gut 1995; 37:434–440.
33. Yotsumoto F, Manabe T, Ohshio G, et al. Role of pancreatic blood flow and vasoactive substances in the development of canine acute pancreatitis. J Surg Res 1993; 55:531–536.
34. Kirkpatrick CJ, Bittinger F, Klein CL, Hauptmann S, Klosterhalfen B. The role of the microcirculation in multiple organ dysfunction syndrome (MODS): a review and perspective. Virchows Arch 1996; 427:461–476.
35. Gullo A, Berlot G. Ingredients of organ dysfunction or failure. World J Surg 1996; 20:430–436.
36. Hotz HG, Foitzik T, Rohweder J, et al. Intestinal microcirculation and gut permeability in acute pancreatitis. Early changes and therapeutic implications. J Gastrointest Surg (in press).
37. Yamanaka, K, Saluja AK, Brown GE, Yamaguchi Y, Hofbauer B, Steer ML. Protective effects of prostaglandin E_1 on acute lung injury of caerulein-induced acute pancreatitis in rats. Am J Physiol 1997; 272(1.1):G23–30.
38. Lewis MPN, Kusske AM, Todd KE, Toyama MT, Ashley SW, Reber HA. An endothelin ETa/ETb receptor antagonist improves the severity of experimental pancreatitis in rats. Surg Forum 1996; 47:135–137.