Receptor Strategies in Pancreatitis

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A variety of receptors on pancreatic acinar and duct cells regulate both pancreatic exocrine secretion and intracellular processes. These receptors are potential sites of action for therapeutic agents in the treatment of pancreatitis.

Cholecystokinin (CCK) receptor antagonists, which may reduce the level of metabolic “stress” on acinar cells, have been shown to mitigate the severity of acute pancreatitis in a number of models. Not all studies have shown a benefit, however, and differences may exist between different structural classes of antagonists. Because increased pancreatic stimulation due to loss of feedback inhibition of CCK has been proposed to contribute to the pain of some patients with chronic pancreatitis, CCK receptor antagonists could also be of benefit in this setting.

Somatostatin and its analogs diminish pancreatic secretion of water and electrolytes and have been effective in treating pancreatic fistulas and pseudocysts. These agents are also being evaluated for their ability to reduce pain in chronic pancreatitis (perhaps by reducing ductal pressure by diminishing secretory volume) and mitigating the severity of acute pancreatitis (possibly by reducing the metabolic load on acinar cells).

Recently described secretin receptor antagonists may also have therapeutic value as a means of selectively inhibiting pancreatic secretion of water and electrolytes.

Potent agonists and antagonists are becoming increasingly available for receptors involved in regulating the function of the gastrointestinal tract, including the exocrine pancreas. One of the first applications of such agents to clinical practice has been the use of secretin with or without cholecystokinin (CCK) or its analog caerulein in testing pancreatic exocrine secretory function [1]. More recently, the development of CCK and secretin receptor antagonists and of octreotide, a clinically useful analog of somatostatin, has raised the prospect that therapies directed at modulating hormonal regulation of the pancreas may prove useful in treating acute or chronic pancreatitis.

CCK RECEPTOR ANTAGONISTS

Evidence that CCK may contribute to the severity of acute pancreatitis has come from a report in which caerulein, a CCK analog, was described as worsening the severity and mortality of acute pancreatitis produced in rats by intraductal injections of bile salts [2] and from numerous studies in the rat (e.g., [3]) and the mouse (e.g., [4]) in which supramaximal stimulation with caerulein produced acute pancreatitis. Such findings suggested that CCK receptor blockade might have a beneficial effect in mitigating the severity of acute pancreatitis.

At least in the rat, caerulein-induced acute pancreatitis appears to be due to the interaction of caerulein with a low-affinity CCK receptor which is involved in

Abbreviations: CCK: cholecystokinin CDE: choline-deficient, ethionine-supplemented (diet)

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high-dose inhibition of enzyme secretion by the pancreas [5]. CCK receptor antagonists would thus be expected to reduce the severity of acute pancreatitis or, if given as a pre-treatment in sufficient amount, to prevent it. This result is indeed the case (Fig. 1) [4,6].

It is hardly surprising that a CCK receptor antagonist can prevent acute pancreatitis produced by excessive stimulation with a CCK analog. A more intriguing observation was the finding that proglumide (a glutaramic acid-derivative CCK receptor antagonist) reduced the severity of injury and significantly improved survival in a necrotizing, highly lethal form of pancreatitis produced in mice by feeding a choline-deficient, ethionine-supplemented (CDE) diet [7]. Proglumide was effective whether administered prior to or following initiation of acute pancreatitis (Fig. 2), under conditions in which plasma CCK levels were not elevated [7]. Similar effects in CDE diet-induced acute pancreatitis have been reported for the more potent glutaramic acid-derivative CCK receptor antagonist lorglumide (CR-1409) [8].

Direct beneficial effects of CCK receptor antagonists have also been reported in other models of acute pancreatitis which do not involve supramaximal stimulation of the pancreas by CCK, caerulein, or other ligands which bind to the CCK receptor. Glutaramic acid-derived antagonists mitigated the severity of acute pancreatitis produced in rats by supramaximal stimulation with a cholinergic agonist [9] or by direct injection of taurocholate into the pancreatic parenchyma [10]. Members of a different structural class of CCK receptor antagonist (asperlicin and its derivatives, related structurally to the benzodiazepines) improved survival and reduced the biochemical and morphological severity in experimental acute pancreatitis produced by perfusion of the pancreatic duct by sodium taurocholate in the rat [11,12] or by mechanical trauma in the guinea pig [12].

Other recent reports provide indirect support for the hypothesis that CCK is an
The glutaramic acid-derivative CCK receptor antagonist proglumide improved survival in CDE diet-induced acute pancreatitis in mice compared to controls (saline), whether administered before (proglumide A) or after (proglumide B) the onset of pancreatitis. The protective effect of proglumide was completely reversed when CCK was given at a dose which does not, in itself, produce pancreatitis (proglumide A + CCK-8) (from [7], reprinted with permission).

Important factor in the pathophysiology of acute pancreatitis. Fasted rats had a reduction in plasma CCK concentration and less severe caerulein-induced pancreatitis than did fed rats [13]. A similar degree of improvement was observed when the fed rats were treated with the CCK receptor antagonist loxiglumide (a glutaramic acid derivative). In another report [14], the severity of CDE diet-induced pancreatitis in mice was markedly reduced by feeding animals taurocholate, a bile salt which reduces plasma CCK levels by inhibiting CCK release from the small intestine (Fig. 3). Conversely, bile salt depletion by feeding cholestyramine led to an increase in plasma CCK concentration and worsened pancreatitis. This deleterious effect of cholestyramine could be blocked by administration of loxiglumide, just as the beneficial effects of taurocholate feeding could be blocked by giving animals CCK.

Not all studies, however, have observed beneficial effects of CCK receptor antagonists in experimental models of acute pancreatitis. Administration of the asperlicin derivative devazepide (formally designated as MK-329 or L-364,718), one of the most potent inhibitors of CCK-stimulated enzyme secretion by the pancreas, failed to show a beneficial effect in CDE diet-induced pancreatitis even at doses which markedly reduced the severity of caerulein-induced pancreatitis [15,16]. Other investigators did not observe a beneficial effect of loxiglumide when given to rats with acute pancreatitis induced by taurocholate infusion into the pancreatic duct [17].

Thus far the conflicting data resulting from the use of different CCK receptor antagonists in different models of acute pancreatitis have defied explanation. Positive results have, however, now been reported by at least five different groups of investigators, using four different models (caerulein stimulation, CDE diet, taurocholate perfusion of the pancreatic duct, and trauma) in three different species (rat, mouse, and guinea pig). This result warrants further investigation in experimental systems and consideration of clinical trials. The striking differences observed in the CDE diet model between glutaramic acid derivatives such as proglumide and the
asperlicin derivative devazepide suggest that the beneficial effects of the former may be regulated by blockade of a CCK receptor unrelated to stimulation of digestive enzyme secretion by the acinar cell but, perhaps, regulating intracellular metabolism in some way. Thus the action of proglumide and related CCK receptor antagonists might be to put the acinar cell “metabolically at rest.”

Another potential clinical use for CCK receptor antagonists may be in the treatment of the pain resulting from chronic pancreatitis if the level of pain is related in some patients to the level of acinar cell metabolic activity or digestive enzyme secretion. Treatment with high doses of pancreatic enzyme supplements have been reported to reduce pain in some patients with chronic pancreatitis [18]. This effect has been hypothesized to be due to enhancement of serine protease-mediated feedback inhibition of CCK secretion by the proximal small intestine. If this explanation proves to be correct, administration of CCK receptor antagonists would be expected to provide a more consistent and, perhaps, greater, beneficial effect.

Unfortunately, despite these tantalizing prospects for the use of CCK receptor antagonists in acute or chronic pancreatitis, their ultimate clinical value (if any) remains to be established.

SOMATOSTATIN ANALOGS

A peptide agonist already in clinical use is the somatostatin analog octreotide, which has proven effective in the treatment of some pancreatic fistulas [19] and pseudocysts [20], presumably primarily through diminishing water and electrolyte secretion by centroacinar and ductal epithelial cells in the pancreas. Octreotide is also being evaluated as a therapeutic agent to reduce pain in chronic pancreatitis in the hope that a decrease in the volume of pancreatic secretion will lead to diminished pain by decreasing the pressure in the pancreatic duct system. If this theory turns out
to be validated, clinical development of recently described secretin receptor antagonists [21] could prove to be as effective as octreotide but more selective.

Somatostatin and its analogs have also been proposed for use in the treatment of acute pancreatitis [22], with the rationale being either to reduce pancreatic enzyme secretion or to lessen the metabolic workload of acinar cells (a beneficial effect also hypothesized for CCK receptor antagonists). The clinical data are as yet too limited to determine whether this approach will be successful. If it is, however, it is more likely that the second rationale will account for its success rather than the first, because pancreatic enzyme secretion appears to be markedly reduced during the development of acute pancreatitis even in the absence of any pharmacologic intervention [23,24].

**CONCLUSION**

The increasing availability of potent and specific agonists and antagonists for regulatory gastrointestinal peptides now opens the way for studies evaluating the extent to which disordered regulatory processes are involved in the development of diseases of the pancreas. In addition, these agents provide the possibility that pancreatic inflammation (both acute and chronic) and its consequences could be treated more directly and effectively than is now possible.

**REFERENCES**

1. Niederau C, Grendell JH: Diagnosis of chronic pancreatitis. Gastroenterology 88:1973–1995, 1985
2. Evander A, Lundquist I, Ishe I: Influence of gastrointestinal hormones on the course of acute experimental pancreatitis. Hepatogastroenterology 29:161–166, 1982
3. Lample M, Kern HF: Acute interstitial pancreatitis in the rat induced by excessive doses of a pancreatic secretogogue. Virchows Arch (A) 373:97–117, 1972
4. Niederau C, Ferrell LD, Grendell JH: Caerulein-induced acute necrotizing pancreatitis in mice: Protective effects of proglumide, benzotript, and secretin. Gastroenterology 88:1192–1204, 1985
5. Saluja AK, Saluja M, Printz H, Zaverntnik A, Sengupta A, Steer ML: Experimental pancreatitis is mediated by low-affinity cholecystokinin receptors that inhibit digestive enzyme secretion. Proc Natl Acad Sci USA 86:8968–8971, 1989
6. Otsuki M, Tani S, Okabayashi Y, Nakamura T, Fujii M, Fujisawa T, Baba S, Itoh H: Effect of a new cholecystokinin receptor antagonist CR 1392 on caerulein-induced acute pancreatitis in rats. Pancreas 4:237–243, 1989
7. Niederau C, Liddle RA, Ferrell LD, Grendell JH: Beneficial effects of cholecystokinin-receptor blockade and inhibition of proteolytic enzyme activity in experimental acute hemorrhagic pancreatitis in mice. Evidence for cholecystokinin as a major factor in the development of acute pancreatitis. J Clin Invest 78:1056–1063, 1986
8. McQuaid KR, Niederau C, Ferrell LD, Grendell JH: Effects of chlorglumide alone or with atropine or gastrin on diet-induced acute hemorrhagic pancreatitis in mice (Abstract). Pancreas 3:607, 1988
9. Bilchik A, Zucker KA, Adrian TE, Modlin IM: Amelioration of cholinergic-induced pancreatitis with a selective cholecystokinin receptor antagonist. Arch Surg 125:1546–1549, 1990
10. Makovec F, Bani M, Cereda R, Chiste R, Revel L, Rovati LC, Setnikar I, Rovati LA: Protective effect of CR 1409 (cholecystokinin antagonist) on experimental pancreatitis in rats and mice. Peptides 7:1159–1164, 1986
11. Wisner JR Jr, Renner IG: Asperlicin, a nonpeptidal cholecystokinin antagonist, attenuates sodium taurocholate-induced acute pancreatitis in rats. Pancreas 3:174–179, 1988
12. Modlin IM, Bilchik AJ, Zucker KA, Adrian TE, Sussman J, Graham SM: Cholecystokinin augmentation of "surgical" pancreatitis. Benefits of receptor blockade. Arch Surg 124:574–578, 1989
13. Otsuki M, Tani S, Okabayashi Y, Fujii M, Nakamura T, Fujisawa T, Koide M, Itoh H: Fasting prevents acute pancreatitis induced by cerulein in rats. Dig Dis Sci 35:840–848, 1990
14. Gomez G, Townsend CM Jr, Green DW, Rajaraman S, Uchida T, Greeley GH Jr, Soloway RD,
Thompson JC: Protective effects of luminal bile salts in necrotizing acute pancreatitis in mice. J Clin Invest 86:323–331, 1990

15. Silverman M, Ilardi C, Bank S, Kranz V, Lendavi S: Effects of the cholecystokinin antagonist L-364,718 on experimental pancreatitis in mice. Gastroenterology 96:186–192, 1989

16. Oshio G, Saluja A, Leli V, Sengupta A, Steer ML: Failure of a potent cholecystokinin antagonist to protect against diet-induced pancreatitis in mice. Pancreas 4:739–743, 1989

17. Tani S, Okabayashi Y, Nakamura T, Fujii M, Itoh H, Otsuki M: Effect of a new cholecystokinin receptor antagonist loxiglumide on two experimental animal models. Pancreas 5:284–290, 1990

18. Slaff J, Jacobson D, Tillman CR, Curington C, Toskes P: Protease-specific suppression of pancreatic exocrine secretion. Gastroenterology 87:44–52, 1984

19. Parekh D, Segal I: Pancreatic ascites and effusion. Risk factors for failure of conservative therapy and the role of octreotide. Arch Surg 127:707–712, 1992

20. Gullo L, Barbara L: Treatment of pancreatic pseudocysts with octreotide. Lancet 338:540–541, 1991

21. Haffar BM, Hocart SJ, Coy DH, Mantey S, Chiang HC, Jensen RT: Reduced peptide bond pseudopeptide analogue of secretin. A new class of secretin receptor antagonists. J Biol Chem 266:316–322, 1991

22. Usadel KH, Uberla KK, Leuschner U: Treatment of acute pancreatitis with somatostatin: Results of a multicenter double blind trial (Abstract). Dig Dis Sci 30:992, 1985

23. Mitchell CJ, Playforth MJ, Kelleher J, McMahon MJ: Functional recovery of the exocrine pancreas after acute pancreatitis. Scand J Gastroenterol 18:5–8, 1983

24. Niederau C, Niederau M, Lüthen R, Strohmeyer G, Ferrell LD, Grendell JH: Pancreatic exocrine secretion in acute experimental models. Gastroenterology 99:1120–1127, 1990