Effects of non-peptidal CCK receptor antagonist (L-364 718) on pancreatic responses to cholecystokinin, gastrin, bombesin, and meat feeding in dogs

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SUMMARY Postprandial pancreatic secretion results from the interaction of neural and hormonal factors but their contribution to the net postprandial secretion is unknown. Recent description of highly specific and potent cholecystokinin (CCK) receptor antagonists allows the determination of the physiological role of CCK in the postprandial pancreatic secretion. In six dogs with chronic pancreatic fistulae, the blockade of CCK receptors by non-peptidal agent (L-364 718) caused little change in basal pancreatic secretion, but decreased significantly ($p < 0.05$) by about 60% the pancreatic protein response to meat feeding and virtually abolished the pancreatic responses to CCK-8 and bombesin. The pancreatic protein responses to pentagastrin, reaching about 37% of CCK maximum, was also significantly reduced but this effect was less pronounced than that observed in tests with CCK-8 or bombesin stimulation. In contrast, cholinergically stimulated pancreatic secretion, reaching about 40% of CCK maximum, was unaffected by L-364 718. Cholecystokinin antagonism also failed to affect the postprandial and bombesin induced increments in plasma CCK and gastrin concentrations, but significantly reduced the PP responses to CCK-8 bombesin and meat feeding possibly as a result of the removal of the CCK mediated release of PP. We conclude that CCK plays a crucial role in the mediation of the postprandial and bombesin induced pancreatic secretion and in the PP release.

Although it is generally accepted that the pancreatic secretion is controlled by interacting neural and hormonal mechanisms, the controversy continues over the relative contribution of these mechanisms in interdigestive and postprandial secretion.^{1,2} The old suggestion that the reflex vagal cholinergic mechanisms play a considerable role in the postprandial pancreatic secretion²⁻⁴ has been undermined by recent evidence that antral gastrin^{5,6} and intestinal CCK⁷⁻⁹ may be also important physiological

mediators in the postprandial pancreatic secretion. The assessment of the hormonal contribution has been possible because of a recent description of highly specific and potent peptidal and non-peptidal CCK receptor antagonists¹⁰⁻¹² which allow the pancreatic responses to be measured in the absence of the effect of CCK.

This study was undertaken to clarify the contribution of CCK and gastrin in the postprandial pancreatic secretion as well as in the pancreatic responses to exogenous hormonal peptides such as CCK-8, gastrin, and bombesin by using one of the most potent antagonists (L-364 718) of CCK receptors⁹⁻¹² in conscious dogs with chronic gastric and pancreatic fistulae.

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Methods

DOGS

Studies *in vivo* were carried out on six mongrel dogs, weighing 18–20 kg, and prepared surgically with gastric (GF) and pancreatic fistulae (PF) as described before.^{8,13} The studies reported here started about five months after surgery. Food was withheld for at least 18 hours before each test. Throughout all tests, except those with feeding, the GF was left open to allow for draining of gastric juice to the outside to prevent gastric acid from entering the duodenum and releasing endogenous hormones.

Secretions from the GF and PF were collected continuously and divided into 15 minute aliquots. The volume was recorded and acid concentration in the gastric juice and bicarbonate and protein concentrations in the pancreatic juice were measured in each sample and presented in 15 or 30 minute outputs.

Several tests were carried out in each animal. In tests with basal secretion, two hour collections were first obtained and then CCK receptor antagonist, L-364 718 (gift of Dr P S Anderson, Merck Sharp and Dohme Labs, West Point, PA) was injected intravenously in gradually increasing doses (3.5–240 µg/kg), each dose being given separately at a 30 minute interval and then increased by the factor of four. L-364 718 is 3S(-)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1, 4-benzodiazepine-3ry1)-1H-indole-2-carboxamide (Fig. 1.).

In tests with meal induced secretion, each dog was offered 500 g of cooked homogenised ground beef for 15 minutes and this was usually completely consumed. Gastric and pancreatic collections were made for 60 minutes before, during, and 210 minutes after the feeding. When the postprandial secretory rate reached a well sustained plateau, L-364 718 was injected intravenously as a single bolus dose (240 µg/kg) and then the secretion was examined for subsequent 150 minutes. In tests with exogenous hormonal stimulation, synthetic CCK octapeptide (CCK-8)

(gift of Prof N Yanaihara, Shizuoka, Japan) was infused iv in a constant dose (0.12 µg/kg/h) throughout the experiment to induce near maximal stimulation of pancreatic protein secretion in these dogs. When the secretory rate reached a plateau, L-364 718 was administered iv in gradually increasing doses (3.5–240 µg/kg), each injection being administered at 30 minute intervals during the same experiment. In control experiments, CCK-8 alone was administered in the same dose during the period of experimentation. For comparison, maximal pancreatic protein response to CCK-8 was determined in separate tests using a dose of 0.25 µg/kg/h. Pentagastrin (ICI, Macclesfield, UK) was infused iv in a constant dose (4 µg/kg/h) and when the gastric acid and pancreatic protein secretion reached plateau, single bolus injections of L-364 718 were given at 30 minute intervals as in tests with CCK-8. In tests with bombesin (Farmitalia, Milano, Italy), the peptide was infused iv in a constant dose for 210 minutes and after 60 minutes of stabilisation of the secretory rate, L-364 718 was injected in gradually increasing doses at 30 minute intervals as in tests with caerulein.

In the tests involving administration of CCK-8, pentagastrin and bombesin, a solution of 0.5% albumin (Sigma Co, St Louis, MO) was used to dissolve these peptides in order to prevent their degradation and adsorption into the plastic tubes during intravenous infusion.

In tests with meal feeding and with infusion of CCK-8, bombesin, blood samples were taken from the peripheral vein at 15 to 30 minute intervals for radioimmunoassay of plasma gastrin and pancreatic polypeptide and for bioassay of CCK. Blood samples were collected in chilled tubes with 10 U heparin and 400 U Kallikrein inhibitor, aprotinin (Trasylol) per millilitre and centrifuged, and the plasma was frozen within 15 minutes of sampling. The plasma gastrin concentration was determined using gastrin antiserum 4562 (gift of Prof J F Rehfeld, Aarhus, Denmark) and plasma PP was assayed using PP antiserum (gift of Dr R E Chance, Eli-Lilly, Indianapolis, IN) as presented previously.¹³ Plasma CCK was determined by bioassay as described before.¹⁴

Results are expressed as means (SE). In tests comparing various hormonal peptides and feeding with and without L-364 718, the increments in pancreatic secretory outputs and plasma hormone concentrations were calculated and averaged to provide the incremental secretory outputs and incremental plasma hormone levels for the experimental period. The significance of the differences between means was evaluated using Student's *t* test for paired values. Differences were considered significant if *p* was less than 0.05.

Fig. 1 Structure of L-364 718.

Table 1 Pancreatic HCO_3 and protein outputs and plasma CCK, gastrin and PP concentrations in fasted dogs without and with iv injections of L-364 718 in gradually increasing doses (3.5–240 $\mu\text{g/kg}$). Means (SE) of six tests on six dogs

	Pancreatic Plasma				
	HCO_3 (μmol / 15 min)	Protein (mg/ 15 min)	Gastrin (pM)	CCK (pM)	PP (pM)
Basal	36 (6)	72 (10)	28 (3)	0.8 (0.3)	17 (4)
L-364 718 3.5 $\mu\text{g/kg}$	39 (7)	102 (22)	32 (4)	0.7 (0.2)	12 (4)
L-364 718 15.0 $\mu\text{g/kg}$	54 (12)	80 (16)	24 (4)	0.7 (0.4)	12 (4)
L-364 718 60.0 $\mu\text{g/kg}$	48 (10)	57 (18)	27 (4)	0.6 (0.2)	17 (4)
L-364 718 240.0 $\mu\text{g/kg}$	44 (12)	32 (10)*	24 (6)	0.6 (0.4)	12 (2)

*Significant ($p < 0.05$) decrease below the basal value.

Results

EFFECTS OF L-364 718 ON BASAL PANCREATIC SECRETION

In fasted dogs, basal gastric acid secretion from the GF was negligible, while the pancreatic secretion showed some fluctuations in individual dogs. Protein outputs varied from about 15 to 250 mg/15 minutes, averaging about 72 (10) mg/15 minutes during two hour basal collection period (Table 1). HCO_3 output also fluctuated from about 32 (5) to 82 (14) $\mu\text{mol}/15$ minutes, averaging about 36 (6) $\mu\text{mol}/15$ minutes. Intravenous injections of L-364 718 in doses of 3.5–240 $\mu\text{g/kg}$ tended to reduce mean basal protein secretion but this was significant only at the highest dose of CCK-antagonist. No changes in basal gastrin, CCK or PP levels were observed after iv infusion of L-364 718 (Table 1).

EFFECTS OF L-364 718 ON PANCREATIC RESPONSES TO EXOGENOUS HORMONES

Infusion of CCK-8 at 0.12 $\mu\text{g/kg/h}$ resulted in increase in pancreatic secretion that was reflected mainly in the protein outputs (Fig. 2) while the volume flow and HCO_3 outputs showed only small increase. This dose of CCK-8 produced near maximal pancreatic protein secretion that in control experiments was well sustained for about 90 minutes but then tended to decline reaching at the end of experiment about 70% of the initial plateau. Maximal protein output achieved with CCK-8 at a dose of 0.25 $\mu\text{g/kg/h}$ was 1240 (236) mg/15 minutes in these animals.

When L-364 718 was injected at 3.5 and 15 $\mu\text{g/kg}$ there was a significant decrease in the protein output falling to the level not different from the basal protein secretion. After the highest doses (60 and 240 $\mu\text{g/kg}$) of L-364 718, protein output remained completely suppressed for the rest of the experiment (90

Fig. 2 Effects of L-364 718 injected iv in gradually increasing doses on CCK-8 induced constant stimulation of pancreatic secretion. In control experiments, CCK-8 alone without L-364 718 was infused for the time of experimentation. Mean (SE) of six experiments on six dogs with chronic gastric and pancreatic fistulae. *Indicates significant decrease below the control value.

minutes). Pancreatic HCO_3 response to CCK-8 was negligible but the administration of L-364 718 also resulted in a significant reduction in this HCO_3 response (Fig. 2).

Plasma gastrin concentrations were unchanged by iv infusion of CCK-8 with or without addition of L-364 718. Plasma CCK concentration rose from the basal value of 0.8 (0.3) pM to about 16.8 (2.4) pM during infusion of CCK-8 and this was not significantly affected by administration of L-364 718. Plasma PP concentrations also showed a significant increment above basal level throughout the period of CCK-8 infusion. Treatment with L-364 718 did not affect basal PP levels but reduced significantly the PP responses to CCK-8. At the dose of 240 $\mu\text{g/kg}$ L-364 718, plasma level of PP was not different from the basal concentration (Table 2).

Pentagastrin infused iv in a constant dose (4 $\mu\text{g/kg/h}$) resulted in a significant increase in gastric acid and pancreatic protein outputs (Figs 3 and 4). Gastric acid output reached the maximal observed outputs in

Fig. 3 Effects of L-364 718 injected iv in gradually increasing doses on pentagastrin induced constant stimulation of gastric acid secretion. In control experiments, pentagastrin alone without L-364 718 was infused for the time of experimentation. Mean (SE) of six experiments on six dogs with gastric and pancreatic fistulae. *Indicates significant decrease below the control value.

these animals (8150 (1420) $\mu\text{mol}/30$ minutes), while pancreatic protein secretion attained only about 37% of the CCK maximum in these animals. Addition of L-364 718 to iv infusion, decreased gastric acid and pancreatic protein responses to pentagastrin. The decrease in gastric acid responses to pentagastrin occurred at all doses of L-364 718 used and was

Fig. 4 Pancreatic bicarbonate and protein secretion in tests as in Figure 2.

Fig. 5 Effects of L-364 718 injected iv in gradually increasing doses on bombesin-induced pancreatic bicarbonate and protein secretion. In control experiments bombesin alone without L-364 718 was infused iv for the time of experimentation. Mean (SE) of six experiments on dogs with chronic gastric and pancreatic fistulae. *Indicates significant decrease below the control value obtained with bombesin alone.

significant at a dose of 15 $\mu\text{g}/\text{kg}$ and higher doses but even at the highest dose of L-364 718 (240 $\mu\text{g}/\text{kg}$) acid output was reduced only to about 50% of the control value obtained with pentagastrin alone. Pancreatic protein output in response to pentagastrin was relatively well sustained throughout the experimentation but when L-364 718 was added to iv infusion, there was a significant reduction in protein output. At the highest dose of L-364 718, the protein output was reduced to about 40% of the control value. After withdrawal of L-364 718 administration, pancreatic protein returned to the control level within about a 30 minute period. Pancreatic HCO_3^- outputs in tests with pentagastrin was negligible and injections of L-364 718 failed to affect these outputs.

Bombesin infused iv in a constant dose of 0.25 $\mu\text{g}/\text{kg}/\text{h}$ resulted in pancreatic protein secretory rate similar to that obtained with pentagastrin or reaching about 50% of CCK-8 maximum in these animals. In control tests, the secretory rate was relatively well sustained with only small decline at the end of experiment to about 70% of the initial peak value.

Table 2 Plasma gastrin, CCK and PP concentrations in tests with iv infusion of CCK-8 (0.12 µg/kg/h) alone, bombesin (0.25 µg/kg/h) alone or combined with iv injections of gradually increasing doses of L-364 718 (as in Figs 2 and 4) and after meat feeding alone and combined with iv injection of a single dose of L-364 718 (as in Fig. 5). In tests with CCK-8 and bombesin, plasma hormone levels are means (SE) of six tests on six dogs recorded during a 15 minute period after injection of L-364 718 or during the corresponding periods of infusion of CCK-8 or bombesin alone. In tests with feeding, the plasma hormone concentrations are mean values (SE) of six tests on six dogs recorded (at 30 minute intervals) during first hour after injection of L-364 718 or during corresponding control postprandial hour without L-364 718 administration.

	Gastrin (pM)	CCK (pM)	PP (pM)
Basal	28 (3)	0.8 (0.3)	14 (3)
CCK-8 alone	24 (4)	16.6 (2.8)	76 (12)
CCK-8+L-364 3.5 µg/kg	30 (6)	16.4 (2.0)	72 (16)
CCK-8+L-364 15.0 µg/kg	23 (4)	17.0 (2.4)	62 (12)*
CCK-8+L-364 60.0 µg/kg	24 (5)	16.8 (3.0)	37 (5)*
CCK-8+L-364 240.0 µg/kg	28 (6)	16.2 (2.2)	18 (4)*
Bombesin alone	186 (24)	9.2 (1.2)	144 (28)
Bombesin+L-364 3.5 µg/kg	211 (34)	10.6 (2.6)	154 (27)
Bombesin+L-364 15.0 µg/kg	235 (41)	9.8 (1.9)	123 (29)
Bombesin+L-364 60.0 µg/kg	229 (36)	11.2 (2.2)	79 (18)*
Bombesin+L-364 240.0 µg/kg	241 (28)	12.2 (2.3)	33 (12)*
Meat feeding alone	124 (28)	6.4 (1.2)	236 (37)
Meat feeding+L-364 240 µg/kg	136 (31)	6.1 (1.4)	94 (14)*

*Significant (p<0.05) decrease below the control value.
NT = not tested.

Injections of L-364 718 in gradually increasing doses resulted in a significant reduction in protein outputs at a dose of 15 µg/kg. The protein secretory response to bombesin fell to the basal level at the highest dose (240 µg/kg) of CCK antagonist. After the last dose of L-364 718, the protein secretion remained suppressed for the rest of the experiment. Pancreatic HCO₃ secretion in response to bombesin was rather small and within the range observed in tests with CCK-8. Injections of L-364 718 in gradually increasing doses resulted in a significant reduction in HCO₃ outputs starting with the dose of 60 µg/kg. Bombesin resulted in a significant increase in plasma concentrations of CCK, gastrin and PP. The rise in plasma CCK, gastrin and PP averaged, respectively, 9.2 (1.2), 186 (24), and 144 (28) pM. After iv injections of L-364 718 in gradually increasing doses, there was a dose dependent decrease in plasma PP concentrations falling at the dose of 250 µg/kg to the level not significantly different from control values. Plasma concentrations of CCK and gastrin remained virtually unchanged by increasing doses of L-364 718 (Table 2).

Fig. 6 Effects of single dose injection of L-364 718 on the postprandial pancreatic bicarbonate and protein outputs. In control tests, the postprandial pancreatic secretion was determined without administration of L-364 718. Mean (SE) of six tests on six pancreatic fistulae dogs. *Indicates significant decrease below the control value obtained with meat feeding alone.

Bethanechol infused iv in a constant dose (100 µg/kg/h) resulted in a well sustained increase of pancreatic protein secretion reaching about 40% of CCK maximum. There was only small increase in pancreatic HCO₃ secretion. L-364 718 added to iv infusion in single bolus doses (3.5–240 µg/kg) did not significantly affect gastric or pancreatic secretory rate and these results have been omitted for the sake of clarity.

EFFECTS OF L-364 718 ON PANCREATIC RESPONSES TO MEAT FEEDING
Meat feeding evoked an increase in pancreatic secretion of HCO₃ and protein (Fig. 6), reaching respective peaks in the second and fourth 15 minute periods after feeding. Both parameters of pancreatic

secretion tended to decline during the 210 minute postprandial period. L-364 718 (240 µg/kg) given iv in a single bolus injection resulted in an immediate reduction in protein outputs falling within first 15 minute period to about 40% of the control value and remaining significantly reduced in the first and second postprandial hour. The HCO₃ response was also significantly reduced by L-364 718 but only in the first hour after injection of L-364 718.

Plasma CCK and gastrin concentration showed a marked rise after feeding and L-364 718 did not affect significantly these levels (Table 2). Pancreatic protein also showed a marked increment that was well sustained throughout the control postprandial period. L-364 718 caused a marked reduction in the PP increment by about 70% throughout the postprandial period.

Discussion

This study provides an evidence that CCK receptors of the acinar cells play an important role in the stimulation of pancreatic protein secretion in response to ordinary meat feeding, gastrin, and bombesin but not in the basal secretion and after cholinergic stimulation.

Previous studies using proglumide, that was originally designed by Rovati *et al*¹⁵ as gastrin receptor antagonist for the treatment of peptic ulcer, showed that this agent administered in conscious dogs in massive dose (300 mg/kg/h) was also an effective inhibitor of the pancreatic responses to CCK-8 and duodenal perfusion with amino acids and fat but not bethanechol.¹⁶ The action of proglumide was specific for CCK but its widespread usefulness was limited because of its very low potency. A series of competitive non-peptide benzodiazepine antagonists of cholecystokinin were synthesised¹² recently and the most potent L-364 718, has been characterised as highly specific and long acting CCK antagonist in a variety of biological systems.¹² It was found to be effective after oral and parenteral administration and exhibited the duration of action of two to three hours after a single iv dose administration.¹⁷ This CCK antagonist has been examined for biliary and pancreatic secretion in conscious dogs.¹⁸ When given orally it was found to inhibit the postprandial biliary secretion but, unexpectedly, failed to affect the postprandial pancreatic secretion despite its ability to antagonise the stimulatory action of exogenous CCK on this secretion.¹⁸

In this study we used L-364 718 by intravenous injections in a dose range several times lower than that used in previous report¹⁸ and found to be highly effective in the inhibition of pancreatic secretion induced not only by caerulein but also by meat

feeding and bombesin. The failure of L-364 718 to suppress the postprandial pancreatic secretion in previous report¹⁸ probably reflected an insufficient absorption of the drug after its intragastric administration rather than the lack of the involvement of CCK in this secretion. Indeed, our results provide a strong support for the notion that the pancreatic secretion induced by feeding and bombesin is mediated mainly by endogenous CCK. As the pancreatic response to bombesin can be completely blocked by L-364 718 at a dose that also totally suppressed pancreatic response to CCK-8, it may be concluded that bombesin stimulation is predominantly mediated by endogenous CCK. The same dose of L-364 718 reduced the postprandial pancreatic secretion by about 60% suggesting that CCK is the major but not the only factor involved in the secretory stimulation. As cholinergically stimulated pancreatic secretion is resistant to the inhibitory action of CCK antagonist, it is likely that cholinergic vagovagal reflexes originating in the stomach and the gut¹⁹⁻²² are involved in the postprandial pancreatic secretion. Such cholinergic gastro- and enteropancreatic reflexes may augment the stimulatory effect of CCK and by themselves may contribute at least 50% to postprandial pancreatic secretion.²²⁻²⁴

This has been supported by several observations that vagotomy^{22 25} and atropine^{22 23} reduced the secretory responses to meal stimuli only from the intact but not from denervated (autotransplanted) pancreas and that the pancreatic enzyme response to luminal stimulation had shorter latency compared with that to intraportal injection of CCK.²³ Using specific radioimmunoassay to measure the postprandial plasma concentrations of CCK, we reported that CCK is released postprandially in sufficient amounts to drive the major portion of the postprandial pancreatic secretion.^{8 9} This study showing that CCK-antagonist eliminates about 60% of the postprandial protein secretion confirms and reinforces the key role of CCK in the gastrointestinal phase of pancreatic secretion. This does not exclude the contribution of other, particularly neural, mechanisms which seem to be activated mainly in the early postprandial period before the humoral mechanisms are fully activated.^{1 2}

The crucial question raised by the use of CCK antagonists is whether these agents also interfere with the effects of gastrin on gastric acid and pancreatic secretion. Gastrin and CCK share a common COOH-terminal pentapeptide amide, therefore, CCK agonists and antagonists should affect in a similar fashion the secretory activity of oxyntic cells and the acinar cells. Our present study shows that, unlike CCK, pentagastrin is only a partial agonist of pancreatic protein secretion. According to our

results, pentagastrin used in the dose producing maximal gastric acid secretion, stimulated the pancreatic protein in conscious dogs only to about 37% of the CCK maximum and this is similar to that achieved by gastrin (G-17) used at a dose of 250 pmol/kg/h.²⁶ This indicates that pentagastrin, though a less potent stimulant than gastrin, mimics, at least in part, the effect of gastrin on the pancreatic secretion. The addition of CCK antagonist to pentagastrin infusion caused only partial inhibition of gastrin induced gastric acid and pancreatic protein secretion suggesting that pentagastrin induced gastropancreatic secretion is less sensitive to the action of our CCK receptor antagonist. This remains in agreement with previous observation¹⁶ that proglumide, a prototype of CCK receptor antagonist, was an effective inhibitor of pentagastrin induced gastric acid secretion in dogs only when larger doses of this agent were used or when lower doses of pentagastrin were used for gastric acid stimulation. As in other systems L-364 718 was found to be highly specific for CCK receptor having no effect on gastrin receptors,¹¹ further studies with authentic G-17 and G-34 are needed to determine whether gastric acid and pancreatic protein responses to gastrin itself is sensitive to the inhibitory action of L-364 718. The fact that the spectrum of biological activity of pentagastrin is similar to gastrin suggests that L-364 718 shows somewhat higher anti-CCK than antagastrin activity and that it is, therefore, more suitable for the study of CCK than gastrin in pancreatic physiology. The reason for the discrepancy in the action of CCK agonists and antagonists on gastric and pancreatic secretion *in vivo* is not apparent from our study but it may be because of the existence of two populations of CCK/gastrin receptors – that is, CCK preferring receptors and gastrin preferring receptors. The former receptors would predominate in the acinar cells and exhibit high affinity for CCK and its selective antagonists, while the latter receptors would predominate in the oxyntic cells and exhibit high affinity to gastrin but lower affinity to CCK and its antagonists. An alternative explanation would be that *in vivo* gastrin and CCK not only activate the CCK/gastrin receptors but also cause the release of local inhibitor of pancreatic and gastric secretion, respectively. Partial support for this notion is provided by recent observation that CCK is more potent than gastrin in releasing somatostatin from the gastric endocrine cells.²⁷ Perhaps a similar inhibitor is released by gastrin in the pancreas but we have no support for such speculation.

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