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Camostate- and caerulein-induced delay of gastric emptying in the rat: effect of CCK receptor antagonists

Gábor Varga [a,*], Carmelo Scarpignato [b,c]

[a] *Institute of Experimental Medicine, Hungarian Academy of Sciences, PO Box 67, 1450 Budapest, Hungary*
[b] *Department of Gastroenterology and Hepatology, Faculty of Medicine, University of Nantes, Nantes, France*
[c] *Institute of Pharmacology, School of Medicine and Dentistry, University of Parma, Parma, Italy*

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Abstract

The effect of camostate, a potent releaser of endogenous cholecystokinin (CCK), and of caerulein, an amphibian peptide mimicking the biological actions of CCK, as well as of selective CCK receptor antagonists on gastric emptying of liquids was studied in the rat. Oral administration of camostate (200 mg/kg with the liquid test meal preceded by the same dose 10 min before the meal) significantly delayed gastric emptying of saline, an effect which was completely blocked by previous administration of the CCK_A receptor antagonist, devazepide, at a dose (1 mg/kg i.v.) unable to modify the emptying rate when administered alone. Caerulein (0.03–30 nmol/kg i.v.) also delayed the emptying rate in a dose-dependent manner, with an ID_{50} of 3.94 nmol/kg. The effect of the peptide was also inhibited by devazepide. The CCK_B receptor antagonist, L365,260 (3*R*-(+)-*N*-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-yl)-*N'*-(3-methylphenyl)-urea; 3 mg/kg i.v.), was completely unable to modify the CCK (both endogenous and exogenous)-induced delay in gastric emptying. Repeated (7 days) camostate administration did not modify the gastric motor response to endogenous CCK, thus, suggesting that adaptation did not take place. These results demonstrate that endogenous and exogenous CCK delays gastric emptying of liquids through stimulation of CCK_A receptors and suggest that adaptation of the gastric motor response to CCK does not occur.

Keywords: CCK (cholecystokinin); Caerulein; Camostate; CCK receptor antagonist; Gastric emptying

1. Introduction

Gastric emptying is one of the most important motor functions in the gastrointestinal tract (Heading et al., 1992). It limits the rate of absorption of nutrients and drugs by controlling delivery into the small intestine (McHugh, 1983). The rate of delivery is modulated by feedback from the small intestine, by the CNS via the vagus and sympathetic nerves and by release of a variety of hormones (Meyer, 1991).

Cholecystokinin (CCK) clearly belongs to the group of substances known as brain-gut peptides: it functions both as a neuropeptide and as a gut hormone (Dockray, 1989). The peptide and its synthetic derivatives (like, for instance, CCK-8 and the amphibian counterpart caerulein) significantly delay emptying of gastric contents in both animals (Anika, 1982; Ayres et al., 1991; Debas et al., 1975; Figlewicz et al., 1989; Moran and McHugh, 1982; Scarpignato et al., 1980) and humans (Liddle et al., 1986; Muurahainen et al., 1988; Scarpignato et al., 1981). The fact that CCK in doses mimicking postprandial plasma levels strongly affects the emptying rate suggests that the peptide is a physiologic mediator of gastric emptying (Debas et al., 1975; Kleibeuker et al., 1988; Liddle et al., 1986).

A specific approach to evaluate the importance of CCK in the physiological regulation of a particular gastrointestinal function is to selectively block the binding of CCK to its receptor, which should lessen or abolish the biological response to endogenous stimulants thought to act through CCK release. Immunoneutralization (i.e. administration of specific, high-affinity anti-CCK antibodies) is one approach to this, but the use of a selective and competitive receptor blocker is certainly better (Fink et al., 1987; Lloyd et al., 1992). Unfortunately, a clear definition of the role of CCK in the physiology of gastric motor activity has been long hampered by the lack of selective and potent

* Corresponding author. Tel.: (36) (1) 210-0819 (ext. 257); fax: (36) (1) 210-0813.

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non-peptide antagonists of CCK receptors. The availability of such compounds (D'Amato et al., 1994; Scarpignato, 1992; Woodruff and Hughes, 1991) has stimulated a broad array of investigations into the physiological actions of this peptide and into its putative role in certain diseases.

In the present investigation, the effect of camostate, a potent releaser of endogenous CCK (Douglas et al., 1990; Göke et al., 1986), and of caerulein, an amphibian peptide mimicking the biological actions of CCK (Bertaccini, 1976), on gastric emptying was studied in the rat. The use of selective CCK_A and CCK_B receptor antagonists allowed the characterization of the receptor subtype involved in controlling gastric emptying. In addition, short-term (7 days) treatment with camostate was performed in order to check whether adaptation of the gastric motor response occurs after repeated stimulation of endogenous CCK release.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (250–300 g) were used. They were purchased from Lati (Gödöllô, Hungary) and were used at least 1 week after their arrival at the laboratory. Animals were housed at constant temperature (24°C) and under a 12–12-h light cycle and were given standard rat chow at libitum.

2.2. Surgery

Surgery was performed as previously described (Varga et al., 1993, 1995). Briefly, under pentobarbital (40 mg/kg i.p.) anesthesia a Gregory-type stainless steel gastric cannula was implanted in the forestomach and an indwelling catheter was inserted into the jugular vein and tunnelled to the neck under the skin. Experiments were started after at least 1 week of recovery, during which the animals were adapted to restraint for some hours twice a week in Bollman-type cages.

2.3. Experimental design

In the first set of experiments, the effect of camostate, in doses capable of releasing endogenous CCK (Douglas et al., 1990), on gastric emptying of liquids was assessed. To this end, 200 mg/kg of the compound was given intragastrically together with the liquid test meal with or without prior (10 min before) administration of the same dose of this proteinase inhibitor. Saline-pretreated rats served as controls. When devazepide was tested against the camostate effect, it was injected i.v. 15 min before the meal.

In the second set of experiments, the action of the CCK receptor agonist, caerulein, on gastric emptying of saline was studied. To this end, different doses of the peptide were injected i.v. 5 min before instillation of the liquid meal. When the effect of the CCK_A receptor antagonist devazepide and the CCK_B/gastrin receptor antagonist L365,260 against caerulein was studied, these compounds were injected i.v. 5 min before the agonist.

Finally, in order to check whether the gastric motor response to endogenous CCK release changed with time, short-term (7 days) camostate administration was performed. To this end, two groups of rats were given camostate (200 mg/kg) or saline each day in the morning (at 10:00 a.m.). On day 7, gastric emptying was measured in both groups after instillation of saline or camostate.

2.4. Measurement of gastric emptying

The animals were fasted overnight and placed in Bollman-type cages. After opening the gastric cannula, the stomach was rinsed with warmed saline and experiments started after at least 30 min. 154 mM NaCl solution containing phenol red (0.6 g/l) was used as a non-caloric liquid test meal. 3 ml of prewarmed (37°C) test meal were slowly (20 s) instilled into the stomach via a plastic catheter passed through a rubber plug fixed to the gastric cannula. 5 min later the cannula was opened by removing the plug and the remaining gastric content was collected by gravity in graduated tubes. The stomach was then rinsed with 3 ml saline and the washing solution was added to the recovered gastric content. The phenol red concentration in the mixture was then measured spectrophotometrically at 560 nm following addition of 0.1 N NaOH, and the total amount of the marker recovered from the stomach was calculated.

2.5. Chronic studies

Two groups of rats were used. They were treated intragastrically with either saline (3 ml) or with camostate (200 mg/kg/diluted to 3 ml of saline) once daily for 7 days through the gastric cannula. On day 7, gastric emptying in response to saline or camostate was tested in fasted animals. The dose of camostate used in these experiments was found to exert a strong and significant trophic effect on the rat pancreas (Douglas et al., 1990; Göke et al., 1986; Wisner et al., 1988).

2.6. Evaluation of data

The amount of meal emptied from the stomach (i.e. *gastric emptying*) was calculated for each rat according to the following formula:

$$\text{Volume Emptied (ml)} = 3 \times \left(1 - \frac{\text{Amount of phenol red recovered from the stomach}}{\text{Amount of phenol red instilled in the stomach}}\right)$$

Under our experimental conditions, in control rats (receiving only physiological saline), the volume of meal

leaving the stomach was 2.46 ± 0.09 ml (range 1.99–2.70) in 5 min.

All data are presented as mean ± S.E.M. The dose-response curve for caerulein was fitted to a sigmoid curve by using a non-linear regression program which provided an estimate of log ID_{50} and maximal response value. One-way analysis of variance (ANOVA) was used to evaluate statistical significance. Differences are considered significant when $P < 0.05$. Computation of the data and statistical analyses were done with the INPLOT and INSTAT statistical program packages (GRAPHPAD, San Diego, CA).

2.7. Drugs

Devazepide (L364,718; 3*S*-(−)-*N*-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine) and L365,260 (3*R*-(+)-*N*-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-yl)-*N'*-(3-methylphenyl)-urea) (both are gifts from Dr. R.S. Chang, Merck, Sharp and Dohme, West Point, PA) were dissolved in DMSO : saline (3 : 1). Vehicle (1 ml/kg), L364,718 (1 mg/kg) and L365,260 (3 mg/kg) were given as i.v. bolus injections. Caerulein (Farmitalia-Carlo Erba, Milan, Italy) was dissolved in 154 mM NaCl containing 0.2% bovine serum albumin (Sigma, St. Louis, MO). Camostate (compound marked FOY-305, Ono Pharmaceuticals, Osaka, Japan) was dissolved in warmed saline. Fresh solutions of each compound were prepared each experimental day.

3. Results

3.1. Effect of camostate on gastric emptying

5 min after instillation of physiological saline into the rat stomach, 18 ± 3% of the fluid was recovered. When camostate (200 mg/kg) was given intragastrically together with the fluid meal, a small non-significant effect (20 ± 6%) was observed. In contrast, when its administration

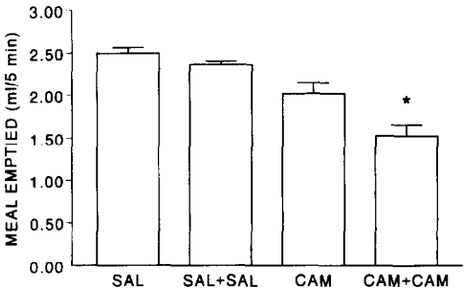

Fig. 1. Effect of camostate (200 mg/kg) administration on gastric emptying of a non-caloric liquid meal (saline) in the rat. CAM, camostate administered with the liquid test meal; CAM + CAM, camostate administration preceded by another camostate load 10 min before the liquid meal. SAL, saline treatment. Each bar refers to the mean of the values obtained from 6–8 rats. Vertical bars are S.E. values. * $P < 0.05$ in comparison with the saline value.

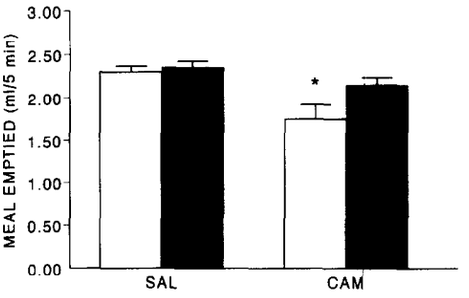

Fig. 2. Effect of vehicle (open column) and devazepide (1 mg/kg, black column) on the camostate-induced delay of gastric emptying in the rat. Each bar refers to the mean of the values obtained from 6–8 rats. CAM, camostate; SAL, saline. Vertical bars are S.E. values. * $P < 0.05$ in comparison with the saline value.

was preceded by preload of the same dose, a significant ($P < 0.05$) delay (39 ± 5%) of gastric emptying became apparent (Fig. 1). Thus, this administration schedule was used in further experiments testing the effect of the different CCK receptor antagonists.

I.v. injection of devazepide (1 mg/kg) almost completely reversed the effect of camostate on gastric emptying (Fig. 2). In contrast, L365,260 (3 mg/kg) was unable to modify the camostate-induced delay in gastric emptying. The amount of meal leaving the stomach after 5 min was 1.6 ± 0.1 ml after camostate alone, and 1.7 ± 0.2 ml after camostate plus the CCK_B receptor antagonist.

Fig. 3 summarizes results obtained after short-term camostate treatment. It is evident that, after 7 days of camostate administration (200 mg/kg daily), the proteinase inhibitor was still capable of delaying gastric emptying with an efficacy comparable to that observed in control animals (i.e. animals receiving physiologic saline for 7 days), thus, showing a lack of adaptation.

3.2. Effect of caerulein on gastric emptying

As previously described (Scarpignato et al., 1980), caerulein dose-dependently delayed gastric emptying of a

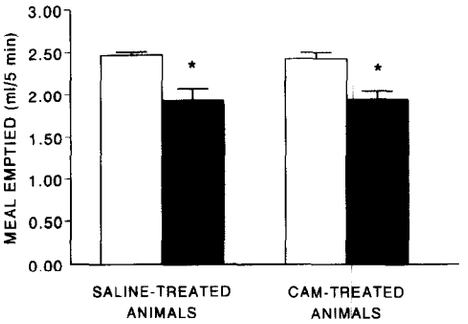

Fig. 3. Inhibitory effect of acute saline (SAL, open column) and camostate (CAM, 2×200 mg/kg, black column) administration on saline or camostate (200 mg/kg daily) pretreated rats. Each column refers to the mean of the values obtained from 10 animals. Vertical bars are S.E. values. * $P < 0.05$ in comparison with saline value. For details, see Materials and methods.

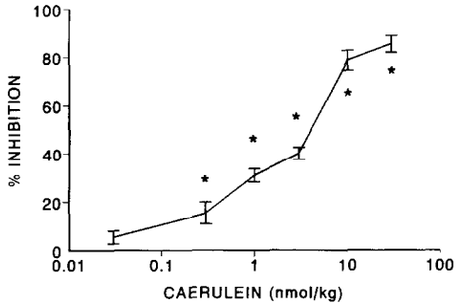

Fig. 4. Caerulein-induced dose-related inhibition of gastric emptying of liquids in rats. Each point refers to the mean of the value obtained from 6–8 rats. Vertical bars are S.E. values. * $P < 0.05$ in comparison with the value obtained for saline-treated rats.

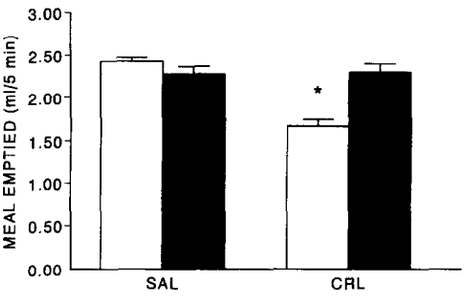

Fig. 5. Effect of vehicle (open column) and devazepide (1 mg/kg, black column) on caerulein-induced delay of gastric emptying of liquids in the rat. Each column refers to the mean of the values obtained from 6–8 animals. CRL, caerulein; SAL, saline. Vertical bars are S.E. values. * $P < 0.05$ in comparison with saline value.

non-caloric liquid meal (Fig. 4), with an ID_{50} (95% C.L.) of 2.90 nmol/kg (1.68–4.99). The effect became significant starting from 0.3 nmol/kg (16 ± 5% inhibition), with the 1 nmol/kg dose giving an effect (i.e. 31.3 ± 2.6% inhibition of gastric emptying) which overlapped that observed after camostate administration. This dose was, therefore, used to identify the CCK receptor subtype involved in the gastric motor activity of this CCK receptor agonist.

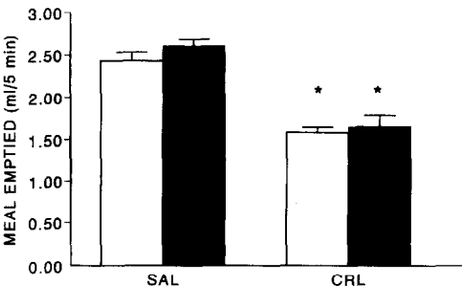

Fig. 6. Effect of vehicle (open column) and L365,260 (3 mg/kg, black column) on caerulein-induced delay of gastric emptying of liquids in the rat. Each column refers to the mean of the values obtained from 6–8 animals. CRL, caerulein; SAL, saline. Vertical bars are S.E. values. * $P < 0.05$ in comparison with saline value.

I.v. administration of devazepide, at a dose (1 mg/kg) that did not affect gastric emptying, almost completely reversed the effect of caerulein (Fig. 5). As was the case for camostate, the CCK_B/gastrin receptor antagonist L365,260 (3 mg/kg) was unable to affect the caerulein-induced delay in emptying rate (Fig. 6).

4. Discussion

In the present study, in control rats 2.46 ± 0.09 ml of the liquid meal left the stomach in 5 min. This emptying rate (82 ± 3%) was similar to that we reported earlier (Varga et al., 1995), but faster than that (92 ± 2%) observed by Green et al. (1988) under similar experimental conditions. In our studies, however, we not only collected the fluid remaining in the stomach, but we also rinsed the stomach and added the rinsing solution to the recovered gastric content. According to our experience, rinsing substantially increases phenol red recovery, thus. leading to a more quantitative estimation of gastric emptying.

In both animals and humans, inhibition of gastric emptying by CCK and related peptides involves a drop in intragastric pressure, due to relaxation of the proximal stomach and contraction of the antropyloric region, where the peptide decreases the motility index and the basal electric activity (for review, see Bertaccini, 1982).

Both direct muscle and neurally mediated effects of CCK have been described in isolated gut from laboratory animals. A *direct* contractile effect has been shown in canine antral muscle (Morgan et al., 1978) and guinea-pig stomach (Gerner and Haffner, 1977). Evidence for a neurally mediated effect of CCK in the longitudinal muscle of guinea-pig ileum is that acetylcholine is released in response to the administartion of the peptide, and that CCK-stimulated contractions are atropine- and tetrodotoxin-sensitive (Vizi et al., 1972, 1973). In addition, it was shown that without the myenteric plexus this tissue responded to acetylcholine but not CCK (Hutchinson and Dockray, 1980, 1981). The contractile effects of cholecystokinin octapeptide (CCK-8) on *human* smooth muscles isolated from the digestive tract (i.e. longitudinal muscles of the stomach, the small intestine and the colon) are not inhibited by atropine or tetrodotoxin (D'Amato et al., 1990; Egberts and Johnson, 1977; Lüdtke et al., 1988), thus, suggesting that the peptide stimulates human alimentary muscles by a *direct action* at sites not involving muscarinic receptors.

Pharmacological investigations (Bitar and Makhlouf, 1982; Grider and Makhlouf, 1987; Menozzi et al., 1989; Morini et al., 1990) have shown gastric smooth muscle to contain selective CCK receptors which are different from those of gastrin (Grider and Makhlouf, 1990). There is now a large body of evidence showing that selective CCK_A receptor antagonists are able to counterbalance the effect of both exogenous and endogenous (e.g. released by

food) CCK (for review, see Scarpignato, 1992). In the present investigation, we examined the effect of two selective CCK receptor antagonists on CCK-induced delay of gastric emptying. Devazepide (L364,718) is reported to have 100–1000-fold higher affinity for CCK_A receptors in pancreas (Hill and Woodruff, 1990; Huang et al., 1989; Lotti and Chang, 1989) than it does for CCK_B/gastrin receptors in brain (Hill and Woodruff, 1990; Lotti and Chang, 1989), stomach (Lotti and Chang, 1989) and pancreas (Huang et al., 1989). Of the selective and competitive CCK_B/gastrin receptor antagonists, L365,260 is one of the most potent. It has a 100–250-fold higher affinity for CCK_B/gastrin receptors in brain (Hill and Woodruff, 1990; Lotti and Chang, 1989), stomach (Huang et al., 1989; Lotti and Chang, 1989) and pancreas (Huang et al., 1989; Lotti and Chang, 1989) than it does for pancreatic CCK_A receptors (Hill and Woodruff, 1990; Huang et al., 1989; Lotti and Chang, 1989).

The effect of camostate or caerulein on gastric emptying was completely blocked by devazepide. The CCK_A receptor antagonist was applied in a dose (1 mg/kg) previously found capable of counterbalancing the maximal stimulation of pancreatic amylase (O'Rourke et al., 1990) and pepsin (Varga et al., 1991) secretion induced by CCK, but not of affecting gastrin-stimulated acid secretion (Varga et al., 1993). In contrast, the CCK_B/gastrin receptor antagonist, L365,260, at a dose capable of completely inhibiting gastrin-17-I-induced maximal stimulation of acid secretion (Varga et al., 1993), proved to be completely ineffective. These data suggest that CCK affects the emptying rate through stimulation of CCK receptors of the A subtype, and that the B subtype is not involved.

Bearing in mind the inhibitory effect of CCK on gastroduodenal motility, one could expect that CCK_A receptor blockade would result in an acceleration of the emptying rate. This prokinetic activity of CCK_A receptor antagonists is rarely observed, however, at least in experimental animals. In fact, while CCK_A receptor antagonists *constantly* block CCK-induced inhibition of gastric motility, their effect on basal gastric emptying is variable and strictly depends on the experimental conditions. Amongst these, the nature (solid or liquid) and composition of the test meal seem to be the most important ones (Buéno and Fioramonti, 1988; Gue et al., 1990; Liberge et al., 1988). Gastric emptying of non-caloric liquid meals was found to be almost invariably unaffected by the different compounds studied (Scarpignato et al., 1993). In contrast, the emptying of nutrient caloric meals, whose components (mainly fat and proteins) release endogenous CCK, is accelerated by administration of devazepide (Bruley des Varannes et al., 1990; Decktor et al., 1988; Defaux et al., 1990; Dubois et al., 1991; Green et al., 1988; Gould et al., 1990), asperlicin (Fioramonti et al., 1988), another benzodiazepine-derived CCK_A receptor antagonist, and by the non-selective CCK receptor antagonist proglumide (Shillaber and Davison, 1987). In accordance with available data (for review, see Scarpignato et al., 1993), devazepide was unable to accelerate the gastric emptying of saline.

It is now well-established that chronic administration of exogenous CCK or chronic stimulation (by, for instance, of proteinase inhibitors) of its endogenous release leads to pancreatic hypertrophy and hyperplasia with a subsequent increase in the secretory capacity of the gland (Douglas et al., 1990; Göke et al., 1986; Scarpignato et al., 1989; Varga et al., 1989; Wisner et al., 1988). Camostate administration results in a significant increase in the stomach weight of rats (Wisner et al., 1988) and an increased muscle weight could account for this. Since the motor function of the stomach depends on its muscular activity, we wanted to establish whether repeated camostate administration resulted in an increased motor response to endogenous CCK. Results obtained clearly show that this was not the case. The adaptive functional response of the pancreas and stomach to repeated CCK stimulation seems, therefore, to be different. Conversely, from its effect on pancreatic exocrine secretion (Scarpignato et al., 1989), the effect of CCK on gastric motor function is not increased by chronic elevation of plasma CCK levels.

In conclusion, the results of the present investigation demonstrate that both endogenous and exogenous CCK delay the gastric emptying of liquids through stimulation of CCK_A receptors and suggest that adaptation of the gastric motor response to CCK does not occur.

Acknowledgements

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