Effect of some gastrointestinal hormones on motor and electrical activity of the digestive tract in the conscious cat

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Three peptides structurally related to gastrin and known to be full agonists of antral motility in the conscious cat, pentagastrin (PG), cholecystokinin (CCK) and synthetic octapeptide of cholecystokinin (OP-CCK), were compared in relation to antral and duodenal electrical activity. They induced the same antral effect in eliciting an increase in the basal electrical rhythm (BER) and a short-lasting decrease in the frequency of the bursts of spikes. The electrical changes were correlated with lumen pressure changes measured in parallel, consisting of a decrease in the frequency of high-amplitude peaks and an increase in low-amplitude peaks. The additive effect of PG and CCK shows that the peptides are full agonists for antral electrical activity, as they are for antral motility and acid secretion. In contrast to the antrum, the three peptides increased the frequency of the duodenal spike bursts, CCK and OP-CCK decreased the BER frequency, while PG increased BER slightly. The increase in antral and duodenal BER obtained after a beef-liver meal, which produced a large endogenous gastrin release, suggests a major role for gastrin in antral motility induced by feeding, at least in the cat.

Gastrointestinal hormones: Motor and electrical activity

Although gastrointestinal motility of the cat shows some unusual features, in common with other species, different regions of the gastrointestinal tract show a characteristic basal electrical rhythm (BER) on which spike activity and, hence, contractions are superimposed (Roche *et al.* 1982). It has been shown that pentagastrin (PG), cholecystokinin (CCK) and the synthetic octapeptide of CCK (OP-CCK) are full agonists for the stimulation of antral motility (Desvigne *et al.* 1980) and also for acid secretion (Way, 1971), but not for pepsin secretion (Desvigne *et al.* 1980). The main purpose in the present study was to compare the effect of these three peptides on antral and duodenal electrical activity and to correlate the antral electromyographic activity response to their effect on antral intralumen pressure. Further, we investigated whether or not the gastrin-related peptides could be responsible for the different postprandial patterns of the gastric BER that we reported previously, in relation to the nature of the meal (increase of antral BER after beef-liver meal, no change after canned food (Roche *et al.* 1982)).

METHODS

In three cats (one female and two males), weighing 3–4·5 kg, a modified Thomas cannula (Thomas, 1941) was surgically implanted under pentobarbital anaesthesia, in the fundic part of the stomach. A duodenal cannula was also inserted (Vagne *et al.* 1982) and was kept open during the experiments to prevent any biliary reflux. Moreover, the animals were equipped with electrodes made of insulated nichrome wire (0·1 mm diameter, 700 mm length), which were inserted in pairs, 2 mm apart, through the serosa and muscular layers

using a needle as a trocar. A total of four pairs of electrodes were implanted on the antrum at 30, 20, 10 and 5 mm from the pylorus. Two other pairs were fixed on the duodenum at 10 and 20 mm from the pylorus. The free ends of all electrodes were passed subcutaneously from the abdomen to the dorso-scapular region, fixed to the skin and placed in a leather bag secured by a thoracic harness. The exact positions of the electrodes were determined post mortem.

Experiments were started 1 week after the electrode implantation. The animals had completely recovered after 2 d. The frequency of the tests was not more than twice weekly. The animals were fasted for about 18 h before each test. They were maintained in a harness. A continuous intravenous infusion of saline (9 g NaCl/l) was given at a rate of 13 ml/h by means of a catheter placed in the front leg vein and connected to a pump (Harvard Apparatus, USA). The gastric and duodenal cannulas were opened and the stomach was washed with water.

Recording of electrical activity

The electrodes were connected to an electroencephalograph apparatus (REEGA VIII; AVAR, Paris, France), using a rotating multichannel connector. The time constant was 0·1 s. Frequency of BER and number of spike bursts were determined at 10 min intervals by direct calculation of the electromyographic (EMG) recordings. Each animal was its own control and the statistical analysis compared the variations between basal and stimulated patterns by both the *t* test for paired values and the Mann–Whitney U test.

Recording of antral intralumen pressure

An open-tip polyethylene tube (1 mm i.d.), cut obliquely with a hole opposite the bisection, was introduced through the gastric cannula and attached to it when placed 10 mm from the pylorus. The catheter was perfused with water at a rate of 6 ml/h (Technicon pump; Domont, France). It was connected via a pressure transducer (Statham P 23 BB; Godart-Statham, Bilthoven, The Netherlands) to an amplifier (Statham SC 1000) and to a potentiometric recorder (Servotrace; Sefram, Paris, France).

Collection of gastric juice

A device was attached to the gastric cannula to collect gastric juice in graduated tubes every 15 min. Volume and acid concentrations were determined in order to verify that the infusion of the test substances was correct. As these findings simply confirmed previous results (Desvigne *et al.* 1980; Vagne *et al.* 1982) they are not presented.

Test substances

PG (Peptavlon; ICI Limited, Macclesfield, Cheshire) was given at doses of 0·5, 4, 8 and 32 μg/kg per h. PG at 0·5 and 8 μg/kg per h was also given during a continuous infusion of 4 Ivy Dog Units (IDU) CCK/kg per h. CCK (GIH Research Laboratories, Stockholm, Sweden) was given at doses of 1, 4 and 16 IDU/kg per h. OP-CCK (Sq 19844; Squibb, New Brunswick, NJ, USA) was given at doses of 0·25, 1, 2 and 4 μg/kg per h. Only one dose was infused daily. For each dose, three experiments were repeated in each cat, not more than three times weekly, in a randomized order.

Blood determination

Gastrin was measured in serum samples collected during the basal period, twice at 15 min intervals and 30, 60 and 90 min after the meal which was either 60 g chopped fresh liver or canned food (Fido; Quaker-France, Marseilles, France). The determination was made for four cats once weekly using about 2 ml blood.

Gastrin was determined by the technique previously described and validated (Vagne *et*

al. 1987), using rabbit anti-gastrin serum obtained after immunization against synthetic human gastrin I 2–17 (ICI Ltd) conjugated to bovine albumin through carbodiimide condensation. Synthetic human gastrin I 1–17 was used as standard and for iodination with ^{125}I by the chloramine T method (Hunter & Greenwood, 1962).

RESULTS

Fasted patterns

Basal period. After an 18 h fast, the mean frequency of BER in the antrum was 4·7 (SEM 0·02; *n* 312) cycles per min. For each cat, the mean was respectively 4·51 (SEM 0·02; *n* 104), 4·79 (SEM 0·02; *n* 104), 4·94 (SEM 0·02; *n* 104). The BER basal frequencies differed statistically between cats (*F*-test, $P < 0{\cdot}01$). However, this variation was very small, equal to 9% of the mean obtained with all the cats. In the duodenum the mean frequency was 19·2 (SEM 0·04; *n* 282). The mean for each cat was 19·3 (SEM 0·04; *n* 94), 19·18 (SEM 0·04; *n* 94), 19·16 (SEM 0·09; *n* 94). The individual means did not differ.

The bursts of spike potentials appeared superimposed cyclically on one to two consecutive antral slow waves, occupying approximately 30% of the recording time. In the duodenum, spike potentials occurred as series of bursts at a mean frequency (per 10 min) of 5·8 (SEM 0·2; *n* 112, *n* being 38, 37 and 37 respectively for each cat).

The parallel recording of antral contractions and EMG activity is shown in Fig. 1. Spiking activity was related to intralumen pressure changes recorded as single peaks of high amplitude, usually higher than 200 mm of water pressure, whereas BER was in complete correlation with low-amplitude peaks ranging from 30 to 200 mm of water pressure.

Effect of gastrointestinal hormones

BER on the antrum. The three peptides induced an increase in the BER as shown in Fig. 2. PG induced the strongest increase, about 40%, with a dose of 8 μg. The increase was

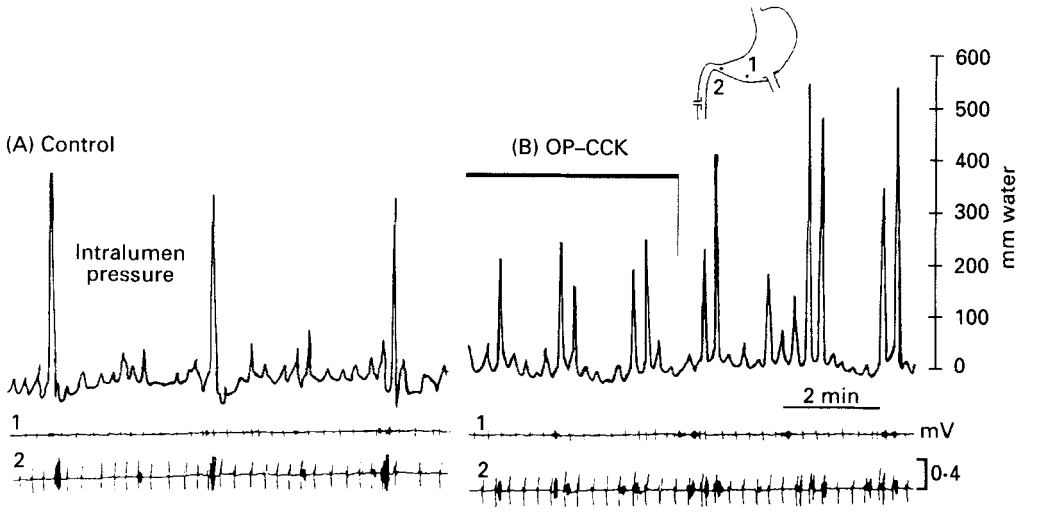

Fig. 1. Simultaneous recording of antral intralumen pressure and electrical activity in the conscious cat, during control and a synthetic octapeptide of cholecystokinin (OP-CCK) intravenous infusion (2 μg/kg per h). During control infusion, spiking activity was associated with high-amplitude peaks, while during OP-CCK stimulation the spike bursts were more frequent and associated with lower-amplitude peaks than during the control periods. For details of animals and procedures, see pp. 371–372.

Table 1. *Effects of dose of gastrin-related peptides on basal electrical rhythm (BER) on the antrum of the conscious cat**

(Values are means with their standard errors for twelve determinations)

Peptide	Cat no.	Dose										r	Statistical significance of correlation of response *v.* dose
PG (μg/kg per h)		0		0·5		4		8		32			
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE		
	1	45	0·4	52	0·9	56	1·2	61	0·9	60	1·4	0·832	
	2	49	0·6	52	0·8	63	0·7	69	1·0	65	0·7	0·854	$P < 0·01$
	3	49	0·7	55	0·7	60	0·8	64	0·6	64	0·4	0·820	
		Statistical significance of difference: Between animals $P < 0·05$											
		Between doses $P < 0·001$											
CCK (IDU/kg per h)		0		1		4		16					
		Mean	SE	Mean	SE	Mean	SE	Mean	SE				
	1	45	0·6	46	0·7	50	0·4	58	0·9			0·901	
	2	48	0·4	48	0·5	45	0·5	63	0·9			0·899	$P < 0·01$
	3	49	0·6	49	0·5	53	0·8	54	1·0			0·582	
		Statistical significance of difference: Between animals NS											
		Between doses $P < 0·01$											
PG (μg/kg per h)		0		0·5		0·5		0		8		8	
CCK (IDU/kg per h)		0		0		4		4		0		4	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
	1	45	0·4	52	0·9	54	0·4	50	0·4	61	0·9	64	0·9
	2	49	0·6	52	0·8	59	0·7	54	0·5	67	1·0	67	1·1
	3	49	0·7	55	0·7	57	0·6	53	0·8	64	0·6	63	0·6
		Statistical significance of difference: Between animals $P < 0·01$											
		Between doses $P < 0·001$											

OP-CCK (μg/kg per h)	0		0·25		1		2		4			
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE		
1	44	0·4	47	0·6	52	1·4	59	1·3	60	0·8	0·814	
2	48	0·4	57	0·4	56	0·6	61	0·6	62	0·6	0·751	$P < 0·01$
3	50	0·6	52	0·9	55	1·0	56	1·2	60	0·4	0·775	
Statistical significance of difference: Between animals $P < 0·05$												
Between doses $P < 0·01$												

Liver meal	Basal		Basal		Meal	
	Mean	SE	Mean	SE	Mean	SE
1	43	1·2	43	0·8	56	0·4
2	46	0·5	46	0·5	54	1·2
3	50	0·5	48	0·3	58	0·6
Statistical significance of difference: Between animals $P < 0·05$						
Between periods $P < 0·01$						

PG, pentagastrin; CCK, cholecystokinin; OP-CCK, synthetic octapeptide of CCK; IDU, Ivy Dog Units; NS, not significant.
* For details of animals and procedures, see pp. 371–373.

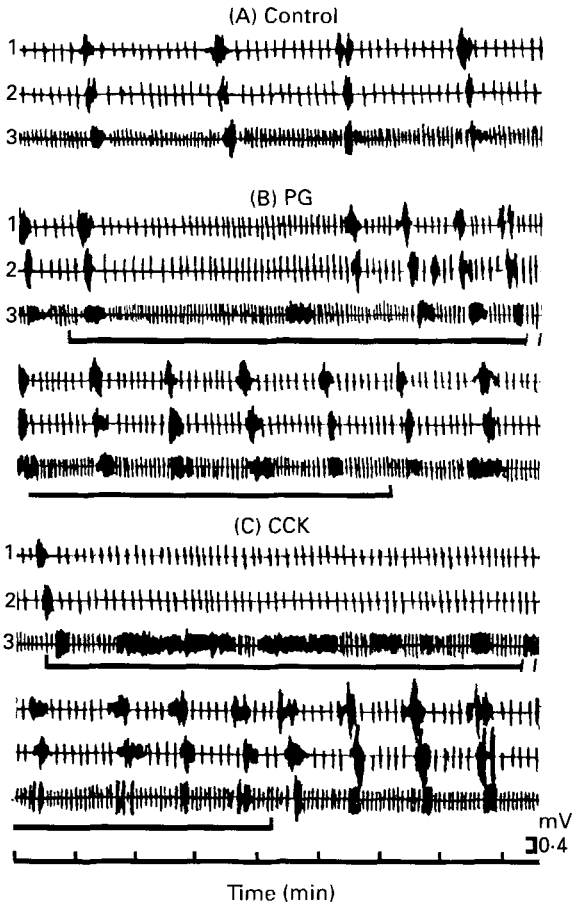

Fig. 2. Typical recording of electrical activity of antrum (1 and 2) and duodenum (3) in one cat. (A) Electrical activity before infusion, (B) electrical activity during the beginning (set 1) and during the end (set 2) of administration for 2 h of pentagastrin (PG; 32 μg/kg per h), (C) electrical activity during the beginning (part 1) and during the end (part 2) of administration of cholecystokinin (CCK; 4 Ivy Dog Units/kg per h). (——), Intravenous infusion. The increase in the basal electrical rhythm induced in the antrum by both peptides, the short-lasting decrease in spike activity in the antrum and its increase in the duodenum can be seen. For details of animals and procedures, see pp. 371–372.

linearly related to the doses of peptide over 0–8 μg. There was no increase between 8 and 32 μg (Table 1). CCK added to PG induced an additive effect at the low dose of PG (Fig. 3); the response was higher than that to each stimulant alone ($P < 0{\cdot}05$ in each case). No potentiation was observed at the maximal dose of PG ($P > 0{\cdot}1$).

BER on the duodenum. CCK and OP-CCK induced a statistically significant decrease in the BER (Table 2), while PG produced a slight but significant increase in two of three cats (Fig. 4 and Table 2). In the duodenum PG activity was different from that for the intestinal hormones.

Spiking activity on the antrum. The three peptides induced a similar effect on the spike activity. The frequency of spike bursts decreased temporarily (range 6–16 min) and then increased to values at least equal to basal values and sometimes higher (Fig. 2). The spike

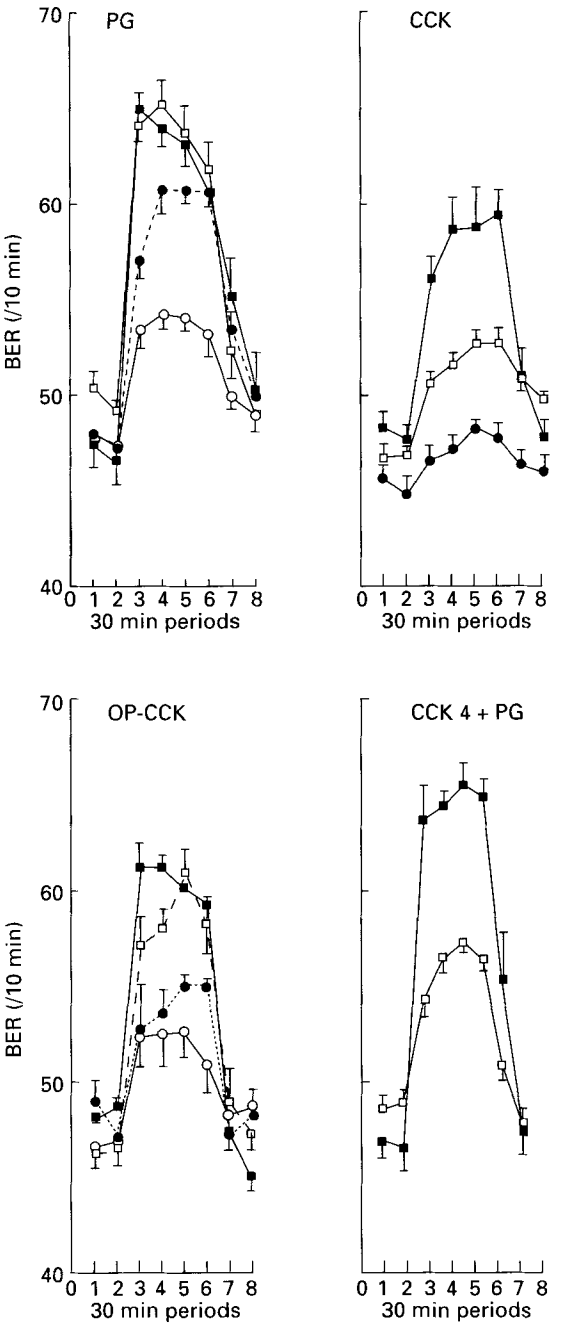

Fig. 3. Antral basal electrical rhythm (BER), before dosing (periods 1 and 2), in response to four doses of pentagastrin (PG; μg/kg per h; (■) 32; (□) 8; (●); 4; (○), 0·5), three doses of cholecystokinin (CCK; Ivy Dog Unit/kg per h; (■), 16; (□) 4; (●), 1), four doses of cholecystokinin octapeptide (OP-CCK; μg/kg per h; (■), 4; (□), 2; (●), 1; (○), 0·25) and two doses of PG added to CCK (4 Ivy Dog Units/kg per h; (■), 8; (□), 0·5; periods 3–6), and after cessation of the infusion (periods 7 and 8). An increase was produced by the three peptides. Points are means with their standard errors, represented by vertical bars, for six to nine experiments for three cats. For details of animals and procedures, see pp. 371–372.

Table 2. *Effects of dose of gastrin-related peptides on basal electrical rhythm (BER) on the duodenum of the conscious cat**

(Values are means with their standard errors for twelve determinations)

Peptide	Cat no.	Dose										*r*	Statistical significance of correlation of response *v.* dose
PG (μg/kg per h)		0		0·5		4		8		32			
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE		
	1	192	1·1	203	1·1	201	2·4	204	1·6	202	0·9	0·402	
	2	192	0·9	195	0·8	197	1·4	192	1·2	202	1·5	0·556	$P < 0·01$
	3	190	1·8	189	1·4	184	1·0	184	2·3	180	1·5	−0·395	
		Statistical significance of difference: Between animals $P < 0·01$											
		Between doses NS											
CCK (IDU/kg per h)		0		1		4		16					
		Mean	SE	Mean	SE	Mean	SE	Mean	SE				
	1	192	1·6	195	1·2	185	0·8	180	1·4			−0·588	
	2	191	1·1	192	0·5	190	0·3	177	1·7			−0·834	$P < 0·01$
	3	187	1·7	183	1·6	180	0·9	173	1·4			−0·634	
		Statistical significance of difference: Between animals $P < 0·01$											
		Between doses $P < 0·01$											
PG (μg/kg per h)		0		0·5		0·5		0		8		8	
CCK (IDU/kg per h)		0		0		4		4		0		4	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
	1	195	1·1	203	1·1	200	0·7	185	0·8	204	1·6	201	1·8
	2	191	0·7	188	0·6	191	1·1	190	0·3	192	1·2	189	2·0
	3	192	2·1	189	1·4	185	0·6	180	0·9	184	2·4	182	1·7

OP-CCK (μg/kg per h)	0		0·25		1		2				
	Mean	SE	Mean	SE	Mean	SE	Mean	SE			
1	192	0·8	194	0·6	182	1·2	180	2·1		−0·716	
2	190	1·1	186	1·1	179	1·0	188	2·0		−0·316	$P < 0·01$
3	189	2·1	179	1·9	177	0·8	176	2·6		−0·371	
Statistical significance of difference: Between animals NS											
Between doses NS											

Liver meal	Basal		Basal		Meal	
	Mean	SE	Mean	SE	Mean	SE
1	192	1·0	193	1·4	207	2·2
2	191	1·0	186	0·7	196	2·0
3	188	0·9	190	3·0	187	1·3
Statistical significance of difference: Between animals NS						
Between periods NS						

PG, pentagastrin; CCK, cholecystokinin; OP-CCK, synthetic octapeptide of CCK; IDU, Ivy Dog Units; NS, not significant.
* For details of animals and procedures, see pp. 371–373.

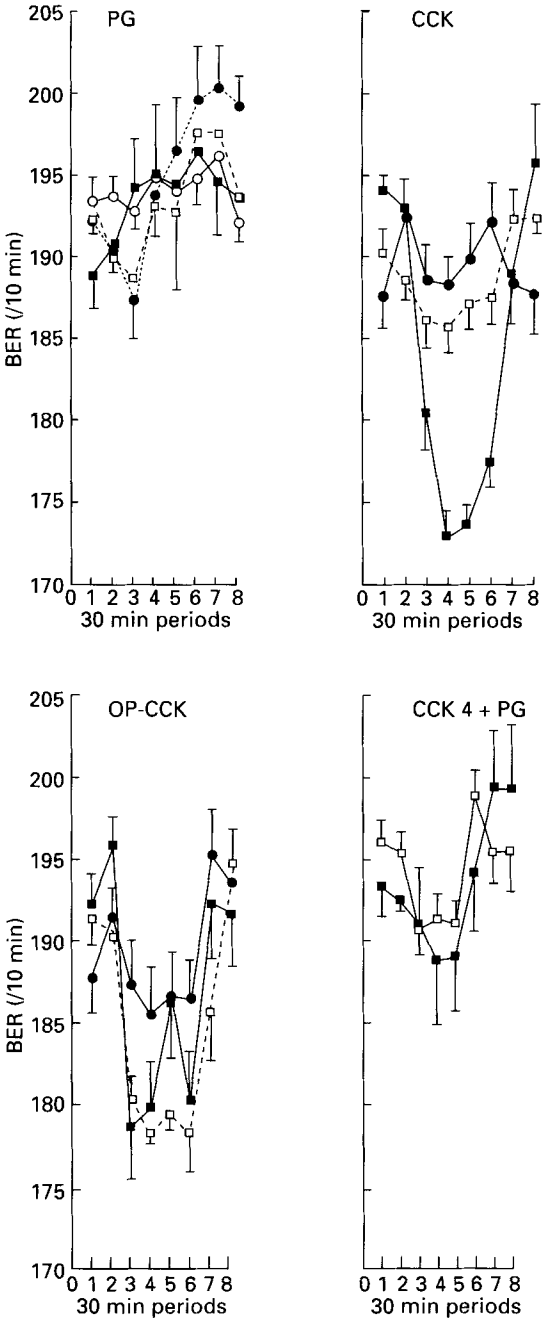

Fig. 4. Duodenal basal electrical rhythm (BER), before dosing (periods 1 and 2), in response to four doses of pentagastrin (PG; μg/kg per h; (■), 32; (□), 8; (●), 4; (○), 0·5), three doses of (*t* 2·74 and 3·17) cholecystokinin (CCK; Ivy Dog Units/kg per h; (■), 16; (□), 4; (●) 1), three doses of cholecystokinin octapeptide (OP-CCK; μg/kg per h; (■), 2; (□), 1; (●), 0·25) and two doses of PG added to CCK (4 Ivy Dog Units/kg per h; (■), 8; (□), 0·5; periods 3–6), and after cessation of the infusion (periods 7 and 8). An increase was produced by the three peptides. Points are means with their standard errors, represented by vertical bars, for six to nine experiments for three cats. For details of animals and procedures, see pp. 371–372.

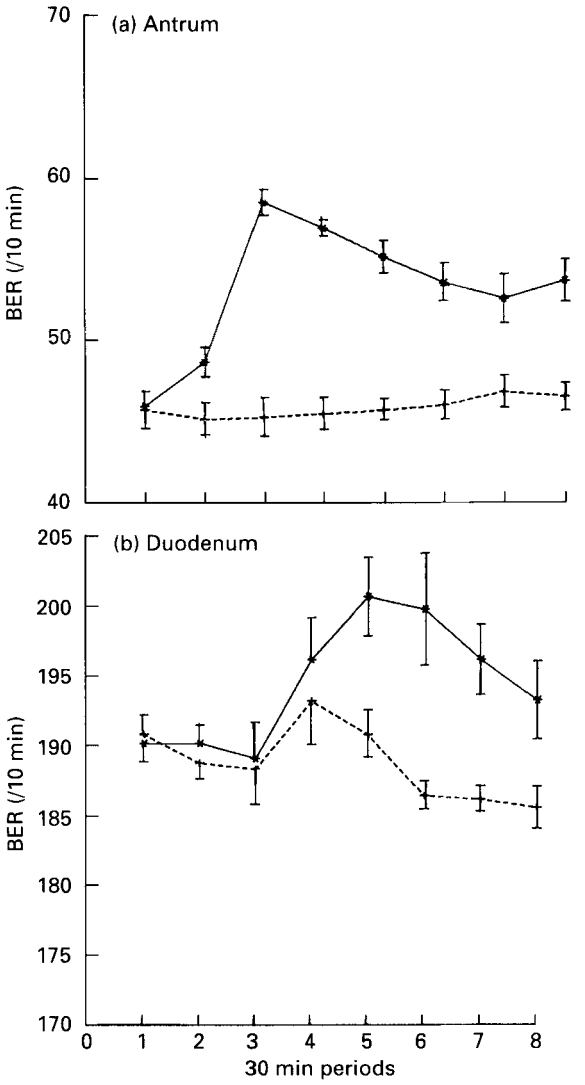

Fig. 5. Antral (a) and duodenal (b) basal electrical rhythm (BER) of conscious cats in response to a liver meal (——): periods 1 and 2, before the meal; periods 3–8, after the meal. (– – –), Control values (without meal). The values are the means with their standard errors, represented by vertical bars, for nine experiments for three cats. For details of animals and procedures, see pp. 371–373.

bursts were associated with contractions of lower amplitude than those in the basal period (less than 200 mm water; Fig. 1).

Spiking activity on the duodenum. An increase in spiking activity was obtained with each of the peptides, corresponding to a permanent spiking activity during antral inhibition. After this primary effect, short bursts of spikes occurred at antral frequency.

Postprandial patterns

A large increase in BER at the antral level was observed after a fresh liver meal (Fig. 5). The multi-factorial analysis of variance showed no difference between animals (Table 1),

Table 3. *Effect of nature of meal on plasma gastrin concentration (pg/ml) of four conscious cats*

(Mean values with their standard errors; no. of experiments per animal in parentheses)

Meal	Cat no.							
60 g canned food (2)		Period after meal (min)						
		Basal		30		60		90	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
	1	14	1	101	6	72	14	84	5
	2	24	10	165	6	122	10	110	6
	3	22	3	103	10	62	10	69	7
	4	20	4	71	0	69	12	58	3
	Total	20	3	110	13	81	10	80	8
Statistical significance of difference:									
Between basal and postprandial periods				$P < 0.001$		$P < 0.001$		$P < 0.001$	
Between animals						NS			
Between periods						$P < 0.01$			
60 g beef liver (3)		Period after meal (min)							
		Basal		30		60		90	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
	1	21	4	277	30	292	47	228	42
	2	16	4	335	10	215	51	158	15
	3	31	5	350	10	300	55	315	5
	4	32	3	350	48	257	15	225	33
	Total	27	2	328	15	266	21	224	21
Statistical significance of difference:									
Between basal and postprandial periods				$P < 0.001$		$P < 0.001$		$P < 0.001$	
Between animals						NS			
Between periods						$P < 0.01$			
Comparison of the delta plasma gastrin (30 min gastrinaemia minus basal gastrinaemia) induced by the 2 meals:									
		Mean	SE						
60 g canned food		84	27						
60 g beef liver		276	22						
Statistical significance of difference:									
Between animals						NS			
Between meals						$P < 0.0001$			

but a statistically significant difference between basal and postprandial BER frequency. In the duodenum the increase was not significant (Table 2).

Feeding increased the mean level of spiking activity; spike bursts were superimposed on 75% of the antral slow waves from 0 to 15 min after feeding compared with 35% in the control period. On the duodenum, spike bursts were superimposed on 82% of the slow waves.

Role of the nature of the meal on gastrin release

Table 3 shows the differences in gastrin release induced by the two different meals. The fresh liver meal was a much stronger releaser of gastrin in the cat, while canned food

released only 30% of the amount released by liver. Both meals induced a statistically significant increase in basal gastrinaemia (Table 3) without any significant variation between animals.

DISCUSSION

The present study has shown that in the cat all three structurally related gastrin peptides, PG, CCK and OP-CCK, have the same effect on the EMG recordings of the antrum in inducing an increase in BER and a short-lasting decrease in the frequency of the bursts of spikes. These electrical changes, already described for gastrin in man (Kwong *et al.* 1972) and in the dog (Bueno & Garcia-Villar, 1979), are well correlated with pressure changes obtained by manometric measurements run in parallel in the same animals and demonstrating a decrease of the high-amplitude contractions and an increase of low-amplitude peaks, confirming our previous findings (Desvigne *et al.* 1980). A supra-maximal dose does not decrease the response, as illustrated by the response to 32 μg PG. All three gastrointestinal peptides are full agonists of the electrical activity of the antrum as well as of antral motility (Desvigne *et al.* 1980) and acid secretion (Way, 1971), but not of pepsin secretion. On the other hand, the three peptides are not full agonists of duodenal motility since PG increased slightly the BER at the duodenal level, while the other two decreased BER significantly.

There seems to be a certain discrepancy between pressure and EMG recordings as far as the duration of the effects is concerned. It has been shown, on the basis of pressure findings, that the motor effect of the peptides was well maintained during a continuous 2 h infusion (Desvigne *et al.* 1980). However, the frequency of the bursts of spiking activity, after a short-lasting decrease, increased in spite of the continuous peptide administration. In fact, the simultaneous recordings clearly showed that there is a dissociation between frequency and amplitude. The bursts of spiking activity are associated with contractions of lower amplitude (less than 200 mm water pressure) than during the basal period (200 to 400 mm water pressure).

There is a species difference since in dog it has been shown that CCK, unlike PG, does not induce any change in BER (Wingate *et al.* 1978). This species difference might be secondary to acid secretion, as pointed out by Wingate *et al.* (1978). BER frequency has been shown to be sensitive to acid in man (Couturier *et al.* 1973). However, under our experimental conditions, gastric juice was continuously collected by a gastric cannula placed in the declivitous part of the fundus.

In contrast to the antrum, the three peptides increased the frequency of the duodenal spike bursts and a decrease in BER frequency was observed with CCK and OP-CCK, while PG increased BER slightly. These findings in cat contrast with those reported in dogs in which PG induces a great increase in BER while CCK does not provoke any change (Wingate *et al.* 1978).

Our findings indicate that gastrin, which has the same effects as PG, might play a role in the electrical changes observed after a liver meal which releases three times more gastrin than a regular canned meal, but it is not known whether the effect is direct or secondary to the acid secretion.

The difference in gastrin release observed during different meals clearly explains why a beef-liver meal but not a canned meal induced an increase in BER of the antrum, as already demonstrated in an earlier study (Roche *et al.* 1982). Thus, it is possible to correlate in the cat the release of endogenous gastrin induced by the food with the increase in BER in the antrum and the increase in low-amplitude contractions which allow a good mixing of the gastric contents (Strunz & Grossman, 1977). Gastrin and CCK are known to slow down

gastric emptying and it has been suggested that this inhibition of emptying by gastrin is due to fundic relaxation (Ruppin & Domschke, 1980). Recent data have shown a relationship between emptying of liquids and motor function of the antropyloric region (Dooley & Valenzuela, 1988; Chikh-Issa *et al.* 1989). The localization of CCK receptors directly on the muscle of the pyloric sphincter (Smith *et al.* 1984) favours a direct role of the pyloric sphincter in the inhibition of gastric emptying produced by CCK, mediated by a capsaicin-sensitive vagal afferent pathway in the rat (Raybould & Taché, 1988). However, in the cat gastrin appears to play a major role in antral motility induced by a meal. It is not known whether the effect of gastrin in the cat is mediated by a vagal pathway, as has been shown for CCK in the rat.

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