The effect of cholecystokinin peptides on ovine duodeno-jejunal slow waves with and without pretreatment with proglumide

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ABSTRACT

Cholecystokinin exerts a composite influence on gastrointestinal motility but little is known about its effect on small-intestinal slow waves. Thus, six rams were implanted with four bipolar serosal electrodes onto the duodeno-jejunal wall. In the course of chronic experiments the myoelectric activity was continuously recorded in the non-fasted animals. After recording of the full normal migrating myoelectric complex (MMC), 0.15 M NaCl or CCK peptides were injected intravenously during various phases of the next MMC cycle. Five mℓ of saline was injected over 30 s during phases 1, 2a, or 2b of the MMC. Cerulein was administered at doses of 1 (over 30 s), 10 (over 30 or 60 s), or 100 ng/kg (over 30, 60, 120 or 300 s) and cholecystokinin octapeptide (CCK-OP) at doses 20 times higher. CCK peptides were applied during early or late phase 1 of the MMC and during phases 2a and 2b of the MMC. In the course of additional experiments, saline and hormone administration was directly preceded by infusion of proglumide, an unspecific CCK receptor antagonist, at a dose of 10 mg/kg. The myoelectric recordings were continued until the arrival of a subsequent regular phase 3 of the MMC. In the duodenal bulb, slow waves were occasionally observed. In the duodenum the slow-wave frequency oscillated between 20 and 24 cpm and in the jejunum between 19 and 22 cpm before or after CCK peptides and proglumide. In the duodenum the slow-wave amplitude increased significantly after all doses of cerulein injected during phase 2b of the MMC. After administration of CCK-OP changes in duodenal slow-wave amplitude were not significant but exhibited a tendency similar to those after cerulein. In the jejunum, injection of cerulein and CCK-OP during phase 2 of the MMC increased the slow-wave amplitude significantly and the duration of these changes was longer than in the duodenum. After infusion of proglumide, administration of cerulein at the low dose over 30 s and at the high dose over 300 s in the course of late phase 1 and phases 2a and 2b of the MMC, significantly increased the duodenal slow-wave amplitude. Cerulein injection during phase 2b of the MMC at the high dose over 30 and 60 s, preceded by proglumide infusion, significantly inhibited the duodenal slow-wave amplitude. In the jejunum these changes were even more pronounced and their duration was much longer. It is concluded that CCK peptides affect slow-wave amplitude in the duodeno-jejunum in non-fasted sheep. This effect is stronger in the jejunum and is altered but not abolished by pretreatment with proglumide. Cerulein evokes more pronounced alterations in the slow-wave amplitude than CCK-OP in conscious sheep.

Key words: cerulein, cholecystokinin octapeptide, duodeno-jejunum, phase of the migrating myoelectric complex, sheep, slow-wave amplitude.

Romański K W **The effect of cholecystokinin peptides on ovine duodeno-jejunal slow waves with and without pretreatment with proglumide**. *Journal of the South African Veterinary Association* (2007) 78(4): 209–214 (En.). Department of Animal Physiology, Faculty of Veterinary Medicine, Wroclaw University of Environmental and Life Sciences, Norwida 31, PL-50-375 Wroclaw, Poland.

INTRODUCTION

Cholecystokinin (CCK), one of the main gastrointestinal hormones, evokes a multidirectional effect on gastrointestinal motility. This comprises modulation of gastric motility, gallbladder contraction, and a composite effect on intestinal motor function[35]. In the stomach, CCK affects spiking activity, gastric emptying, and antral slow-wave frequency in monogastrics[5,11,37]. Similar actions have been reported in sheep[33]. CCK also participates crucially in the control of intestinal motility. It stimulates small-intestinal contractions and inhibits the migrating motor complex (MMC) in man and monogastric animals[9,14,15,20]. In sheep, these effects are not much different[2,24,26]. However, little is known about the alterations of small-intestinal slow waves by CCK. No effect of the hormone upon the frequency of duodenal pacesetter potentials was described in rabbits, while in dogs the results were somehow controversial[9,22,38]. There is no information as to the effect of CCK on slow-wave amplitude or frequency in the small bowel in sheep. Since CCK usually enhances the spiking activity in the small bowel and CCK receptors are present on interstitial cells of Cajal[32], it might be expected that this hormone can modulate the slow waves in the small bowel not only in monogastric animals, but also in sheep. Among the several molecular forms of biologically active CCK[18], 2 CCK peptides are commonly in use[8,13,21,26,30]: the CCK octapeptide, the natural form of CCK, also present in sheep[33] and cerulein, the amphibian CCK analogue, which exhibits high specificity and potency. Therefore, both peptides were applied here for comparison. To explore further possible mechanism of CCK action, the effects of the CCK peptides on duodeno-jejunal slow waves were also tested after administration of proglumide, a putative unspecific CCK receptor antagonist[12].

MATERIALS AND METHODS

Six adult rams of the Polish Merino breed weighing 38–43 kg each were used. Before surgery the animals were fasted for 24 h. After general and local anaesthesia a right laparotomy was performed and bipolar platinum electrodes were attached at the serosal side of the duodenal bulb (one electrode located 5.5–6 cm from the pyloric ring), the distal duodenum (one electrode situated 50 cm distally to the bulbar electrode), and the jejunum (2 electrodes sewn 200 and 300 cm distally to the duodenal electrode). The marked electrode wires were exteriorised near the upper part of the incision and fixed. Within 3–4 days the rams exhibited normal appetite. The skin sutures were removed 10 days after surgery. Other details of this procedure are described elsewhere[26].

During chronic experiments, the myoelectric activity was continuously recorded with a multichannel electroencephalograph (Reega Duplex TR XVI, Alvar Electronics, Montreuil, Paris) with a time constant of 0.01 s and at a paper speed of 2.5 mm/s. After registration of 1 full, normal MMC, 5 mℓ of 0.15 M NaCl or of the

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Received: March 2007. Accepted: October 2007.

drugs were slowly injected into the jugular vein through a thin indwelling polyethylene cathether inserted before the experiment. In separate experiments, the following doses of the drugs were used: cerulein (Farmitalia Carlo Erba, Milan) 1, 10, or 100 ng/kg and CCK-OP (Sincalide, Squibb Inst., Princeton, NJ)[20], 200, and 2000 ng/kg of body weight. The injections were randomly applied during phase 1 of the duodenal MMC, 5 (early phase 1) and 15 min (late phase 1) after termination of phase 3 of the previous MMC cycle, during phase 2a (about 30 min after termination of phase 3) or during phase 2b of the MMC (about 50 min after termination of phase 3). The low doses of both CCK peptides were administered over 30 s, the moderate doses over 30 and 60 s, and the high doses over 30, 60, 120, and 300 s. Additionally, 5 mℓ of saline injected over 30 s or cerulein administration was directly (15–40 s) preceded by a 30-min intravenous infusion of proglumide (Sigma Chemical Co., St. Louis, MO, USA), an efficient CCK receptor antagonist, at a dose of 10 mg/kg of body weight. The total amount of proglumide was dissolved in 9 mℓ of absolute alcohol and then mixed with phosphate buffer, pH 8.3 and the pH was adjusted to 7.4, reaching a final proglumide concentration of 1 mg/mℓ. Dissolved proglumide and proglumide solvent were also infused alone in additional experiments at the rate 1.5 mℓ/min for 30 min. After the high doses of the CCK peptides and proglumide experiments with at least 2 days' break were designed. The MMC cycle and its phases were visually determined according to criteria proposed earlier[6,7,26]. In total, 582 experiments, each lasting 4–5 h, were conducted.

The maximal slow-wave amplitudes with periods of 40–60 s without spike bursts before (selected within the 4-min period directly preceding CCK peptide or saline administration) and after CCK peptide administration (selected within the 4-min period without spike bursts and directly following CCK peptide or saline injection) are presented as medians within these periods and are expressed in μV. The slow-wave frequencies of these periods are expressed in cycles per minute (cpm). The results are tabulated and analysis of variance followed by Student's *t*-test for paired values was performed[29].

RESULTS

In the duodenal bulb, clear slow waves were occasionally identified, making calculations of their amplitude or frequency difficult and erratic.

Injection of 0.15 M NaCl during the various phases of the MMC induced no alterations in the duodeno-jejunal slow-wave amplitude and frequency. Infusions of proglumide and its solvent separately, at the same rates, had no effect. These results are not shown here.

Administration of smaller doses of cerulein during phase 2b of the MMC increased the duodenal slow-wave amplitude significantly compared with the control period (Table 1). Administration of the moderate dose over 60 s and the high dose over 240 s, during phase 2b of the MMC, also increased slow-wave amplitude significantly (Table 1). When the hormone was given during phase 2a of the MMC, an increasing tendency was observed although the differences were not significant.

The changes in the duodenal slow-wave amplitude following CCK-OP were also not significant especially during phase 2a of the MMC but there was a tendency towards increased the slow-wave amplitude.

The duration of the changes in the duodenal slow-wave amplitude evoked by CCK peptide administration during phases 2a and 2b of the MMC was dose-dependent. These changes, for example lasted 10–55 s after the smaller doses of cerulein, 25–70 s after the moderate doses, and 40–130 s after the high doses administered during phases 2a of the MMC (see Table 1). CCK-OP often induced a more pronounced effect than cerulein on duration of the effect. No significant alterations in the duodenal slow-wave amplitude after administration of CCK peptides during phase 1 of the MMC were noted (Table 1).

In the jejunum (proximal jejunal electrode), the administration of CCK peptides at the low, moderate or the high doses injected more slowly during phase 2a or 2b of the MMC produced a significant increase in slow-wave amplitude and the changes were more pronounced than those in the duodenum (Tables 1, 2). However, the significant increase in slow-wave amplitude was more frequently observed following cerulein than after CCK-OP administration. The duration of these changes evoked by cerulein was often shorter that after CCK-OP administration. The duration of these alterations in the jejunum were dose-dependent, as in the duodenum. Slow-wave amplitude remained unchanged when the CCK peptides were applied during phase 1 of the MMC (Table 2). The intra-individual variations in the slow-wave amplitude were higher in the duodenum than in the jejunum.

After pretreatment with proglumide, administration of cerulein at the low dose given over 30 s and at the high dose given over 240 s, in the course of late phase 1, phase 2a, and phase 2b of the MMC, significantly increased slow-wave amplitude in the duodenum, while cerulein injection at the high dose administered over 30 and 60 s in the course of phase 2b of the MMC significantly decreased the duodenal slow-wave amplitude (Table 3). Administration of cerulein at the high dose over 120s evoked no significant response while the slow injection of the hormone over 240 s caused the reversed (stimulatory) response. The duration of these effects was clearly related to the dose of cerulein, but it was generally about half as long as without proglumide pretreatment. In the jejunum (proximal jejunal electrode), the effects of cerulein on slow-wave amplitude after blockade of the CCK receptors and the duration of these changes were similar, but even more evident than in the duodenum (Table 4). Experiments with CCK-OP administration following CCK receptor blockade with proglumide were not performed. The effects of cerulein administration with or without pretreatment with proglumide on slow-wave amplitude recorded at the distal jejunal electrode were roughly similar to though less pronounced than those at the proximal jejunal electrode (results not shown).

Administration of CCK peptides with or without proglumide pretreatment induced no changes in duodeno-jejunal slow-wave frequency and the results are omitted here. Control values in the duodenum remained between 19 and 24 cpm and in the jejunum 17–21 cpm (proximal jejunal electrode) or 16–19 cpm (distal jejunal electrode).

DISCUSSION

Unlike its effect on slow-wave frequency, administration of both CCK peptides, i.e. cerulein and CCK-OP, evoked significant alterations in duodeno-jejunal slow-wave amplitude. In the ovine pyloric antrum, similar doses of the same CCK peptides transiently increased slow-wave frequency and amplitude[24,25]. The lack of a modulatory effect of CCK peptides on small-intestinal slow-wave frequency can be due to a less precise control of the slow waves in sheep since the intra-individual variations in slow-wave frequency were greater in sheep than, for example, in dogs[31]. The waning and waxing phenomenon[28] also exists in sheep, therefore median values were used for the statistical elaboration of the data. This phenomenon, described in the duodenum, could be a reason for the greater instability of the slow-wave amplitude in the duodenum than in the jejunum. Generally it is more

Table 1: **Duodenal slow-wave amplitudes before** (control) **and after** (treatment) **administration of cerulein or CCK-OP at different** (low, moderate, and high) **doses given during various periods and during various phases of the MMC in non-fasted sheep.**

				Low dose	Moderate dose		High dose			
				30 s	30 s	60 s	30 s	60 s	120 s	240 s
Cerulein, slow-wave amplitude (μV)	Early ph. 1	C	mean	**16**	**17**	**16**	**15**	**14**	**18**	**16**
			±SD	5	8	7	6	7	7	8
		T	mean	**17**	**19**	**17**	**16**	**16**	**16**	**17**
			±SD	8	6	7	9	5	10	6
	Late ph. 1	C	mean	**15**	**18**	**19**	**18**	**17**	**19**	**19**
			±SD	6	9	8	7	6	7	10
		T	mean	**18**	**16**	**16**	**17**	**15**	**21**	**20**
			±SD	7	7	6	8	9	9	9
	ph. 2a	C	mean	**14**	**15**	**14**	**13**	**13**	**16**	**15**
			±SD	6	6	5	6	6	6	7
		T	mean	**23**	**18**	**21**	**10**	**16**	**26**	**25**
			±SD	8	7	7	5	9	9	12
	ph. 2b	C	mean	**15**	**13**	**16**	**15**	**14**	**17**	**16**
			±SD	6	5	5	8	5	8	8
		T	mean	**27***	**17**	**30***	**7**	**10**	**28**	**35***
			±SD	7	8	9	4	7	11	10
Cerulein, duration of changes (s)	ph. 2a	T	mean	**22**	**–**	**48**	**–**	**–**	**78**	**87****
			±SD	9		21			46	32
	ph. 2b	T	mean	**76**	**–**	**88**	**31***	**–**	**96**	**148***
			±SD	24		32	22		38	59
CCK-OP, slow-wave amplitude (μV)	Early ph. 1	C	mean	**15**	**18**	**16**	**19**	**17**	**18**	**18**
			±SD	8	7	8	7	6	7	6
		T	mean	**17**	**16**	**18**	**17**	**19**	**17**	**18**
			±SD	6	8	7	9	9	6	8
	Late ph. 1	C	mean	**17**	**21**	**19**	**18**	**16**	**17**	**16**
			±SD	6	9	8	7	5	5	7
		T	mean	**16**	**19**	**20**	**20**	**18**	**20**	**18**
			±SD	5	10	11	9	9	7	7
	ph. 2a	C	mean	**12**	**15**	**14**	**16**	**14**	**15**	**14**
			±SD	5	7	6	5	6	5	5
		T	mean	**21**	**22**	**23**	**18**	**16**	**21**	**20**
			±SD	7	9	10	8	8	7	9
	ph. 2b	C	mean	**13**	**14**	**16**	**15**	**13**	**16**	**15**
			±SD	6	8	7	6	7	8	6
		T	mean	**23**	**20**	**25**	**12**	**14**	**24**	**27**
			±SD	8	6	11	9	10	9	11
CCK-OP, duration of changes (s)	ph. 2a	T	mean	**32**	**87***	**–**	**124*****	**141***	**–**	**66***
			±SD	11	30		51	105		24
	ph. 2b	T	mean	**54**	**116**	**–**	**287****	**212***	**–**	**89**
			±SD	43	45		156	113		47

Key: C, control, T, treatment, ph., phase of the MMC. Statistical significance: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ *vs* relevant control value (slow-wave amplitude) or *versus* the relevant value of the low dose of CCK peptide (duration of changes). Other explanations as in Materials and Methods.

difficult to demonstrate regular changes in slow-wave amplitude than in slow-wave frequency. Since the slow-wave frequency is not stable during the MMC and can differ between periods when the spike bursts are present or absent[4,17,23], only those fragments of an intestinal recording deprived of spike bursts during the particular phase of the MMC were taken into account.

Slow waves are myogenic in origin and are resistant to the ganglionic, neural, and receptor blockers which usually exert little or no effect on their frequency and amplitude[27]. Nevertheless, some modulatory action of CCK peptides on small-intestinal slow waves could be expected. CCK receptors were found in the interstitial cells of Cajal also present in the myenteric plexus of the small intestine[32]. These cells are believed to be the intestinal pacemaker cells generating the slow waves. This can explain the influence of CCK on small-intestinal slow waves presented here. However, the effect of CCK peptides upon slow-wave amplitude, observed in the present study was limited.

The greatest effect of CCK peptides upon duodeno-jejunal slow-wave amplitude was observed when the peptides were applied during phase 2b of the MMC compared with those when the peptides were given during phase 1 or 2a of the MMC. During phase 2b of the MMC, most slow waves are superimposed on the spike bursts and it was noticeable that they were accompanied by increases in the slow-wave amplitude. Thus, an increase in slow-wave amplitude during this phase in response to CCK peptides seems to be easier to evoke than during phase 1 and even during phase 2a of the MMC since the refractory period occurring during phase 1 of the MMC and partially also during phase 2a of the MMC was absent.

As can be seen from the presented results,

Table 2: **Jejunal slow-wave amplitudes before** (control) **and after** (treatment) **administration of cerulein or CCK-OP at different** (low, moderate, and high) **doses given over various periods and during various phases of the MMC in non-fasted sheep.**

				Low dose	Moderate dose		High dose			
				30 s	30 s	60 s	30 s	60 s	120 s	240 s
Cerulein, slow-wave amplitude (μV)	Early ph. 1	C	mean	**15**	**18**	**17**	**16**	**19**	**17**	**18**
			±SD	4	5	4	6	6	5	4
		T	mean	**16**	**17**	**19**	**15**	**17**	**15**	**19**
			±SD	3	7	6	4	4	4	5
	Late ph. 1	C	mean	**17**	**16**	**15**	**17**	**18**	**18**	**17**
			±SD	5	4	5	5	5	6	5
		T	mean	**17**	**15**	**16**	**16**	**20**	**18**	**19**
			±SD	6	6	7	6	5	4	6
	ph. 2a	C	mean	**12**	**13**	**14**	**12**	**13**	**14**	**15**
			±SD	5	4	5	4	3	4	4
		T	mean	**24***	**16**	**22**	**12**	**16**	**15**	**28***
			±SD	7	5	6	7	5	7	9
	ph. 2b	C	mean	**14**	**13**	**13**	**14**	**12**	**13**	**14**
			±SD	6	3	4	3	5	3	3
		T	mean	**36****	**17**	**28****	**10**	**19**	**28****	**37*****
			±SD	9	6	6	6	6	7	8
Cerulein, duration of changes (s)	ph. 2a	T	mean	**33**	**–**	**66**	**–**	**–**	**–**	**421*****
			±SD	13		27				32
	ph. 2b	T	mean	**87**	**–**	**109**	**–**	**–**	**321*****	**465*****
			±SD	21		36			123	204
CCK-OP, slow-wave amplitude (μV)	Early ph. 1	C	mean	**16**	**19**	**16**	**18**	**15**	**17**	**18**
			±SD	5	4	3	6	6	4	4
		T	mean	**18**	**21**	**18**	**16**	**18**	**16**	**17**
			±SD	7	7	4	7	5	5	5
	Late ph. 1	C	mean	**17**	**18**	**17**	**19**	**17**	**18**	**20**
			±SD	6	8	5	5	5	6	5
		T	mean	**19**	**19**	**16**	**21**	**16**	**19**	**19**
			±SD	8	7	4	7	4	5	4
	ph. 2a	C	mean	**14**	**16**	**13**	**15**	**14**	**15**	**14**
			±SD	6	6	3	4	3	3	5
		T	mean	**22**	**20**	**21***	**12**	**20**	**20**	**18**
			±SD	7	8	4	6	6	7	4
	ph. 2b	C	mean	**11**	**14**	**15**	**14**	**15**	**14**	**15**
			±SD	5	3	4	3	5	4	3
		T	mean	**23***	**18**	**24***	**11**	**22**	**23**	**25***
			±SD	7	6	4	5	6	8	5
CCK-OP, duration of changes (s)	ph. 2a	T	mean	**65**	**102**	**84**	**786*****	**424*****	**–**	**112**
			±SD	32	35	49	219	183	–	38
	ph. 2b	T	mean	**87**	**166**	**147**	**1154*****	**665*****	**–**	**223****
			±SD	38	72	63	367	284		76

Key as in Table 1.

the duration of the alterations in slow-wave amplitude evoked by CCK peptides was dose-dependent, but the incidence of the observed changes was greater in response to the smaller dose of CCK peptide or to the high dose administered much more slowly than the other doses. After proglumide these effects were rather greater than smaller compared with the experiments where pretreatment with proglumide was carried out and the high dose of CCK peptides administered within the shortest time triggered the opposite result. These unexpected but interesting effects may be related to a final putative stimulation or blockade of various CCK receptors by the combination of CCK peptides and proglumide. CCK inevitably exhibits greater affinity to CCK 1 (CCK A) receptors than to CCK 2 (CCK B/gastrin) receptors[18]. It is also possible that 3 CCK receptor subtypes are present in the gut[19,36]. However, it is not known which CCK receptor subtype predominates in the interstitial cells of Cajal in the small intestine[31]. Nothing is known regarding the presence of CCK receptor subtypes in ovine interstitial cells of Cajal, since these cells have not yet been identified in sheep, although it is quite clear that they must be present there. Proglumide is probably an unspecific CCK receptor antagonist and its applied dose was similar to the doses used in dogs and sheep[3,10]. It is still in use, and the question arises whether its affinity for the CCK 1 receptor is not greater than for the CCK 2 receptor[16]. The present results suggest that proglumide can block the CCK 1 receptor subtype more specifically than the CCK 2 receptor subtype although there is rather no doubt that it also blocks the CCK 2 receptor subtype[1]. In the present study the smaller doses of cerulein stimulated slow-wave amplitude after proglumide pretreatment while the higher doses evoked the opposite effect. When

Table 3: **Duodenal slow-wave amplitudes before** (control) **and after** (treatment) **administration of cerulein at different** (low, moderate, and high) **doses given over the various periods and during various phases of the MMC in non-fasted sheep. Administration of the CCK peptide was preceded by proglumide infusion.**

				Low dose	Moderate dose		High dose			
				30 s	30 s	60 s	30 s	60 s	120 s	240 s
Cerulein, slow-wave amplitude (μV)	Early ph. 1	C	mean	**17**	**16**	**18**	**20**	**18**	**19**	**17**
			±SD	8	9	10	9	7	8	9
		T	mean	**16**	**18**	**19**	**18**	**14**	**16**	**20**
			±SD	7	8	9	10	6	7	7
	Late ph. 1	C	mean	**19**	**20**	**17**	**19**	**17**	**15**	**18**
			±SD	9	7	8	8	8	6	8
		T	mean	**41***	**24**	**29**	**12**	**11**	**14**	**32***
			±SD	11	11	13	7	4	8	7
	ph. 2a	C	mean	**14**	**12**	**15**	**14**	**13**	**12**	**13**
			±SD	6	7	7	6	6	7	6
		T	mean	**25***	**23**	**18**	**8**	**7**	**11**	**24***
			±SD	6	9	8	5	4	5	5
	ph. 2b	C	mean	**13**	**14**	**11**	**13**	**11**	**13**	**14**
			±SD	7	7	6	5	4	6	5
		T	mean	**27***	**21**	**15**	**6***	**5***	**15**	**29***
			±SD	6	9	8	3	3	8	8

Key as in Table 1.

no proglumide was given, these effects were much less evident. This suggests that the smaller dose of cerulein stimulated the slow-wave amplitude effectively because proglumide efficiently blocked the antagonistic CCK receptor subtype, perhaps the CCK 1 subtype and the action of cerulein through the CCK 2 receptor was unmasked. When the higher dose of cerulein was applied, it stimulated the CCK 1 receptor subtype directly, apparently overriding the proglumide blockade. It is also possible that the inhibitory effect of cerulein on duodeno-jejunal slow-wave amplitude results from the interactions between CCK peptide and peptides such as somatostatin or tachykinins whose receptors are also present in the interstitial cells of Cajal, although nothing is known about possible interactions within the pacemaker tissue[34].

Cerulein exerted a stronger effect on the duodeno-jejunal slow-wave amplitude than did CCK-OP administered at a 20-times higher (by weight) dose. Since cerulein is a dekapeptide and CCK-OP is an octapeptide, the molar difference between the doses is even greater. This suggests that CCK-OP can affect the interstitial cells of Cajal more effectively than cerulein and that the alterations in the duodeno-jejunal slow-wave amplitude are rather the consequence of pharmacological than physiological actions. However, information confirming this speculation is lacking since there are no data regarding the transport of regulatory substances from the blood to the interstitial cells of Cajal. Several extensive studies are necessary to explore this further.

Table 4: **Jejunal slow-wave amplitudes before** (control) **and after** (treatment) **administration of cerulein at different** (low, moderate, and high) **doses given over various periods and during various phases of the MMC in non-fasted sheep. Administration of the CCK peptide was preceded by proglumide infusion.**

				Low dose	Moderate dose		High dose			
				30 s	30 s	60 s	30 s	60 s	120 s	240 s
Cerulein, slow-wave amplitude (μV)	Early ph. 1	C	mean	**18**	**19**	**17**	**18**	**20**	**18**	**21**
			±SD	5	6	6	5	6	5	7
		T	mean	**22**	**24**	**20**	**13**	**16**	**17**	**20**
			±SD	7	5	4	3	7	6	6
	Late ph. 1	C	mean	**17**	**18**	**18**	**17**	**19**	**20**	**18**
			±SD	5	4	5	5	8	6	5
		T	mean	**28***	**33****	**24**	**13**	**11**	**21**	**24**
			±SD	4	5	6	6	7	8	7
	ph. 2a	C	mean	**15**	**14**	**12**	**14**	**13**	**15**	**13**
			±SD	5	4	5	4	3	4	4
		T	mean	**24***	**23***	**22**	**6***	**8**	**18**	**28****
			±SD	5	4	8	2	4	7	6
	ph. 2b	C	mean	**13**	**14**	**14**	**12**	**14**	**12**	**13**
			±SD	6	5	5	4	4	3	5
		T	mean	**28***	**26***	**23**	**4****	**6***	**15**	**34****
			±SD	7	7	7	1	3	6	8

Key as in Table 1.

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