Stimulatory and inhibitory actions of cholecystokinin octapeptide on myoelectric activity of ovine duodenum

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ABSTRACT

Cholecystokinin (CCK) affects the intestinal motility but the character of hormone-evoked alterations is not clear. The aim of this study was to examine precisely the effects of CCK-octapeptide (CCK-OP) on duodenal myoelectric activity in non-fasted sheep in the course of chronic experiments. In five rams the bipolar platinum electrodes were surgically attached to the wall of the duodenal bulb, the distal duodenum and jejunum. Strain gauge force transducer was mounted near the duodenal electrode to verify the myoelectric recordings. During continuous myoelectrical recordings, 0.15 M NaCl or CCK-OP was administered intravenously. Slow injections of CCK-OP at the doses of 20 (over 30 s), 200 (over 30 or 60 s), and 2000 (over 30, 60, or 120 s) ng/kg of body weight were each administered in the course of duodenal phase 1, 2a, or 2b of the migrating motor complex (MMC), i.e. 5 min after the onset of each phase. Injections of the smallest dose of CCK-OP exerted a slight and mostly not significant effect on the duodenal bulb and the duodenal myoelectric activity index (MAI) values. In the duodenal bulb, the effects of CCK-OP on myoelectric activity were dose-dependent and closely related to the phase of the MMC. In the duodenum, the higher doses of the hormone evoked short stimulatory followed by longer inhibitory biphasic effects on MAI. These effects were inversely related to the duration of hormone injection. Infusions of hormone at the higher doses caused less pronounced biphasic effect. It is concluded that CCK evokes stimulatory and inhibitory (biphasic) physiological effect on duodenal motility in non-fasted sheep.

Key words: sheep, duodenal bulb, duodenum, myoelectric and motor activity, cholecystokinin octapeptide, migrating myoelectric complex

Introduction

Duodenal motility is a basic function for normal digestion and absorption, and is controlled by complex neurohormonal mechanisms. Cholecystokinin (CCK) is one of
the main gastrointestinal hormones involved in this control (OUYANG and COHEN, 1981). The regulatory role of the hormone is relatively broad thus it also contributes in the control of other physiological functions (LIDDLE, 1994). The recognized effect of CCK on small-intestinal motility is evident. The hormone, usually applied as CCK-octapeptide (CCK-OP) as the natural CCK form present in sheep (TITCHEN, 1984) inhibits the arrival of the migrating motor or myoelectric complex (MMC) and induces a fed-like pattern in the upper small bowel (HEPPELL et al., 1982; MACZKA et al., 1993). CCK thus rather stimulates the duodenal digestive motility. It evokes the specific spike burst pattern (NIEDERAU and KARAUS, 1991; SNINSKY et al., 1984) and may increase spiking activity in vivo and in vitro (MERLE et al., 2000; NGU, 1985; XU et al., 1998). However, opposite and dual effects of CCK-OP and its amphibian analogue, cerulein, have been reported (GIULIANI et al., 1990; MARTINS et al., 2006). In sheep, CCK peptides also inhibit the arrival of the MMC in the upper small intestine (ROMAŃSKI, 2007), but their effect on intestinal motility has not been fully elucidated so far in spite of several studies performed (BUENO and PRADDAUDE, 1979; ONAGA et al., 1997; ROMAŃSKI, 2004). Thus in sheep, the dual effect of CCK upon the small-intestinal motility can also be expected. It still remains poorly elucidated what is the character of duodenal spiking activity response to CCK (stimulatory or inhibitory), and what is the difference in this response between duodenal bulb and duodenum in relation to the various MMC phases in sheep.

Materials and methods

Animal preparation. Five healthy adult rams of the Polish Merino breed weighing 38-43 kg each were used. The rams were fed with good quality hay, 1 kg daily, and with grain mixture (Dolpasz, Wrocław), then fasted for 24 h before surgery but freely allowed the drinking water. After general and local anesthesia, right lateral laparotomy was performed and two bipolar platinum electrodes were implanted at the serosal side to the duodenal bulb, 5-6 cm distally to the pyloric ring and to the distal duodenum, 50 cm below the bulb electrode. Additional two electrodes were placed in the jejunum, 200 and 300 cm from the duodenal electrode to confirm the presence of the MMC cycles. A strain gauge force transducer (RB Products, Madison), calibrated individually before the surgery, was attached just near the duodenal electrode to verify the myoelectric activity tracings. Other details of this procedure have been described elsewhere (ROMAŃSKI, 2004; ROMAŃSKI, 2007). Marked wires were exteriorized through the stab incision, soldered to the plug and fixed to the wool. Within two-three days the animals returned to normal feeding. The skin sutures were removed 10 days after the surgery.

Experimental procedure. A total of 110 experiments lasting 5-6 h each were conducted. Myoelectric and motor activities were continuously recorded using a multichannel electroencephalograph (Reega Duplex TR XVI, Alvar Electronics, Montreuil) also
adapted for mechanical activity recordings. Twenty four hours before each experiment, food was removed from the cage. At least two consecutive phases 3 of the MMC including one full normal cycle of the MMC were recorded each time. During control recordings, injections of 5 mL 0.15 M NaCl were performed over 30 s into the jugular vein through a thin polyethylene catheter introduced before the experiment. Infusions of saline at a rate of 1 mL/min for 60 min were also performed. The saline injections were performed during the course of phases 1 (5 min after its start in the duodenum), 2a (5 min after its start in the duodenum), or phase 2b (5 min after its start in the duodenum) of the MMC. The saline infusions were started 5 min after the origin of duodenal phase 2b of the MMC. In the group of appropriate experiments, slow intravenous injections of CCK-OP (Sincalide, Squibb Institute, Princeton) at the smallest, moderate, and highest doses, i.e. 20, 200, or 2000 ng/kg were applied. The smallest dose of CCK peptide was administered over 30 s, the moderate dose over 30 or 60 s, and the highest dose over 30, 60, or 120 s. Each dose was given in separate randomized experiments at the same periods as the saline injections. After saline or CCK peptide administration, the myoelectric and motor activities were recorded until the arrival of the first organized phase 3 of the MMC. After cessation of all the experiments, the animals were sacrificed and the positions of the electrodes and the strain gauge force transducer were confirmed during autopsy.

Data analysis. The MMC cycles and their phases were identified in the duodenum and jejunum according to the criteria proposed by CODE and MARLETT (1975) with a slight modification (ROMAŃSKI, 2002). The division of phase 2 into phases 2a and 2b of the MMC, proposed earlier by DENT et al. (1983) was performed according to more precise criteria (ROMAŃSKI, 2007). The myoelectric and motor recordings of duodenjejunal myoelectric activity were visually analysed and the myoelectric activity index (MAI) values were calculated (ROMAŃSKI, 2004). The MAI values were calculated by multiplying the average amplitude of each spike burst within the period examined, as described previously (ROMAŃSKI, 2006), by the duration of this spike burst and expressed as the sum of the areas of all the spike bursts during one minute (μV · s · min⁻¹). Spike bursts with amplitudes below 2-3 μV were omitted. The duration of the periods was equal to one minute. In the recordings obtained from the experiments with saline and CCK peptide injections, the MAI values were calculated in four one-minute periods, i.e. before the injection and ten one-minute periods after the CCK-OP injection. On the tracings, the measurements were performed using a caliper with an accuracy of about 0.2-0.3 mm.

Statistical elaboration of data. All the values were grouped and the means and standard deviations were calculated. Statistical significances, i.e. when P<0.05, P<0.01 or P<0.001 were calculated using the Student’s t-test for paired and unpaired values, where appropriate, preceded by one-way analysis of variance (SNEDECOR and COCHRAN, 1971).
Results

Injections of saline evoked no effect and these data were not shown here. The results obtained from the motor recordings were relevant to the myoelectric correlates and also were not included to the presented results.

Table 1. Duration of the stimulatory and inhibitory effects of the injections of CCK-OP given during phase 1 of the MMC on the myoelectric activity index (MAI) of the duodenum in non-fasted sheep

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<td>30 s</td>
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<td>0.21</td>
<td>0.07</td>
<td>0.02</td>
<td>0.01</td>
<td>0.02</td>
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<td>0.18</td>
<td>0.08</td>
<td>0.27</td>
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<td>0.14</td>
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<td>0.28</td>
<td>0.10</td>
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<td>0.05</td>
<td>0.07</td>
<td>0.07</td>
<td>0.09</td>
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Explanations: values expressed in μV·s·min⁻¹, period 0 - control, i.e. the last minute before injection of CCK peptide. The values of three previous control periods, insignificantly different from period 0, are not shown. Periods 1-10 - consecutive one-minute periods after CCK peptide administration. Means (bold numbers) ± S. D. *P<0.05; †P<0.01; ‡P<0.001. Statistical significances vs. the relevant value of period 0. Student’s t-test for paired values preceded by ANOVA I.

In the myoelectrical recordings, slow injections of CCK-OP at the smallest dose during phase 1 of the MMC (over 30 s) evoked a transient but significant excitatory effect in the duodenum over the first minute after cessation of the peptide injection, lasting 5-15 s (Table 1). When CCK peptide was injected at the moderate dose during phase 1 of the MMC over 30 or 60 s, the stimulatory effect was greater. Furthermore, the MAI values slightly and not significantly increased within the last two minutes of observation. Administration of the peptide at the highest dose in the course of phase 1 of the MMC over 30 s induced significant and sustained excitatory response. The greatest MAI values were obtained during the first minute following CCK administration. During next two minutes the values were greater than in control and not significantly different from control while during the remaining minutes the MAI values increased exceeding the border of significance (Table 1). When CCK-OP was given at the highest dose during 60
s, the effect was similar but not significantly different values were observed during 2-5 minutes following hormone administration. The application of the highest dose of CCK-OP over 120 s produced similar effect as that after CCK administration over 60 s while the not significantly different but elevated MAI values were obtained within 2-6 and during eight minute following CCK peptide application (Table 1).

Table 2. Duration of the stimulatory and inhibitory effects of the injections of CCK-OP given during phase 2a of the MMC on the myoelectric activity index (MAI) of the duodenum in non-fasted sheep

<table>
<thead>
<tr>
<th>Duration</th>
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<tbody>
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<td>0.23</td>
<td>0.14</td>
<td>0.15</td>
<td>0.19</td>
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<td>0.22</td>
<td>0.26</td>
<td>0.27</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>60 s</td>
<td>0.21</td>
<td>1.64</td>
<td>0.35</td>
<td>0.18</td>
<td>0.19</td>
<td>0.21</td>
<td>0.34</td>
<td>0.32</td>
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<td>0.41</td>
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<td>2000 ng/kg</td>
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<td>0.19</td>
<td>1.76</td>
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<td>0.78</td>
<td>0.09</td>
<td>0.27</td>
<td>0.26</td>
<td>0.21</td>
<td>0.18</td>
<td>0.23</td>
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<tr>
<td></td>
<td>60 s</td>
<td>0.24</td>
<td>2.69</td>
<td>0.78</td>
<td>0.09</td>
<td>0.14</td>
<td>0.17</td>
<td>0.22</td>
<td>0.24</td>
<td>0.33</td>
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<tr>
<td>200 ng/kg</td>
<td>30 s</td>
<td>0.20</td>
<td>2.63</td>
<td>1.19</td>
<td>0.71</td>
<td>0.10</td>
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<tr>
<td></td>
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<td>0.06</td>
<td>0.19</td>
<td>0.18</td>
<td>0.15</td>
<td>0.23</td>
<td>0.21</td>
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Explanations as in Table 1

When CCK-OP was given in the course of phase 2a of the MMC at the smallest dose (over 30 s) the excitatory response, observed within the first minute was slight and not significant (Table 2). Administration of a moderate dose of CCK peptides during phase 2a of the MMC induced the significant stimulatory effect within the first minute when the peptides were given within 30 s while during the second and last four minutes the values were higher although did not reach the statistical significance threshold. When the peptide was introduced at the moderate dose within 60 s during phase 2a of the MMC, after the statistically significant excitatory period lasting first three minutes following peptide administration the values returned to the control level. Administration of CCK-OP at the highest dose was the most effective since the increase in MAI values within the first minute was the highest regardless of the duration of injection (Table 2). Following injection of the high dose of CCK-OP in the course of phase 2a of the MMC over 30,
after significant increase in the duodenal MAI values were elevated during the next two minutes while the significantly different was the value obtained during the fourth minute. Then during next two minutes the transient, not significant inhibition was observed. When the hormone was given over 60 s the results were similar but the significant excitatory period lasted first four minutes following hormone administration.

When CCK-OP was given during phase 2a of the MMC over 120 s the significant stimulatory effect arrived within first two minutes, not significant increase in MAI was seen during the third minute and significant inhibitory response was observed in the course of the next two minutes. The remaining values were not much different from the control (Table 2).

Table 3. Duration of the stimulatory and inhibitory effects of the injections of CCK-OP given during phase 2b of the MMC on the myoelectric activity index (MAI) of the duodenum in non-fasted sheep

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<td>30 s</td>
<td>10.4</td>
<td>15.2</td>
<td>4.11</td>
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<td>11.8</td>
</tr>
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<td>14.3</td>
<td>5.12</td>
<td>5.22</td>
<td>1.31</td>
<td>0.79</td>
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<tr>
<td>30 s</td>
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<td>0.21</td>
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Explanation as in Table 1

Injection of CCK-OP at the smallest dose in the course of phase 2b of the MMC (over 30 s), induced slight and not significant elevation of MAI values within the first minute following hormone administration and during the second minute the effect was reversed. The remaining values were close to those during the control period (Table 3). Injection the moderate dose of CCK in the course of phase 2b of the MMC over 30 s evoked significant increase of MAI values within the first minute following hormone application while during the next six minutes the effect was inhibitory and statistically significant. Administration of CCK at the moderate dose over 60 s produced roughly similar but little more attenuated response. The elevation of MAI values during the first minute following peptide injection was slight and not significant and statistically significant inhibitory phase of the response comprised next four minutes (Table 3). Introduction of the highest
The biphasic motor response to CCK observed here raises a question regarding the possible mechanism of dual CCK action on gastrointestinal motility. It is well known that the motor action of CCK is mediated by at least two peripheral subtypes of CCK receptors present in the gastrointestinal tract, including duodenal smooth muscles, enteric neurons, vagal afferent fibers and the brain, and that CCK can exert its modulatory actions, including motility, within these structures (Beinfeld, 2001; Mantyh et al., 1994; Miyasaka and Funakoshi, 2003; Noble et al., 1999). Therefore, the three most plausible mechanisms are presented below. One possibility is that CCK at the smaller doses stimulates a given CCK receptor subtype and in the higher dose further activates another CCK receptor subtype in the gut. If it is the case, the effect of CCK peptide can be due rather to the greater CCK receptor density in the duodenum than CCK receptor density than due to the greater affinity of CCK receptors than of CCK receptors to CCK peptide (Miyasaka and Funakoshi, 2003; Wank, 1995). Thus, the primary stimulatory response can be followed by inhibition. It is well known that CCK is a gut hormone and
it is also a neuronal modulator (BEINFELD, 2001). Its action on intestinal motility can be either direct or can be mediated by several factors including the cholinergic system. This is probably also the case in sheep. Therefore, the second possibility is that the excitatory response to the direct action of CCK on smooth muscles can be followed by an inhibitory neuronal response. Since some gastrointestinal hormones can interact with CCK, the most convincing mechanism of the dual action of CCK on small intestinal motility (third possibility) is that the first stimulatory response is elicited by the rapid action of CCK and the subsequent inhibitory action is induced by one of the inhibitory hormones including somatostatin that is released by CCK (MIYASAKA and FUNAKOSHI, 2003; ZAVROS and SHULKES, 1997).

The smallest dose of CCK-OP induced weak effect in the duodenum although the discernible inhibitory changes preceded by short excitation were observed after moderate doses. As it was discussed earlier (ROMAŃSKI, 2007), the moderate doses of CCK-OP and even the highest doses administrated over 120 s might remain within the physiological range. Thus the only reasonably inference can be drawn from these findings that endogenous CCK may also inhibit the myoelectric activity in the duodenal bulb and that the inhibitory effect of CCK represents the primary response in this region. In the duodenum, the small doses of CCK peptides elicited transient stimulation in the myoelectric and motor activities and the moderate doses evoked the dual effect. These observations may argue for the notion that also in the duodenum the action of CCK can be physiological and comprise both excitatory and inhibitory responses.

The still unresolved question is whether CCK can be classified as a stimulatory or an inhibitory hormone in respect to its actions on duodenal motility. The described retardation of duodenal phase 3 of the MMC by CCK, reversed by administration of the specific antagonist (ONAGA et al., 1997; THOR et al., 1990), can be considered as inhibitory action, while the induction of the fed pattern and stimulation of the duodenal spike bursts (ROMAŃSKI, 2004; THOR et al., 1990), also observed in the present study, can be interpreted as a stimulatory effect. The stimulatory effect of a moderate dose of CCK on duodenal motility seems to be primary (MIZUMOTO et al., 1992), and this conclusion can be inferred also from the present study. Since both stimulatory and inhibitory alterations in the duodenal myoelectric activity is accountable to CCK’s action, it is plausible to corroborate that CCK can either enhance or suppress the duodenal motility and its action can occur either in the interdigestive or digestive periods (ONAGA et al., 1997; ROMAŃSKI, 2007; THOR et al., 1990). Similarities between the effect of CCK peptide administration upon the duodenal and upper jejunal myoelectric activity suggests the functional continuity between these small-intestinal segments. These effects on the duodenal bulb MAI were more distinct but the duodenal bulb plays a reservuar role for the gastric content and the role of inhibitory mechanisms in the control of its motility seems to be greater.
Finally, the obtained results showed that the effect of CCK-OP was dependent upon the MMC phase. In the course of phase 1 of the cycle exhibiting no spike bursts, the effect of the hormone was stimulatory. During phase 2b of the MMC, when the duodenal myoelectric activity was intensive although irregular, the effect of CCK was inhibitory. This suggest that CCK controls the duodenal motility during various phases of the MMC cycle and is able to play its role depending on luminal stimuli in various motor conditions. Thus in sheep physiological doses of CCK peptides evoked vast effect on duodenal myoelectric activity, suggesting that in sheep, as in monogastric species, the role of CCK in the control of this function is remarkable. CCK might thus be considered as a physiological regulator of duodenal motility in sheep.

References


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Inhibicioni (bifazni) dejstvo dozama uzrokovala je manje izražen bifazni transversoaktivni kompleks u duodena bootu neizglađenih vaca. Ovi učinci imale su kratak stimulacijski i prijelazom na dugi inhibicioni bifazni učinak, bio je istražiti u ovce, duodenalna ampula, dvanaesnik, mioelektrična i motorička aktivnost, kolecistokinin-oktapeptida, migrirajući mioelektrični kompleks.

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SAŽETAK
Kolecistokin utječe na crijevni motilitet, ali još nije razjašnjen način njegova djelovanja. Cilj ovoga rada bio je istražiti učinke kolecistokinin-oktapeptida na mioelektričnu aktivnost dvanaesnika u normalno hranjenih neizglađivanih ovaca u tijeku dugotrajnoga pokusa. Bipolarna platinasta elektroda bila je u pet novina kirurški bio postavljen blizu duodenalne elektrode da bi se provelo mioelektrično snimanje. U tijeku neprekidnoga snimanja bio je u ovca, duodenalna ampula, dvanaesnik, mioelektrična i motorička aktivnost, kolecistokinin-oktapeptida bio je postavljen blizu duodenalne elektrode da bi se provelo mioelektrično snimanje. U tijeku neprekidnoga snimanja bio je intravenski primijenjen 0,15 M NaCl ili kolecistokinin-oktapeptid. Polagano ubrizgavanje kolecistokinin-oktapeptida u dozi od 20 (tijekom 30 s), 200 (tijekom 30 ili 60 s) i 2000 (tijekom 30, 60, ili 120 s) ng/kg tijesne mase bilo je primijenjeno za vrijeme duodenalne faze 1, 2a, ili 2b migracijskoga motoričkoga kompleksa, tj. 5 minuta nakon pojave svake faze. Ubrizgavanje najmanje doze kolecistokinin-oktapeptida dalo je slab, pretežito nesignifikantan učinak na duodenalnu ampulu i na vrijednosti pokazatelja duodenalne mioelektrične aktivnosti. Učinci kolecistokinin-oktapeptida na mioelektričnu aktivnost duodenalne ampule bili su ovisni o doži i usko povezani s fazom migrirajućega motornoga kompleksa. Veće doze hormona u dvanaesniku imale su kratak stimulacijski i prijelazom na dugi inhibicijski bifazični učinak na indeks mioelektrične aktivnosti. Ovi učinci bili su obratno razmjerni s trajanjem ubrizgavanja hormona. Primjena hormona u većim dozama uzrokovala je manje izraženi bifazični učinak. Može se zaključiti da kolecistokin ima stimulacijski i inhibicijski (bifazični) fiziološki učinak na motilitet dvanaesnika u neizglađivanim ovaca.

KLJUČNE RIJEČI: ovca, duodenalna ampula, dvanaesnik, mioelektrična i motorička aktivnost, kolecistokinin-oktapeptid, migrirajući mioelektrični kompleks