Effects of Various Doses of Cholecystokinin Octapeptide and Cerulein on Antral Slow-Wave Frequency and Amplitude in Conscious Sheep

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Abstract


It is suspected that cholecystokinin (CCK) might affect antral slow-wave frequency and amplitude, but in sheep this problem is virtually unknown. Therefore the myoelectric activity was continuously recorded before and after intravenous administration of 0.15 M NaCl or CCK peptides in adult rams, equipped with platinum bipolar electrodes in the abomasal antrum, duodenum, and jejunum. CCK octapeptide (CCK-OP) was given to five rams at doses of 17.5, 175, or 1750 pmol/kg and cerulein was administered to six rams at doses of 0.735, 7.35, or 73.5 pmol/kg of body weight. Each dose was infused to fasted or non-fasted animals for 30, 60, 120, or 300 s during phase 1, 2a or 2b (the less or more intense) of the migrating myoelectric complex (MMC). The 300-sec infusion of the moderate CCK-OP dose during the less intense or more intense phase 2b of the MMC increased the antral slow-wave amplitude from 79 ± 7 to 124 ± 26 μV (p < 0.01) and from 82 ± 8 to 175 ± 40 μV (p < 0.001), respectively. The 300-sec infusion of the highest CCK-OP dose under the same conditions increased antral slow-wave amplitude from 79 ± 6 to 121 ± 24 μV (p < 0.05) and from 84 ± 9 to 138 ± 27 μV (p < 0.01), respectively.

Administration of the moderate dose of CCK for 120 s in the course of the less or more intense phase 2b of the MMC increased antral slow-wave frequency from 6.1 ± 0.2 to 6.6 ± 0.4 cpm (N.S.) and from 6.1 ± 0.3 to 6.8 ± 0.4 cpm (p < 0.05), respectively. Administration of the highest dose of CCK-OP for 120 s in the course of the less or more intense phase 2b of the MMC increased the antral slow-wave frequency from 6.2 ± 0.3 to 7.2 ± 0.4 (p < 0.05) and from 6.0 ± 0.3 to 7.8 ± 0.6 cpm (p < 0.001), respectively. It is concluded that CCK in physiological and putatively pharmacological doses can affect the slow-wave frequency and amplitude in sheep related in part to the small-intestinal MMC phase and the intensity of the antral motor activity.

Sheep, abomasal antrum, myoelectric activity, slow-wave frequency and amplitude

It is well established that cholecystokinin (CCK) is one of the most important gut hormones, exerting multiple effects on gastrointestinal motility (Grider 1994). In monogastrics, CCK is known to switch the interdigestive motility pattern to the digestive pattern, stimulate pyloric motility, and also to inhibit gastric motility and emptying (Grider 1994; Thomas et al. 1979; Thor et al. 1988). However, when the hormone was given intra-arterially to anaesthetized animals or when its motor effect on the stomach was studied in vitro, the effect on the gastric motor activity was stimulatory (Kuwahara et al. 1986; Morgan et al. 1978). A close derivative of CCK, amphibian cerulein, is active in mammals as well and exerts similar effects on gastrointestinal motility (Ogawa and Tanaka 1992; Scarpignato et al. 1993). Thus the role of CCK in the control of gastric motility in non-ruminant species is not fully established. In ruminants, endogenous CCK exerts its regulatory functions and its effect on gastric motor activity is inhibitory (McLeay and Bell 1980; Ruckebusch 1988; Tachibana et al. 1995). Both CCK-octapeptide (CCK-OP), which is the form of CCK present in sheep, and cerulein are used in motility studies (Titchen 1986; Romański 2004a). These actions of CCK are mediated by specific receptors expressed...
by gastrointestinal smooth muscles and by central and peripheral neurons (Noble et al. 1999). As CCK receptors are also present on the interstitial cells of Cajal (Patterson et al. 2001), it might be expected that CCK may affect the antral slow-wave frequency and amplitude. It has been reported that the motor effects of CCK also comprise an increase in slow-wave frequency (Ohkawa and Watanabe 1977). However, as this effect was not always observed in monogastric species (Chen et al. 1995), the role of CCK in the control of gastric slow waves remains uncertain. No information is available regarding the effect of CCK on antral slow waves in ruminants. In a preliminary study in sheep, CCK-OP and cerulein seemed to affect antral slow waves. Thus the objective of this study was to assess the precise effect of various doses of CCK-OP and cerulein administered over different periods of time and during various phases of the migrating myoelectric complex (MMC) on antral slow-wave frequency and amplitude in fasted and non-fasted conscious sheep.

Materials and Methods

Animal preparation

Six healthy rams of the Polish Merino breed weighing 38–44 kg each were used. Before the surgery the rams were fed regularly according to the standard procedure (see Romański 2004b) and were adapted for the experiments for at least two weeks. This study was performed in accordance with the relevant allowance number of animals with regard to animal welfare and approval of the whole experimental protocol by the local Ethics Committee (87/03) in Wroclaw. In 24-h fasted animals, right lateral laparotomy was performed under general and local anaesthesia and a bipolar platinum electrode was sutured to the right lateral surface of the pyloric antrum, 4 cm from the pylorus, on the serosal side. For a reliable recognition of the MMC and identification of its phases, four additional electrodes were attached to the small intestinal wall. These electrodes were located as follows: on the duodenal bulb 6 cm distally to the pylorus, on the duodenum 50 cm distally from the bulbular electrode, on the jejunum 200 cm distally from the duodenal electrode, and on the jejunum 100 cm distally from the first jejunal electrode. Only rams exhibiting normal myoelectric activity after the postoperative recovery period were included in the study. Other details of animal preparation were similar to those described earlier (Romański 2004a).

Experimental protocol

A total of 484 experiments lasting 3–4 h each were performed. Continuous myoelectrical recordings were performed in the conscious rams using a multichannel electroencephalograph (Reega Duplex TR XVI, Alvar, Montreuil, France). Before the experiments (performed in non-fasted animals) the rams received standard food for the last time the day before the experiment; fodder was available from midday of that day. The second set of experiments was performed in 40–42 h fasted rams. Each experiment comprised two main parts. Initially, at least two consecutive phases 3 of the MMC were recorded (the so-called “own control”). Then, in the course of the control experiments, 5 ml of 0.15 M NaCl were injected over 30 s into the jugular vein through a thin polyethylene catheter introduced before the experiment and at least one full MMC cycle was recorded. During the remaining experiments, after recording the “own control” part, random injections of CCK-OP (Sincalide, Squibb Inst., Princeton, USA) at doses of 17.5, 175, or 1750 pmol/kg and cerulein (Farmitalia Carlo Erba, Milan, Italy) at doses of 0.735, 7.37 or 73.5 pmol/kg of body weight were given. Each dose (the lowest, moderate and highest) of the hormonal peptide was administered over 30, 60, 120, or 300 s through the indwelling jugular catheter. In non-fasted rams, either hormonal peptide was randomly injected during phase 1, 2a, or 2b of the MMC, identified in the duodenum, about 10 min after the initiation of the given MMC phase. During this time the antrum exhibited an interrupted spiking activity. The experiments with hormonal peptide administration during phase 2b of the MMC were further differentiated depending on its intensity. After hormone administration the recording was continued until the arrival of phase 3 of the MMC. Calibrations of the myoelectric recording were performed thoroughly. Similar experimental protocols were designed in previous studies (Romański 2002, 2004a, 2005a), where other details of the whole procedure can be found.

Calculations

The MMC cycles were identified in the small intestine and their phases were recognized mostly in the duodenum according to the criteria of Code and Marllett (1975). Furthermore, phase 2 of the MMC was subdivided into phase 2a and 2b according to the suggestion of Dent et al. (1983). A less (weak) and more (strong) intense phase 2b was also distinguished. Phase 2b of the MMC was considered weak when the contribution of slow waves with spike bursts in the duodenum during this phase was 20% or less. Spike bursts of amplitude below 20 μV and duration below 0.5 s were omitted. Antral slow-wave frequency and amplitude were calculated in 1–2 minute control periods and for ten minutes following the injection of the hormonal peptides. These data are expressed in cycles per minute (cpm) and μV, respectively. Their accuracies were about 0.1 cpm and about 5 μV. Control antral slow-wave frequencies are presented as averages for two-minute control periods. Increased slow-wave frequencies after CCK peptide administration are presented as the average data for a period lasting 30 s or more starting no earlier than immediately after the termination of hormone injection and no later than 1 min afterwards.
(first or primary response). The durations of these periods are presented separately. To demonstrate the subsequent inhibitory response (second or secondary response), the durations of the inhibitory periods were measured and the average values of the slow-wave frequency during these periods are depicted. Control slow-wave amplitudes were measured for 1 min just before hormonal peptide administration. The increased slow-wave amplitudes (inhibitory secondary responses were not observed here) are presented as average amplitudes of one-minute periods directly following the beginning of hormone administration. The overall duration of these responses, expressed in seconds (s) is presented separately.

The data were statistically evaluated and the mean values with standard deviations were calculated and presented. Statistical significances between the control data and data obtained in response to hormonal peptide administration were calculated using Student’s $t$-test for paired values preceded by one-way analysis of variance (Snedecor and Cochran 1971).

**Results**

**Control experiments**

During the control experiments performed in fasted and non-fasted animals, the injection of saline evoked alterations neither in the antral slow-wave frequency nor the amplitude compared with the relevant data obtained from the control experiments with hormone administration (data not shown). All the values of the antral slow-wave frequency and amplitude (but not the duration) were compared with the “own control” data.

**Effects of the lowest dose of CCK peptides upon the antral slow-wave frequency in non-fasted sheep**

Administration of the lowest doses of CCK-OP or cerulein evoked significant changes neither in antral slow-wave frequency nor the amplitude compared with the relevant control values; these data are therefore omitted.

**Effects of the moderate and the highest doses of CCK-OP on the antral slow-wave frequency in non-fasted sheep**

Slow injection of the moderate or highest dose of CCK-OP initially evoked a significant increase in the antral slow-wave frequency, these changes in response to the highest dose of CCK-OP were more pronounced (Fig. 1). The duration of hormone injection was also important. The weakest effect was observed when the hormone was administered during phase 2a of the MMC. After the enhancement period of the slow wave frequency, its periodical suppression was observed (Fig. 1). The durations of the stimulatory changes were directly proportional to the dose of the hormone and the duration of hormone administration (Table 1). Accordingly, the longest period during which the slow-wave frequency values were elevated was observed after the highest dose of CCK-OP administered in the course of

**Table 1. The durations of periods (in seconds) in which the antral slow-wave frequency was altered in response to the moderate and highest dose of CCK-OP, administered in non-fasted sheep during the various phases of the migrating myoelectric complex (MMC)**

<table>
<thead>
<tr>
<th>Phase of MMC</th>
<th>CCK-OP 175 pmol/kg</th>
<th>CCK-OP 1750 pmol/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMC phase:</td>
<td>MMC phase:</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2a</td>
</tr>
<tr>
<td>30 s mean</td>
<td>182</td>
<td>441</td>
</tr>
<tr>
<td>± S.D.</td>
<td>113</td>
<td>514</td>
</tr>
<tr>
<td>60 s mean</td>
<td>259</td>
<td>68</td>
</tr>
<tr>
<td>± S.D.</td>
<td>113</td>
<td>435</td>
</tr>
<tr>
<td>120 s mean</td>
<td>108c</td>
<td>36</td>
</tr>
<tr>
<td>± S.D.</td>
<td>36</td>
<td>218c</td>
</tr>
<tr>
<td>300 s mean</td>
<td>16</td>
<td>126c</td>
</tr>
<tr>
<td>± S.D.</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td>300 s mean</td>
<td>16</td>
<td>126c</td>
</tr>
<tr>
<td>± S.D.</td>
<td>16</td>
<td>31</td>
</tr>
</tbody>
</table>

Explanations: 2b(w) – weak phase 2b MMC; 2b(s) – strong phase 2b MMC; 30 s, 60 s, 120 s, 300 s – the duration of hormone injections in seconds. Statistical significances vs. relevant 30 s value: $^a p < 0.05$, $^b p < 0.01$, $^c p < 0.001$, n = 5, Student’s $t$-test for paired values preceded by ANOVA I.
The stimulatory effect of CCK-OP on the antral slow-wave frequency was followed by its transient decrease (Fig. 1). Although the first response to CCK-OP administration was stimulatory, the second response exhibited an inhibitory character. Significant inhibition of the antral slow-wave frequency was observed after the moderate and highest dose of CCK-OP given over 30–120 s in the course of phases 1, 2a, and weak phase 2b of the MMC (Fig. 1). The duration of the post-stimulatory (inhibitory) period following CCK-OP administration regarding the antral slow-wave frequency is not shown. However, in non-fasted sheep the highest dose of CCK-OP administered for 120 and 300 s in the course of strong phase 2b of the MMC caused significantly longer inhibition than after CCK-OP given for 30 s.

Effects of the moderate and highest doses of cerulein on the antral slow-wave frequency in non-fasted sheep

Injections of the moderate and highest doses of cerulein exerted effects which were mostly comparable to those evoked by CCK-OP. However, administration of the moderate dose of cerulein was efficient only when the hormonal peptide was given for 30 or 60 s during phase 2b of the MMC (Fig. 2). The injection of the highest dose of cerulein also produced a smaller increase in slow-wave frequency.

![Graphs showing effects of CCK-OP and cerulein on antral slow-wave frequency](image-url)

**Fig. 1.** Effects of moderate (upper panel) and highest doses (lower panel) of cholecystokinin octapeptide on antral slow-wave frequency (cpm) during the various phases of the migrating myoelectric complex (MMC) in non-fasted sheep. Explanations: CP-CCK, cholecystokinin octapeptide; cpm, cycles per minute; s, seconds; open bars, control; closed bars, first response; grey-shadowed bars, second response. Values presented as means ± S.D. Student's *t*-test for paired values followed by ANOVA I. Statistical significance: *p* < 0.05, **p** < 0.01, ***p*** < 0.001 vs. relevant control value.
than the highest dose of CCK-OP. The relationship between the dose and time of administration of cerulein and its effect on the antral slow-wave frequency was roughly similar to that of CCK-OP administration. The duration of the stimulatory effect of cerulein on slow-wave frequency was clearly dose-dependent and was highest when the hormonal peptide was given during phase 2b of the MMC (Table 2). During the longest cerulein administration, the duration of the response was the shortest. Significant changes were observed in response to the moderate and highest doses of cerulein given for 30–60 s in the course of phase 1 and 2b of the MMC (Fig. 2). The duration of the stimulatory effect of cerulein on slow-wave frequency was similar to that of CCK-OP administration. The duration of the stimulatory effect of cerulein was clearest in response to the highest dose of CCK-OP given during phase 2b of the MMC (Table 2).
Table 2. The durations of periods (in seconds) in which the antral slow wave frequency was altered in response to the moderate and highest dose of cerulein, administered in non-fasted sheep during the various phases of the migrating myoelectric complex (MMC)

<table>
<thead>
<tr>
<th></th>
<th>Cerulein 7.35 pmol/kg MMC phase:</th>
<th>Cerulein 73.5 pmol/kg MMC phase:</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 s mean ± S.D.</td>
<td>47 ± 21 47 ± 21 196 ± 72</td>
<td>427 ± 185 94 ± 38 678 ± 239 1168 ± 431</td>
</tr>
<tr>
<td>60 s mean ± S.D.</td>
<td>33 ± 17 141 ± 48 215 ± 49</td>
<td>217 ± 108 63 ± 27 485 ± 181 875 ± 318</td>
</tr>
<tr>
<td>120 s mean ± S.D.</td>
<td>27c ± 11 68c ± 25</td>
<td>86c ± 33 39c ± 16 146c ± 65 211c ± 87</td>
</tr>
<tr>
<td>300 s mean ± S.D.</td>
<td>- - - 45c ± 19</td>
<td>55c ± 24c 64c ± 9 84c ± 22 29</td>
</tr>
</tbody>
</table>

Explanations: 2b (w) – weak phase 2b MMC; 2b (s) – strong phase 2b MMC; 30 s, 60 s, 120 s, 300 s – the duration of hormone injections in seconds. Statistical significances vs. relevant 30 s value: *p < 0.05, **p < 0.01, ***p < 0.001, n = 6, Student’s t-test for paired values preceded by ANOVA I

Table 3. The durations of periods (in seconds) in which the antral slow wave amplitude was altered in response to the moderate and highest dose of CCK-OP, administered in non-fasted sheep during the various phases of the migrating myoelectric complex (MMC)

<table>
<thead>
<tr>
<th></th>
<th>CCK-OP 175 pmol/kg MMC phase:</th>
<th>CCK-OP 1750 pmol/kg MMC phase:</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 s mean ± S.D.</td>
<td>343 ± 118 143 ± 44 208 ± 74 259 ± 121</td>
<td>327 ± 133 78 ± 21 266 ± 117 378 ± 175</td>
</tr>
<tr>
<td>60 s mean ± S.D.</td>
<td>139b ± 58 54b ± 26 141 ± 62 207 ± 84</td>
<td>147b ± 63 126 ± 54 193 ± 86 276 ± 127</td>
</tr>
<tr>
<td>120 s mean ± S.D.</td>
<td>54c ± 23 76c ± 41 63c ± 24 46c ± 41</td>
<td>54c ± 24 52 ± 41 122 ± 39 108c ± 43</td>
</tr>
<tr>
<td>300 s mean ± S.D.</td>
<td>36c ± 11 18c ± 7 31c ± 32 23c ± 38</td>
<td>34c ± 21 - 43c ± 17 30c ± 24</td>
</tr>
</tbody>
</table>

Explanations: 2b (w) – weak phase 2b MMC; 2b (s) – strong phase 2b MMC; 30 s, 60 s, 120 s, 300 s – the duration of hormone injections in seconds. Statistical significances vs. relevant 30 s value: *p < 0.05, **p < 0.01, ***p < 0.001, n = 5, Student’s t-test for paired values preceded by ANOVA I

Table 4. The durations of periods (in seconds) in which the antral slow wave amplitude was altered in response to the moderate and high dose of cerulein, administered in non-fasted sheep during the various phases of the migrating myoelectric complex (MMC)

<table>
<thead>
<tr>
<th></th>
<th>Cerulein 7.35 pmol/kg MMC phase:</th>
<th>Cerulein 73.5 pmol/kg MMC phase:</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 s mean ± S.D.</td>
<td>52 ± 17 - - - -</td>
<td>245 ± 94 263 ± 107 178 ± 123 345 ± 118</td>
</tr>
<tr>
<td>60 s mean ± S.D.</td>
<td>30 ± 8 - - - -</td>
<td>202 ± 86 194 ± 75 126 ± 85 266 ± 174</td>
</tr>
<tr>
<td>120 s mean ± S.D.</td>
<td>- - - - - -</td>
<td>84b ± 31 123b ± 48 79 ± 44 163b ± 77</td>
</tr>
<tr>
<td>300 s mean ± S.D.</td>
<td>- - - - - -</td>
<td>38c ± 17 49c ± 22 63 ± 28 107c ± 56</td>
</tr>
</tbody>
</table>

Explanations: 2b (w) – weak phase 2b MMC; 2b (s) – strong phase 2b MMC; 30 s, 60 s, 120 s, 300 s – the duration of hormone injections in seconds. Statistical significances vs. relevant 30 s value: *p < 0.05, **p < 0.01, ***p < 0.001, n = 6, Student’s t-test for paired values preceded by ANOVA I
Fig. 3. Effects of moderate (upper panel) and highest doses (lower panel) of cholecystokinin octapeptide on antral slow-wave amplitude (μV) during the various phases of the migrating myoelectric complex in non-fasted sheep. Explanations: OP-CCK, cholecystokinin octapeptide; μV, microvolts; s, the duration of hormone injection in seconds; open bars, control; closed bars, treatment. Values presented as means ± S.D. Student's t-test for paired values followed by ANOVA I. Statistical significance: 
*<i>p < 0.05</i>, **<i>p < 0.01</i>, ***<i>p < 0.001</i> vs. relevant control value.
Fig. 4. Effects of moderate (upper panel) and high doses (lower panel) of cerulein on antral slow-wave amplitude (μV) during the various phases of the migrating myoelectric complex in non-fasted sheep. Explanations: s, the duration of hormone injection in seconds; open bars, control; closed bars, treatment. Values presented as means ± S.D. Student’s t-test for paired values followed by ANOVA I. Statistical significance: *p < 0.05, **p < 0.01, ***p < 0.001 vs. relevant control value.
the effect of the highest dose (Fig. 3). The differences between the doses of CCK-OP given for 30, 60, or 120 min were not marked. The effect of the hormone on slow-wave amplitude was monophasic and was most evident when the CCK peptide was given during phase 2b or phase 1 of the MMC (Fig. 3). The duration of increased slow-wave amplitude was also prolonged. The duration of these changes was longest when CCK-OP was administered for 60 min.

Fig. 5. Two-to-five minute fragments of antral myoelectric recordings during two separate experiments performed in non-fasted sheep. Upper panel: the recording before (control), during and after administration of cholecystokinin octapeptide 175 pmol/kg for 30 s, in the course of duodenal phase 1 MMC. Antral slow-wave frequencies: control (mean value of two-minute fragment just before hormone administration), 6.2 cpm; treatment (mean value of one-minute fragment just after hormone administration), 7.4 cpm. Antral slow wave amplitudes: control (the average value of one-minute period just before hormone administration), 72 μV; treatment (mean value of one-minute fragment just after hormone injection), 162 μV.

Lower panel: the recording before (control), during and after administration of cerulein 73.5 pmol/kg for 60 s, in the course of duodenal phase 1 MMC. Antral slow-wave frequencies: control (mean values of two-minute period just before hormone administration), 6.6 cpm; treatment (mean value of one-minute period just after hormone injection), 7.4 cpm. Antral slow-wave amplitudes: control (the average value of one-minute period just before hormone administration), 104 μV; treatment (mean value of one-minute period just after hormone injection), 189 μV.

Explanations: upper record in each panel, time in seconds; lower two tracings in each panel, continuous antral myoelectrical recordings; C, electrode calibration 100 μV; horizontal bar, hormone administration.
30 s or when the hormone was given during phase 2b of the MMC (Table 3). This effect was thus of a dose-response type.

Comparison of the effects of CCK-OP and cerulein on the antral slow-wave amplitude and frequency in non-fasted sheep

The increase in slow-wave amplitude following cerulein administration was usually smaller than after CCK-OP, but the differences between the moderate and highest dose of the hormone were much greater (Fig. 4). In some cases, the effect of the hormone administered during phase 1 was more pronounced than the effect of the given dose of the hormone administered during phase 2b of the MMC. However, the effect of cerulein administered for 300 s, even at the highest dose, was the smallest. The duration of these changes was usually significant and was related to the hormonal peptide dose and MMC phase (Table 4). The duration of changes in slow-wave amplitude was shortest when the duration of cerulein administration was 300 s. The effect of the moderate dose of CCK-OP on the antral slow-wave frequency and amplitude was often not much different from the effect of the high dose of cerulein (Fig. 5).

Effects of CCK peptides on the antral slow-wave frequency and amplitude in fasted sheep.

There were no marked differences in the antral myoelectric response to CCK peptides between fasted and non-fasted sheep although the changes in antral slow-wave frequency and amplitude were slightly less evident in fasted sheep. These results are therefore not shown.

Discussion

Both CCK peptides given in moderate and higher doses significantly affected the ovine antral slow-wave frequency and amplitude and the response was usually biphasic. The increase in slow-wave frequency from about 6–7 cpm to about 8 cpm cannot be interpreted as a tachygastria-evoking effect despite the preservation of the regular rhythm of the slow waves. During tachygastria, the increase in antral slow-wave frequency in monogastrics is much higher (Kohagen et al. 1996). Furthermore, tachygastria has never been described in sheep. It is known that during inhibition of spike activity, the antral slow-wave frequency can increase slightly, but in sheep these changes usually oscillate within 5.5–7 cpm (Romaniński 2002). The evident modulatory action of CCK peptides on antral slow waves can occur when CCK receptors are present on the gastric cells generating the slow waves. It has recently been demonstrated that CCK receptors are present on the interstitial cells of Cajal (Patterson et al. 2001). These cells have never been found in sheep, but it is rather obvious that they occur also in this species.

There are some reports suggesting that CCK can increase the slow-wave frequency in various animal species, including dogs and cats (Ohkawa and Watanabe 1977; Thomas et al. 1979). A preliminary study also showed that a similar effect could be observed in sheep (Romaniński 2004a). Other reports present opposite results (Chen et al. 1995; Wingate et al. 1978) and are contrary to the presented results. Several reasons for this discrepancy should be taken into account. CCK’s action is mediated by at least two distinct receptor subtypes, i.e. the CCK-1 (CCK-A) receptor subtype and the CCK-2 (CCK-B/gastrin) receptor subtype. CCK, as a circulating hormone, can reach the target organ in different ways, including along an endocrine and probably a paracrine pathway, and it has long been thought that CCK is also a neuromodulator and can exert its effects via a neurocrine (most probably with brain involvement) or neuroendocrine mechanism (Miyasaka and Funakoshi 2003; Reidelberger et al. 2003; Dockray 2006). Furthermore, CCK can affect the release of other hormones, thus potentiating their effects (Zavros et al. 1998). In principle it can be expected that CCK-OP administered intravenously can act peripherally, since CCK-OP does not cross the blood-
brain barrier. In spite of this, a central action of at least other forms of CCK or cerulein after intravenous administration cannot be excluded (Fioramonti and Bueno 1988). Thus it is also possible that the myogenic control of gastrointestinal motility comprises central and peripheral components which can produce a biphasic response. It is also possible that this post-stimulatory effect was evoked by increased release of somatostatin in response to CCK administration (Zavros and Shulkes 1997).

There are no data available regarding the effect of CCK on the slow-wave amplitude and it appears that the effect on the slow-wave frequency is more important physiologically than the effect upon the slow-wave amplitude. It is well known that slow waves do not induce contractions unless they exceed the mechanical threshold, and in the terminal antrum slow waves can contribute to phasic contractions (Szurszewski 1987). Therefore the increase in slow-wave amplitude can stimulate or facilitate the occurrence of mechanical events, but to a limited extent. CCK is one of the relatively few hormonal regulators affecting slow waves and the most common neural receptor blockers have little or no effect on their frequency or amplitude (Sanders and Publicover 1989). CCK is a physiological regulator of gastric function, at least when gastric emptying is considered (Grider 1994; Reidelberger et al. 2001). However, the response to the highest doses of CCK peptides used in this study seems to be pharmacological, at least in part. There are no precise data in sheep indicating what doses can still be considered physiological. Zavros and Shulkes (1997) showed that in 12–18 h fasted sheep a 45-min infusion of CCK-OP at a rate of 150 pmol/kg/h caused stabilization of the plasma CCK level at 34 ± 7 pmol/l, i.e. almost six times above the basal level. However, the postprandial plasma concentration of CCK in sheep can be higher and, considering the relatively high metabolic clearance rate, it can be assumed that this dose could be supraphysiological rather than pharmacological. In calves, a CCK dose of 30 pmol/kg/min infused during 40 min stimulating pancreatic secretion was physiological (Le Drean et al. 1999). In humans 40 ng/kg/h of CCK-OP was suggested to be a supraphysiological dose and 10 ng/kg/h a physiological dose (Soudah et al. 1992). In dogs, CCK-OP infusion at a rate of 125 ng/kg/h inhibited gastric emptying and this dose was also considered physiological (Debas et al. 1975). Thus it seems likely that most of the doses of CCK peptides used in this study are physiological. The highest dose used here may be supraphysiological as well.

The present results indicate that CCK-OP given at over 20-times higher doses than those of cerulein evoked a stronger effect on antral slow waves in sheep. However when the same dose of CCK peptides was infused, cerulein evoked stronger effects than CCK-OP, which suggests its greater affinity to CCK receptors.

The considerably small differences in the effects of CCK peptides on antral slow waves between fasted and non-fasted sheep can be explained by the species-specific function of the gastrointestinal tract. Even in two-day fasted ruminants, the rumen is not empty; thus the digesta flow from the rumen to the duodenum continues. Therefore there are relatively small differences in duodenal hormone release and neural stimulation by the flow of digesta between fasted and non-fasted animals.

Finally, it can be concluded that cholecystokinin can alter slow-wave frequency and amplitude in the ovine pyloric antrum and these effects are often biphasic. This suggests a direct influence of the hormone on the interstitial cells of Cajal.

Vliv různých dávek oktapeptidu cholecystokininu a ceruleinu na snížení frekvence a amplitudy pomalé antrální peristaltické vlny u ovce domácí

Existuje obecný předpoklad, že cholecystokinin (CCK) je schopen snížit frekvenci a rozsah peristaltických vln, ale tato problematika nebyla dosud u ovce domácí prostudována. Proto byl pořízen kontinuální záznam myoelektrické aktivity před a po intravenózní aplikaci 0.15 M NaCl nebo peptidu CCK u dospělých beranů s implantovanými bipolárními plati-
novými elektrodami v abomasální dutině, duodenu a jejunu. Pěti beranům byl podán CCK oktapeptid (CCK-OP) v dávkách 17.5, 175, nebo 1750 pmol/kg a šesti beranům byl aplikován cerulein v dávkách 0.735, 7.35, nebo 73.5 pmol/kg télesné hmotnosti. Jednotlivé dávky těchto látek byly podávány v infuзи lanícím nebo krmeným zvířatům po dobu 30, 60, 120, nebo 300 s během více či méně intenzivní fáze 1, 2a nebo 2b migrujícího myoelektrického komplexu (MMC). Infuзи obsahující střední dávky CCK-OP podávaná po dobu 300 s během nízké nebo vysoké intenzity fáze 2b MMC měla za následek vznrůst amplitudy pomalé antrální peristaltické vlny z 79 ± 7 na 124 ± 26 μV (p < 0.01) resp. z 82 ± 8 na 175 ± 40 μV (p < 0.001). Aplikace nejvyšší dávky CCK-OP po dobu 300s za stejných podmínek zvýšil amplitudu pomalé antrální peristaltické vlny z 79 ± 6 na 121 ± 24 μV (p < 0.05) a z 84 ± 9 na 138 ± 27 μV (p < 0.01). Po podání střední dávky CCK po dobu 120 s během fáze MMC vznrostla frekvence pomalé antrální peristaltické vlny z 6.1 ± 0.2 na 6.6 ± 0.4 cpm (N.S.) během vysoké intenzity 2b a z 6.1 ± 0.3 na 6.8 ± 0.4 cpm (p < 0.05) během nízké intenzity 2b.

Infuze s obsahem nejvyšší dávky CCK-OP po dobu 120 s během vysoké nebo nízké intenzity fáze 2b MMC zvýšila frekvenci pomalé antrální peristaltické vlny z 6.2 ± 0.3 na 7.2 ± 0.4 (p < 0.05) respektive z 6.0 ± 0.3 na 7.8 ± 0.6 cpm (p < 0.001). Tato studie tedy potvrzuje, že CCK ve fyziologických nebo v uvedených farmakologických dávkách působí na frekvenci i rozsah pomalých antrálních peristaltických vln u ovce domácí částečně související s fází MMC tenkého střeva a intenzitou antrální motorické aktivity.

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