Multiple effects of cholecystokinin administered during various phases of the migrating myoelectric complex upon the small intestinal interdigestive and digestive motility in sheep

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Summary

There is no detailed data regarding the effect of cholecystokinin on the migrating myoelectric complex (MMC) in sheep. Thus, in five rams seven bipolar platinum electrodes were implanted to the abomasal antrum and entire small intestine. The strain gauge force transducer was also attached near the duodenal electrode in four of these animals. In the course of chronic experiments, the myoelectric and motor activities were continuously recorded in fasted and non-fasted sheep. During control recordings, at least two normal consecutive phases 3 of the MMC were recorded. Then, slow injections of cholecystokinin-octapeptide (CCK-OP) of 0.02, 0.2 and 2.0 micrograms per kg of body weight were given intravenously during phase 1, 2a or 2b of the MMC, identified in the duodenum, and next two consecutive phases 3 of the MMC were recorded. The moderate dose of CCK-OP administered during phase 2a in non-fasted rams shortened the MMC cycles significantly while the highest dose of the hormone increased the MMC cycle duration and inhibited phase 3 of the MMC in the duodenum. No such effect was observed in the jejunum. However, duration of phase 3 of the MMC in this region was shortened principally by the highest dose of CCK-OP. It is concluded that CCK may inhibit the MMC pattern in ovine small bowel and its effect in the duodenum is the most evident. However, this effect seems to be the consequence of pharmacological rather than physiological action of CCK. Thus, CCK does not appear to play as important a role in the control of the small-intestinal MMC in sheep as in monogastric animals.

Key-words: Sheep, duodenum, jejunum, migrating myoelectric complex phase, cholecystokinin.

Introduction

Cholecystokinin (CCK) is one of the most effective gastrointestinal hormones and exerts multiple physiological and pharmacological actions [4]. It is one of the most important regulators of the gastrointestinal motility [25]. Its role in the control of small intestinal motility is well established, at least in monogastric species, and its regulatory effect on gastrointestinal peristalsis is included to the physiological actions of the hormone [28]. The presence of specific CCK receptors...
represents the basis for these actions [14, 28]. However, the spectrum, character and mechanism of CCK effects have not been recognized in details. Thus, the hormone is still the subject of the extensive investigations [5, 6]. CCK is considered as one of the digestive hormones. Thus, its expected effect of upon the fundamental interdigestive motor pattern in the small bowel, i.e. the migrating motor or myoelectric complex (MMC) is inhibitory. The studies on dogs first indicated that CCK administration switches the gastrointestinal MMC into the irregular motor activity roughly resembling the digestive pattern [15, 23]. WINGATE et al. [29] showed that this effect was observed only in the proximal small intestine. In sheep, CCK also exerts the effects on gastrointestinal motility. These effects were shown for CCK-peptides or for cerulein, the amphibian CCK analogue as well [2, 17]. The inhibitory effect of CCK on the MMC in ruminants was first suggested by GREGORY but was not satisfactorily documented [3]. Thus, the aim of this study was to assess the precise effect of CCK-octapeptide (CCK-OP) on the MMC in the entire small intestine of conscious sheep.

Material and Methods

Five adult rams of Polish Merino breed with the body weight of 38-42 kg each were used. Before the surgery animals were fed with good-quality hay and were supplemented with a standard grain mixture. Drinking water was not limited.

ANIMAL PREPARATION

In 24 h-fasted animals the right lateral laparotomy was performed under the general and local anesthesia as described previously [20]. Seven bipolar platinum electrodes were implanted onto the serosal side of the pyloric antrum (one electrode), the duodenal bulb (one electrode), duodenum (one electrode), jejunum (two electrodes) and ileum (two electrodes). The strain gauge force transducer was attached near the duodenal electrode in four of these animals. The marked electrode wires were exteriorized and were connected with the recorder throughout the experiment.

EXPERIMENTS

The total of 180 experiments were performed. The scheme of experiments was similar as published previously [19]. During control recording two normal consecutive phases 3 of the MMC were recorded in 48 h fasted or in non-fasted sheep (fed 18-20 h before the experiment). Then, the CCK-OP was administered at the doses 0.02, 0.2 and 2.0 µg/kg of body weight during 30 (two lower doses) and 60 seconds [21] into the jugular vein through the indwelling polyethylene catheter inserted before the experiment. The hormone was randomly injected during phase 1, 2a or 2b of the MMC identified in the duodenum. The motility recordings were continued until two consecutive phases 3 of the MMC were observed following hormone administration. After the termination of all the experiments sheep were sacrificed and positions of the electrodes and of the transducer were confirmed.

ANALYSIS OF TRACINGS AND CALCULATIONS

All the recordings were visually analysed and MMCs and their phases were identified in the small intestine, especially in the duodeno-jejunum. The onset and duration of an activity front were estimated and the duration of the whole patterns was calculated. The percentage of activity fronts observed in each segment of the small intestine was also calculated. The durations of phase 3 of the MMC and of the whole MMC pattern underwent the statistical analysis. For this purpose Student t-test for paired and unpaired values, where appropriate, preceded by ANOVA I, was applied [24].

**FIGURE 1:** The retropropagated phase 3 of the MMC following CCK-OP administration at the dose 2.0 µg/kg in non-fasted sheep. MMC is the four-phase-containing motor cycle arriving within the gastrointestinal tract in the fasting state in monogastric animals and both in fasting and fed states in ruminant intestines. Phase 1 of the MMC is the relative lack of contractions. Phases 2a and 2b of the MMC represent the gradually increased irregular motor activity and during phase 3 of the MMC the maximal, regular motor activity occurs. Transient, irregular phase 4 of the MMC terminates the MMC cycle but is not always observed. The physiological role of phase 1 of the MMC is to facilitate the rest and collection of slowly secreted digestive juices in the gastrointestinal lumen. The main roles of phases 2a, 2b and 4 of the MMC is mixing of the gastrointestinal content and its transport over the relatively short distances. Phase 3 of the MMC transports the digesta most effectively and over the longer distance. Thus it prevents harmful influences of the temporarily undesired digestive secretions upon the gastrointestinal mucosa.

Explanations: arrow indicates four minutes following the termination of CCK-OP injection. Electrode localization: 2 – duodenal bulb, 3 – duodenum, 4 and 5 – jejunum, 6 and 7 – ileum; 0.2 mV - calibration, 30 s - time
Results

In the abomasal antrum no typical MMC cycles were observed, thus the effect of CCK-OP on antral MMC could not be defined. Duration of the MMC cycle in fasted animals did not vary significantly before and after CCK-OP administration except of it highest dose given during phase 2b of the duodenal MMC (Table I). When the hormone was applied during phase 2a of the MMC, an increasing tendency in the MMC cycle length was observed. Similar tendency was seen in non-fasted sheep after the moderate dose of CCK-OP given during phase 2b of the MMC. When CCK-OP was given at the moderate dose during phase 2a of the MMC, it shortened the MMC cycle duration significantly since in three of five non-fasted sheep (and in one fasted sheep) it induced the premature phase 3 of the MMC (Table I). The highest dose of CCK-OP during phase 2b of the MMC significantly prolonged the MMC cycle.

The increase in the MMC cycle duration in response to CCK-OP administration was accompanied by inhibition of phase 3 of the MMC in the duodenum because the first phase 3 of the MMC after both higher doses of CCK-OP but especially after the higher dose started usually from the jejunum (Table II). However, its occurrence was also delayed. These changes were roughly similar in fasted and non-fasted sheep.

Duration of phase 3 of the MMC in the duodenum also differed markedly in dependence on the CCK-OP dose both in fasted and non-fasted animals. After the both higher doses of CCK-OP, phases 3 of the MMC were shortened in the duodenum significantly or the decresing tendency was observed (Table III).

First phase 3 of the MMC arriving after the highest dose of the hormone was, in most cases, abnormal. It was found to be abortive, not fully developed, less regular or in two cases even retropropagated (Fig. 1).
Table 3: Duration of duodenal phase 3 of the MMC before and after CCK-OP administration in fasted and non-fasted sheep.

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<th>CCK-OP 0.02 µg/kg</th>
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<td>ph. 1</td>
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<td>F Ctr mean</td>
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<td>F CCK mean</td>
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<td>±S.D.</td>
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<td>NF CCK mean</td>
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Explanations: duration of phase 3 of the MMC calculated in the recordings obtained from the duodenal electrode before (control, n=10) and after (n=5) CCK-OP administration. Statistical significance: Student t-test for unpaired values preceded by analysis of variance. For other explanations, see Table I.

Discussion

The presented results indicate that CCK may inhibit phase 3 of the MMC and increase cycle duration in fasted and non-fasted sheep. CCK-OP used in this study represents one of circulating forms of CCK in sheep [27]. Since OP-CCK does not cross the blood-brain barrier [7], its effect occurred following intravenous administration might be considered peripheral. The effect of CCK-OP on the MMC cycle length was significant mostly after its highest dose. Similar results were obtained in dogs [26, 29, 30]. The authors also used the relatively high doses of the hormone. No such a study has been reported in sheep, except the suggestion of GREGORY [3], thus the comparison of the doses cannot be made.

However, it is known that in sheep the dose of CCK-OP 150 pmol/kg/h, i.e. the dose below 2 pmol/kg/30 s is the maximal dose elevating the plasma CCK level to the relatively high physiologic value [31] and thus can be called the maximal physiological dose. The higher doses used in the present study which produced significant changes in the MMC cycle duration and inhibited phase 3 of the MMC in the duodenum were greater than physiologic doses suggested previously [31], although the total amount of CCK-OP infusion was not markedly different. Thus, this action can probably be interpreted as pharmacological or remain within the border between physiological and pharmacological range.

In the previous study it was suggested that CCK, as the typical digestive hormone, is able to change the interdigestive myoelectric activity to a postprandial (fed) pattern [12]. However, the myoelectric activity following CCK not always resembled the fed pattern [15]. In sheep the fed pattern formerly does not occur since the MMC is not inhibited by feeding [22].

Even if some changes in the myoelectric activity arrive after feeding, they were not accurately defined. Thus, it is difficult to state that in sheep CCK converts the interdigestive motor activity to the digestive pattern.

The inhibition of phase 3 of the MMC by CCK-OP administration was more efficient in the duodenum than in the jejum. Though the distribution of CCK receptors along the small intestine is not well known in sheep it is possible that in the duodenum the CCK receptor density is the greatest. In the dog the concentration of CCK receptors in the duodenum is higher than in the distal small bowel [13]. Furthermore, concentration of the small forms of CCK appears to be greater in the upper small bowel [28]. It has also been reported that the presence of hormone in upper small intestine is greater than in distal parts of the bowel [1].

It is also possible that the mechanism of CCK action in the duodenum can be different than in the jejunum. The inhibitory effect of CCK on duodenal phase 3 of the MMC in sheep can be expected since ONAGA et al. [16] showed that the specific CCK receptor antagonist L-364, 718 could induce the premature phase 3 of the MMC in ovine duodenum. This action seemed to be peripheral because the opposite effect after central administration of CCK antagonist was observed by KANIA et al. [11]. The differences in the regulatory mechanisms of CCK actions in the small bowel can comprise its role in somatostatin release [9, 31]. It is known that somatostatin can be directly responsible for inhibition of phase 3 of the MMC in the duodenum [28]. However, the small doses of CCK can be more active in the proximal jejunum than in the distal duodenum [8]. Thus, the exact mechanism of CCK action on the small intestinal motility is still far to be fully elucidated.

The results showed that the effect of CCK upon the small-intestinal MMC in non-fasted sheep is more pronounced than in fasted animals. CCK is the digestive hormone and long with other hormonal factors may contribute to the induction of the fed pattern and also to the inhibition of the MMC cycles [7, 10]. Notwithstanding, in ruminants its physiological role seems to be smaller than in monogastrics. In sheep there is practically no interdigestive period since the gastrointestinal flow of digesta is constant [22]. Thus, the release of CCK from intestinal mucosa can be less changeable. Herein the results indicate that the physiological role of CCK in the control of intestinal motility is not marked. Thus, the diminished role of CCK in sheep can be roughly compared with the role of motilin in this species [18].

It is concluded that CCK may increase MMC cycle duration in the small bowel and inhibit phase 3 of the MMC in the duodenum of fasted and non-fasted sheep. However, this action was observed in response to pharmacological rather than physiological dose of CCK. Thus, the present study supports the view that CCK does not play as important a role in the control of the small intestinal motility in sheep as in monogastric animals.

References


