Regional effects of cholecystokinin octapeptide on colonic phasic and tonic motility in healthy humans

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Coffin, Benoit, Sophie Fossati, Bernard Flourié, Marc Lémann, Pauline Joutet, Claire Franchisseur, Raymond Jian, and Jean-Claude Rambaud. Regional effects of cholecystokinin octapeptide on colonic tonic activity, measured by a barostat, and phasic activity, measured by manometry. On 2 consecutive days, recordings were performed in the unprepared proximal and distal colons during intravenous infusion of saline and CCK-8 at 5, 20, and 40 ng·kg⁻¹·h⁻¹. In the proximal colon CCK-8 induced, at the 20 and 40 ng·kg⁻¹·h⁻¹ doses, a tonic relaxation with an increase in intrabag volume to 156 ± 25 and 157 ± 19% of basal (P < 0.01) and a decrease in phasic activity to 72 ± 7 and 76 ± 7% of basal (P < 0.01). In the distal colon, CCK-8 induced, at the 20 and 40 ng·kg⁻¹·h⁻¹ doses, a tonic relaxation (increase in intrabag volume to 133 ± 12 and 149 ± 15%, respectively; P < 0.01), whereas phasic activity increased (128 ± 8 and 132 ± 6%, respectively; P < 0.01). Effects of CCK-8 on tonic and phasic activities are different according to the colonic segment. Because meals induce colonic tonic contraction, our results suggest that CCK, as a hormone, is not an important mediator of the response of the colon to feeding in humans.

In addition to phasic motor activity, the tonic component of the muscular activity, i.e., slow contraction or relaxation of the smooth muscle, is important to consider because it determines gut capacitance. Tonic activity can be recorded in the human colon by the electronic barostat (31). With the use of this technique in humans, dissociation between tonic and phasic activities and regional variations in tonic activity have been evidenced recently (7, 11, 19, 32).

The effects of CCK-8 on human colonic tonic and phasic activities after meal ingestion have been recently assessed by O'Brien et al. (21) using a tube assembly positioned in the cleansed transverse and left colon. These authors could not demonstrate any significant effects of intravenous administration of CCK-8 at supraphysiological levels.

The aim of the present study was to determine, in healthy subjects, the effects of CCK-8 on phasic and tonic motor activity of both proximal and distal colon. We used a tube assembly that was introduced by mouth and progressed through the whole gut (11, 17). This technique, which obviates the need of colonic cleansing and sedation for previous colonoscopy, allows a regular access to the proximal colon and does not remove the colonic contents, which can act on motor activity and propulsion.

MATERIALS AND METHODS

Subjects. Studies were performed in nine healthy volunteers (6 males, 3 females, aged 20–31 yr) with no gastrointestinal symptoms or previous abdominal surgery except for appendectomy. They gave a written informed consent to the protocol that was approved by the Ethics Committee of Saint-Louis Hospital. All volunteers were healthy on physical examination, and none was taking any medication excepted for oral contraception.

Colonic barostat and tube assembly. The barostat (Institut National de la Recherche Agronomique, Toulouse, France) maintains a constant pressure within an air-filled bag by use of a feedback mechanism that consists of a strain gauge linked by an electronic relay to an air injection-aspiration system (1). Both the strain gauge and the injection-aspiration system are connected by separate lumens to a cylindrical noncompliant bag (10 cm longitudinal axis, 450 ml capacity) made of ultrathin polyethylene. A dial in the electronic system allows selection of pressure level. When a decrease in pressure higher than 0.3 mmHg is detected by the strain gauge, the barostat injects air into the bag until the pressure is corrected to the selected pressure; conversely, a pressure increase triggers the air-aspiration system.

We used a multilumen tube assembly (10 mm OD, 3.5 m long) ending with a latex balloon and consisting of six manometric catheters and the barostat bag. Its performance has been previously validated (4). The barostat bag was...
mounted over and sealed airtight to the tube; it was connected to the strain gauge and to the air pump by two vinyl tubes. The latex balloon placed at the tip of the tube was 32 cm caudad to the bag of the barostat and could be filled with mercury and air to facilitate the progression of the tube. Six manometric ports were located 2, 7, and 12 cm distal from and proximal to the barostat bag. Manometric catheters were connected to a low-compliance perfusion system (0.1 ml/min flow rate), and phasic activity and pressure and volume of the barostat were recorded by a data processing system (Synetics-ABS, Saint-Dié, France).

Experimental procedure. After an overnight fast, participants were intubated by mouth. The progression of the tube through the small bowel was aided by inflation of the distal balloon with 15 ml air and monitored by fluoroscopic controls. When the bag of the barostat reached the colon, the distal balloon was deflated and the subject was instructed to stay in a semirecumbent position to avoid further progression of the tube. The mean duration of the progression to the colon was 30 h (range 24–36 h). On the first experimental day, the barostat bag was located in the proximal part of the colon (ascending colon, hepatic flexure, or right part of the transverse colon) and on the second experimental day in the distal part (splenic flexure, descending colon, sigmoid colon). The exact location of the barostat bag in the colon was checked by fluoroscopy at the beginning and at the end of each experiment that was performed in the nine volunteers in the proximal colon but in only six of them in the distal colon on the second experimental day, because of nonmigration of the tube in one subject and anal expulsion of the barostat bag in two others.

Recordings were performed in the fasting state. On each experimental day, the barostat bag was unfolded with 100 ml air, and thereafter completely deflated and connected to the barostat. The minimal distending pressure needed to overcome the intra-abdominal pressure was determined (11); its mean value was 9 ± 1 mmHg (range 8–11 mmHg). A pressure level in the bag 2 mmHg above the minimal distending pressure was chosen to record intrabag volume variations.

Intrabag volume and phasic motor activity were then recorded for four 60-min periods. During the first 60-min period, defined as the basal period, 50 ml of saline were continuously infused intravenously with an infusion pump (model SE 200 B, Becton Dickinson, Vial Medical, Grenoble, France). During the three subsequent 60-min periods, CCK-8 (Kinevac, Squibb, Princeton, NJ) diluted in 50 ml of sterile water was continuously infused intravenously at 5, 20, and 40 ng·kg⁻¹·h⁻¹. Data analysis. Intrabag volume recordings were visually analyzed to exclude motion artifacts and phasic events, defined as rapid changes of the volume ≥15% (4, 33). Intrabag volume was measured at 10-min intervals and then averaged for each 60-min period and expressed as a percentage of the individual basal value measured for the 60-min basal period.

A motility index (area under the curve of phasic contractions) from each perfused catheter was computerized for each 60-min period. It was expressed as a percentage of the basal value measured for the 60-min basal period. Results were averaged as orad, caudad, and overall motility indexes. Manometric recordings were also visually analyzed to detect high-amplitude propagated contractions (HAPCs). These motor events are easy to recognize because of their amplitude (>60 mmHg) and their rapid propagation over the colon (17).

Statistical analysis. Results are expressed as means ± SE. ANOVA was used to compare changes in intrabag volume and motility indexes, followed by the Newman-Keuls test for multiple comparisons. To compare basal volume in the proximal and distal colon in the six subjects who completed the entire study, the Wilcoxon-signed rank test was used. Correlations between changes of motility index and intrabag volume were assessed using the Spearman correlation test. P < 0.05 was considered to be statistically significant.

RESULTS
Basal period. In the six subjects who completed the entire study, the mean volume of the barostat bag during the basal period was not significantly different between the proximal and distal part of the colon (126 ± 17 and 98 ± 25 ml, respectively, P = 0.25). At both locations there was no significant difference between the orad and caudad motility indexes, and no HAPC was recorded.

Effects of CCK-8 on proximal colonic motility in nine healthy subjects. The intrabag volume and motility index variations after CCK-8 infusions are reported in Fig. 1. Compared with the basal period, CCK-8 produced an increase in intrabag volumes, which was significant for the 20 and 40 ng·kg⁻¹·h⁻¹ doses (156 ± 25 and 157 ± 19%, respectively; Figs. 1 and 2). Orad and caudad motility indexes, which were not different from each other (P = 0.30), and overall motility index were significantly decreased during CCK-8 infusions at the three doses (P < 0.01; Fig. 1). No significant correlation was found between areas under the curve of intrabag volumes and overall motility indexes for the three doses tested (r = 0.33, n = 27). No HAPC was recorded during the experiments.

Effects of CCK-8 on distal colonic motility in six healthy volunteers. The intrabag volume and motility index variations after CCK-8 infusions are reported in Fig. 3. Compared with the basal period, CCK-8 produced a significant increase of intrabag volume for the 20 and 40 ng·kg⁻¹·h⁻¹ doses (133 ± 12 and 149 ± 15%, respectively; P < 0.01; Figs. 3 and 4). In contrast to the proximal colon, CCK-8 increased significantly the overall, orad, and caudad motility indexes for the 20 and 40 ng·kg⁻¹·h⁻¹ doses (P < 0.01; Figs. 3 and 4). Orad and CCK-8 5 ng/kg/h CCK-20 ng/kg/h CCK-40 ng/kg/h

![Fig. 1. Effects of CCK octapeptide (CCK-8) on intrabag volume recorded by barostat and on orad, caudad, and overall motility indexes recorded by perfused catheters in proximal colon of 9 healthy subjects. Results are expressed as percentage of basal values. © 1992 by the American Physiological Society. All rights reserved.](http://ajpgi.physiology.org/)
caudad motor indexes were not different from each other \((P = 0.70)\). No significant correlation was found between areas under the curve of the intrabag volumes and overall motility indexes \((r = 0.30, n = 18)\). The increase in motility index was not related to an increase in the number of HAPCs, inasmuch as only one HAPC was recorded in four of the six subjects.

**DISCUSSION**

Using the electronic barostat and perfused catheters in the unprepared colon, we showed that the phasic and tonic motor activities of the proximal colon were decreased by the intravenously infusion of 20 and 40 \(\text{ng} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}\) of CCK-8. In the distal colon, tonic activity was also decreased, whereas phasic activity was increased by the intravenously infusion of 20 and 40 \(\text{ng} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}\) of CCK-8.

In the present study, CCK blood concentrations were not measured, and the choice of CCK-8 doses was based on previous dose-range studies using CCK-8 (Kinevac, Squibb) (12, 14, 15, 35). As reported by Kellow et al. (14, 15) and Kamath et al. (12), the concentrations of CCK-8 we delivered to the subjects were probably close to 50% of the prepared concentrations as a consequence of propensity for CCK to adhere to tube infusions. By using a specific radioimmunoassay to determine CCK blood concentrations or by measuring gallbladder volume with ultrasound, as an indirect measure of the physiological effect of CCK, these authors demonstrated that interindividual variations were weak. In their studies, the dose of 5 \(\text{ng} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}\), corresponding to \(4.4 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}\), led to blood concentrations close to those measured in the fasting state, and 20 or 17.5 \(\text{pmol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}\) led to concentrations close to those measured in the postprandial state. Infusion of 40 or 35.0 \(\text{pmol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}\) resulted in nonphysiological blood concentrations and could be regarded as a pharmacological dose.

Because of the relative inaccessibility of the human proximal colon, the effect of CCK on phasic activity in this part of the colon has been assessed only by Kellow et al. (14) and by O’Brien et al. (21). In the first study, phasic activity was assessed by one or two perfused catheters located in the unprepared ascending colon in eight healthy volunteers. Results are expressed as percentage of basal values. CCK-8 increased intrabag volume (decrease in tone) and decreased motility indexes. An inhibitory effect of CCK-8 on proximal colonic motility was also demonstrated in animal studies (16, 26). By using our method, which allows a regular access to the unprepared proximal colon of humans (11, 17), we were able to confirm a decrease in phasic activity for the three CCK-8 tested doses and also to demonstrate that 20 and 40 \(\text{ng} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}\) of CCK-8 produced a significant and simi-
lar decrease in colonic tone. Conversely, O'Brien et al. (21) could not demonstrate significant modifications in colonic tone and phasic activity in eight healthy volunteers. The authors used a very high dose of CCK-8 consisting of a 10-min infusion of 30 ng/kg followed by a 50-min infusion of 60 ng·kg$^{-1}$·h$^{-1}$. Moreover, the tube assembly was located usually in the transverse colon after previous colonic cleansing and sedation, and subjects received a 300-kcal liquid meal before infusion of CCK-8.

Several studies have previously shown that CCK, or its analog caerulein, increased phasic activity recorded by electromyography or manometry in the distal colon of healthy humans (6, 10, 20, 25, 30). As expected, we found that CCK-8 significantly increased colonic phasic activity in this part of the colon, but it decreased, at the 20 and 40 ng·kg$^{-1}$·h$^{-1}$ doses, tonic activity recorded by the barostat. This latter effect is in contradiction with the results of Niederau et al. (20) who suggested that CCK increases tone in the left colon. However, in this study, modifications of tone were estimated by changes in baseline pressure using manometric catheters, a method that is inaccurate to measure tone in a large-capacity organ such as the colon (32). Similar dissociations with decrease in tonic activity of the human distal colon and increase in phasic activity have been previously found with other experimental models. Intrarectal injection of glycerol induced a sigmoidal tonic relaxation associated with an increase in long spike burst activity (19). Likewise, the somatostatin analog octreotide produced a decrease in tone associated with an increase in phasic activity (32).

Although the electrophysiological basis of such dissociation remains to be elucidated, it suggests that phasic and tonic activities are under different mechanisms of control.

Effects of CCK are mediated by specific receptors, which have been characterized to be of type A or B. Initially, it was thought that type A receptors were located in the alimentary tract, whereas type B receptors were located in the central nervous system. Data support the fact that, in a same anatomic structure of the gut, like the lower esophageal sphincter, the two types of receptors may coexist and their specific stimulation can produce opposite motor effects (24). Distribution of each type of receptor has not been fully investigated in the human colon. With the use of specific CCK receptor antagonists, contradictory results have been obtained according to the experimental model. In dogs the decrease in fasting and postprandial colonic motility induced by loxiglumide, a CCK-A antagonist, suggests that CCK increases colonic motility by stimulating peripheral CCK-A receptors (13). In the distal colon of rats, the phasic motor response to feeding was inhibited by CCK-A and -B receptor antagonists, whereas they were inactive in the proximal colon (2). In humans, loxiglumide cannot prevent the colonic response to meals (20), suggesting that CCK is not an important mediator of the gastrocolonic response, a finding previously stated by Renny et al. (25) during study of myoelectric activity of the human distal colon.

Division of the human colon into two segments, proximal and distal, is based on differ embryology, innervation, and blood supply (3). In vitro and in vivo animal studies in rabbit and cat demonstrated regional differences in motor response to electrical stimulation (28) or to neuropeptides (29). In humans, in vitro and in vivo studies showed regional differences in viscoelastic properties or motor responses to physiological stimulations or distensions (7, 8, 34). Transit studies by scintigraphy also demonstrated regional differences, inasmuch as the right and transverse colon acted

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Fig. 4. Recordings of intrabag volume and phasic motility in distal colon before (A) and during (B) intravenous infusion of 20 ng·kg$^{-1}$·h$^{-1}$ of CCK-8. Tracings 1, 2, 3, 4, 5, and 6 refer to perfused catheters located 2, 7, and 12 cm proximal to and distal from barostat bag. Tracing 7 is volume registration. Note that intrabag volume increased (decrease in tone) in association with increase in phasic motility.
mainly as a reservoir, whereas the left colon acted mainly as a conduit (22, 23). Reasons underlying such regional differences remain largely undetermined. In addition to anatomic differences, some intraluminal factors, such as bacterial flora or products resulting from its metabolism, which are known to be different between the ascending and transverse colon (5), may participate in the regulation of colonic motility.

With the use of electronic barostat and perfused catheters, it has been shown that a meal produced an increase in both human colonic tonic and phasic activities (7, 11), but the magnitude of this response was different according to colonic segments. In the ascending and transverse colon, the increase in tone after eating appears to be the main event, whereas in the descending and sigmoid colon both the phasic and tonic activities increase significantly (7, 11). The decrease in tone at both locations and the decrease in phasic activity in the proximal colon that we demonstrated in the present study after intravenous infusion of CCK-8 at a dose corresponding to blood levels measured in postprandial period are the opposite of what it would be expected if CCK by its humoral effect played an important role on the colonic motor response triggered by a meal. Because intravenous CCK-8 poorly crosses the blood-brain barrier (36), our results do not exclude that CCK, acting as a hormone, participates in the regulation of colonic motility.

In summary, intravenous administration of CCK-8 at physiological and supraphysiological levels modifies tonic and phasic activities of the unprepared colon in healthy subjects. However, our results as well as others (20, 21) do not support that CCK, acting as a hormone, is an important mediator of the response of the colon to feeding.

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