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Role of Spinal Afferents and Calcitonin Gene-Related Peptide in the Postoperative Gastric Ileus in Anesthetized Rats

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Objective
The object of this study was to investigate the mechanisms of postoperative gastric ileus in an experimental model of abdominal surgery in anesthetized rats.

Summary Background Data
Sensory neurons partly mediate postoperative gastric ileus. Among other neuropeptides, sensory neurons contain calcitonin gene-related peptide (CGRP) and release CGRP in response to noxious stimulation. Because CGRP inhibits gastric motility, it was hypothesized that abdominal surgery stimulates sensory neurons, which then releases CGRP, thereby inhibiting gastric motility.

Methods
Postoperative ileus was induced by abdominal surgery. Gastric corpus motility was measured by an intragastric catheter. CGRP action was blocked by CGRP immunoneutralization or by a CGRP receptor antagonist. Spinal sensory neurons were ablated by application of a sensory neurotoxin (capsaicin) to the celiac and superior mesenteric ganglia.

Results
Abdominal surgery decreased gastric corpus motility in the first 5 minutes after abdominal surgery by 59 ± 5% and by 24 ± 4% during the 1st postoperative hour. Capsaicin pretreatment of the celiac and superior mesenteric ganglia, CGRP immunoneutralization, or CGRP receptor antagonism reversed the postoperative decrease in gastric corpus motility during the 1st postoperative hour by 50%, 100%, and 59%, respectively.

Conclusions
These data indicate that spinal sensory neurons and CGRP partly mediate postoperative gastric ileus. CGRP may be released from spinal sensory neuron terminals in the celiac and superior

mesenteric ganglia as part of an extraspinal intestinogastric inhibitory reflex activated by abdominal surgery.

Abdominal surgery is known to cause disturbances of gastrointestinal motility at all levels of the gastrointestinal tract. The duration of postoperative ileus is variable; usually, gastric ileus lasts about 24 to 48 hours after surgery. However, there are patients in which the duration of ileus is considerably longer, and gastric decompression by nasogastric tubing might be necessary for several days.[1-3]

Abdominal surgery in rats causes inhibition of gastric emptying,[4-6] and the mechanisms of postoperative gastric ileus have been studied using rats as an experimental model. Studies of gastric emptying after abdominal surgery have shown that an increased sympathoadrenergic tone,[4,7,8] vagal nonadrenergic noncholinergic inhibitory pathways,[9] and spinal adrenergic pathways[10] are involved. However, despite these insights into the efferent transmission mechanisms, there is still a need for clinically useful agents for the treatment of postoperative gastric ileus.[2]

By treating newborn rats systemically with the neurotoxin capsaicin, Holzer et al.[11,12] demonstrated that afferent C fibers partially mediate postoperative small intestinal and gastric ileus. Similarly, Barquist et al.[13] found that capsaicin-sensitive afferent pathways partially mediate inhibition of gastric emptying after abdominal surgery. Capsaicin-sensitive afferent nerve fibers throughout the gastrointestinal tract are known to contain neuropeptides including calcitonin gene-related peptide (CGRP).[14,15] Recently, it has been shown that CGRP is released from visceral sensory neurons by noxious stimulation.[16]

Because the systemic administration of CGRP inhibits gastrointestinal transit[17] and central or peripheral administration of CGRP delays gastric emptying,[18] we hypothesized that CGRP, released from spinal sensory neurons by abdominal surgery, might inhibit gastric motility and thus be a principal agent causing postoperative gastric ileus. In the present study, this hypothesis was tested in a rat model using a monoclonal antibody to immunoneutralize CGRP and a CGRP receptor antagonist, human $CGRP_{8-37}$. The monoclonal antibody to rat CGRP has been shown to reverse the effect of CGRP on gastric acid secretion and on somatostatin release in rats.[19] Human $CGRP_{8-37}$ is able to reverse in a dose-dependent manner the inhibitory action of CGRP on opossum and guinea pig smooth muscle cells.[20,21]

METHODS

Animals

Experiments were performed on male Sprague-Dawley rats (Harlan Sprague Dawley, San Diego, CA) weighing 200 to 250 g and fasted for 16 to 24 hours but allowed water *ad libitum* before the experiments. The rats were housed under conditions of controlled temperature (22 ± 1 C) and illumination (lights on 6 A.M. to 6 P.M.). The institutional guide for the care and use of laboratory animals was followed throughout the study.

Drugs

The CGRP monoclonal and KLH antibodies were obtained from John Walsh and Helen Wong (CURE/UCLA Digestive Diseases Center, Los Angeles, CA; Antibody Core National Institutes of Health Grant DK41301). The $CGRP_{8-37}$ was from S. St-Pierre (INRS Santé, Point-Claire, Québec, Canada). All other chemicals were purchased from Sigma (St. Louis, MO).

Recording of Gastric Corpus Motility

The rats were anesthetized with urethane (1.25 g/kg intraperitoneally), and a cannula was placed into the trachea to ensure a clear airway. A catheter was introduced either into the jugular vein, the femoral vein, the splenic artery, or into the cisterna magna (see experimental protocols). The stomach was exposed by an upper abdominal midline incision, a silastic catheter (2-mm inner diameter and 3.2-mm outer diameter) was introduced into the gastric corpus through an incision in the forestomach; the pylorus was ligated. The stomach was gently flushed with warm saline and allowed to drain freely for at least 60 minutes. Baseline intragastric pressure was standardized to 5 cmH_2O. Gastric corpus motility was recorded by a Gould Statham P23ID pressure transducer and a Beckman R 611 pen recorder.

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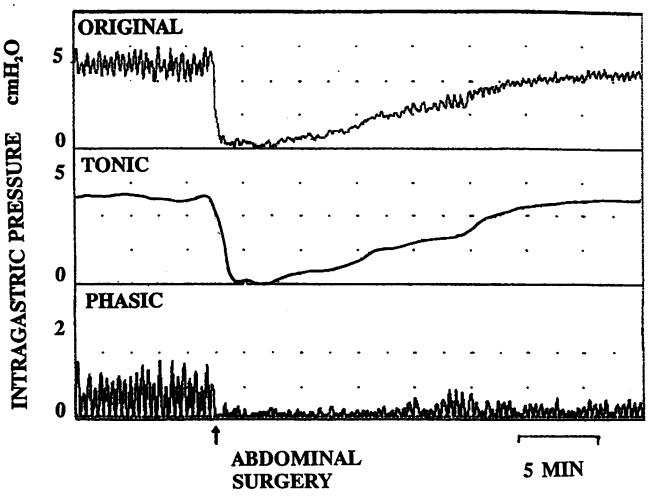

Figure 1. Original trace of gastric corpus motility and effect of abdominal surgery (upper panel). Division of original trace into gastric tone (middle panel) and gastric phasic contractions (lower panel) by software developed in collaboration with S. N. Reddy.

Data Acquisition and Analysis

Pressure signals were acquired and analyzed on a personal computer system employing GiPC software by Redtech (developed by S. N. Reddy). The signals were precalibrated in centimeters of water. Preprocessing was used to remove artifacts, and the signals were filtered to remove noise. A given pressure signal was then decomposed into tonic and phasic components by detecting the start and end of each contraction and curve fitting the result over the duration of the signal (Fig. 1). This yielded a tonic component representing the gastric tone and a phasic component representing the contractile activity. The motility index (MI) was then calculated for each of the three signals, that is, the total, tonic, and phasic signals, as the area under the curve. The tonic area represented 93 ± 0.6% (range, 72% to 99%) of the total area, depending on the gastric corpus motility recordings.

The baseline gastric corpus MI for the total, tonic, and phasic components was set at 100% and represented the mean of three time periods preceding the induction of gastric ileus or injection of CGRP. Data for experiments 1 to 3 represented the MIs of 5-minute periods of recordings, and experiment 4 represented the areas of 2-minute periods.

Abdominal Surgery (Induction of Postoperative Gastric Ileus)

Sixty minutes after implantation of the recording catheter and after an additional 30 minutes of baseline recording, the cecum was exposed through a lower abdominal midline incision, wrapped in a compress soaked with warm saline, and gently manipulated for 1 minute. The cecum was returned into the abdominal cavity, and the wound was closed with metal clips.

Experimental Protocols

Experiment 1: Effect of CGRP Monoclonal Antibody or CGRP Antagonist Intravenously on Abdominal Surgery-induced Inhibition of Gastric Corpus Motility:

The rats were prepared as described earlier. The vehicle (bovine serum albumin [BSA] 0.1%, 300 μL/hr, n = 7) or $CGRP_{8-37}$ (10 nmol in 300 μL of BSA 0.1%, bolus 5 nmol, followed by a continuous infusion of 10 nmol/hr) was infused continuously through the jugular vein starting 20 minutes before the abdominal surgery. The CGRP monoclonal antibody (2 mg in 1 mL of BSA 0.1%, n = 6) or control antibody (KLH antibody, 1.8 mg in 1.2 mL of BSA 0.1%, n = 2) was given as a bolus through the jugular vein 1 hour before the abdominal surgery.

Experiment 2: Effect of CGRP Antagonist Through the Splenic Artery or the Cisterna Magna on Abdominal Surgery-induced Inhibition of Gastric Corpus Motility:

To determine the site of action of the CGRP antagonist, the rats were prepared as described earlier, and a catheter was implanted into either the splenic artery close to the stomach or the cisterna magna. $CGRP_{8-37}$ was given through the splenic artery (a bolus of 5 nmol followed by a continuous infusion of 10 nmol/hr, n = 4) or injected slowly into the cisterna magna (6.7 nmol of $CGRP_{8-37}$ in 25 μL of BSA 0.1%, n = 4, or 25 μL of BSA 0.1%, n = 2) 20 minutes before abdominal surgery.

Experiment 3: Effect of Capsaicin Pretreatment of Celiac and Superior Mesenteric Ganglia on Abdominal Surgery-induced Inhibition of Gastric Corpus Motility:

Fourteen days before the experiment, the rats were anesthetized with pentobarbital (50 mg/kg intraperitoneally), and the celiac and superior mesenteric ganglia were exposed and treated with either vehicle (0.1 mL of Tween 80 in olive oil) or capsaicin (1%) as described previously.[22] Fourteen days after capsaicin (n = 4) or vehicle (n = 3) pretreatment of the celiac and superior mesenteric ganglia, the rats were prepared as described earlier, and the vehicle (300 μL/hr) was infused through the jugular vein starting 20 minutes before the abdominal surgery.

Table 1. EFFECT OF ABDOMINAL SURGERY ON GASTRIC CORPUS MOTILITY

	Motility Index		
Time* (min)	Total	Tone	Phasic
0-5	41 ± 5	43 ± 6	17 ± 7†
5-10	56 ± 6	58 ± 6	54 ± 11
15-20	75 ± 6	76 ± 6	83 ± 23
25-30	80 ± 6	81 ± 5	82 ± 26
35-40	84 ± 6	85 ± 6	81 ± 40
45-50	82 ± 5	84 ± 5	62 ± 30
55-60	86 ± 5	88 ± 5	77 ± 22
0-60	76 ± 4	77 ± 4	76 ± 21

Results are expressed as percent of preoperative motility index (mean ± SEM).
* Time periods after abdominal surgery.
† $p < 0.05$ *versus* tonic.

Table 2. EFFECT OF CGRP MONOCLONAL ANTIBODY OR CGRP RECEPTOR ANTAGONIST ON THE INHIBITION OF GASTRIC CORPUS MOTILITY AFTER ABDOMINAL SURGERY

	Treatment		
Time* (min)	Vehicle	CGRP Mab	$CGRP_{8-37}$
0-5	41 ± 5	48 ± 5	52 ± 5
5-10	56 ± 6	67 ± 6†	67 ± 5†
15-20	75 ± 6	103 ± 6‡	87 ± 6
25-30	80 ± 6	110 ± 6§	93 ± 5
35-40	84 ± 6	115 ± 7‡	100 ± 6
45-50	82 ± 5	112 ± 5§	102 ± 4‡
55-60	86 ± 5	108 ± 6‡	104 ± 5†
0-60	76 ± 4	100 ± 5‡	90 ± 4†

Results are expressed as percent of preoperative gastric corpus motility (mean ± SEM).
* Time periods after abdominal surgery.
† $p < 0.05$ *versus* vehicle.
‡ $p < 0.01$ *versus* vehicle.
§ $p < 0.001$ *versus* vehicle.

Experiment 4: Effects of CGRP Intravenously on Gastric Corpus Motility:

A dose of CGRP of 1 to 100 pmol was injected through the jugular vein (n = 14, not all doses tested in each animal). The effects on gastric corpus motility were recorded for 10 minutes.

Statistics

The data are presented as the mean ± the standard error of mean (SEM). Differences between treated groups were determined by analysis of variance followed by Fisher's least significant differences test. A probability level of $p < 0.05$ was taken as significant.

RESULTS

Experiment 1: Effect of CGRP Monoclonal Antibody or CGRP Antagonist Intravenously on Abdominal Surgery-Induced Inhibition of Gastric Corpus Motility

Abdominal surgery caused an initial decrease in gastric corpus motility consisting of a decrease in both the gastric tone and the amplitude of phasic contractions (Fig. 1). Gastric corpus motility gradually returned toward the preoperative level but was still decreased after 1 hour (Table 1).

Administration of CGRP monoclonal antibody or CGRP receptor antagonist did not significantly change gastric corpus motility (total MI preceding abdominal surgery for CGRP monoclonal antibody, 100 ± 3%, n = 8; for $CGRP_{8-37}$, 96 ± 3%, n = 4). The initial decrease in gastric corpus motility (0 to 5 minutes) was not significantly altered by the different treatments (Table 2). However, treatment with the CGRP monoclonal antibody or CGRP antagonist significantly improved the recovery of gastric corpus motility after abdominal surgery. Both treatment groups showed significant improvement of gastric corpus motility in the 5- to 10-minute period after abdominal surgery. In the 55- to 60-minute period after abdominal surgery, gastric corpus motility of the CGRP monoclonal antibody and the CGRP receptor antagonist treatment groups were not significantly different from the preoperative level; the gastric corpus motility was still decreased in the vehicle-treated group. The total area under the curve calculated for 1 hour after abdominal surgery was significantly increased in both CGRP monoclonal antibody- and $CGRP_{8-37}$-treated groups (Table 2 and Figs. 2 and 3).

KLH antibody treatment had no significant effect on the postoperative gastric corpus motility compared with vehicle treatment (total MI at 0 to 60 minutes for vehicle, 76 ± 4%; KLH antibody, 83 ± 12%; not significant).

Further analysis of recordings by dividing the signal into tonic and phasic areas showed that abdominal surgery decreased phasic contractions more than gastric tone (at 0 to 5 minutes with vehicle, tonic MI, 43 ± 6%; phasic MI, 17 ± 7%; $p < 0.05$). This was similar in all treatment groups with no significant differences between the groups.

The return of gastric tone to control levels after abdominal surgery in CGRP monoclonal antibody-or CGRP receptor antagonist-treated rats was similar to the

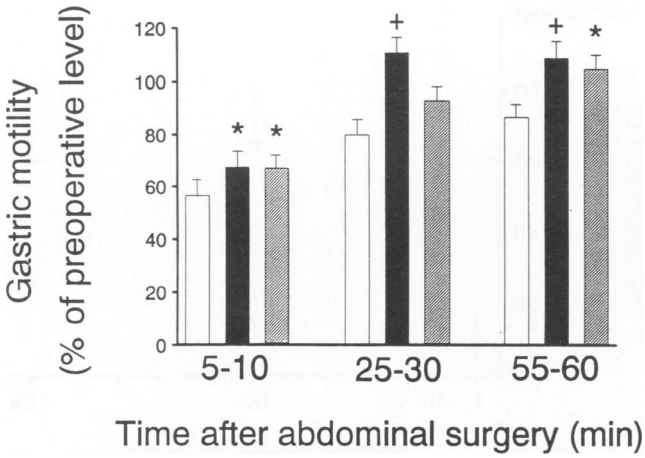

Figure 2. Effect of vehicle (intravenous, □), CGRP monoclonal antibody (2 mg intravenous, ■), or $CGRP_{8-37}$ (10 nmol/kg/hr intravenous, ▨) on recovery of gastric corpus motility from abdominal surgery. The preoperative gastric corpus motility was set at 100%. The values represent 5-minute segments of the area under the curve ± SEM.

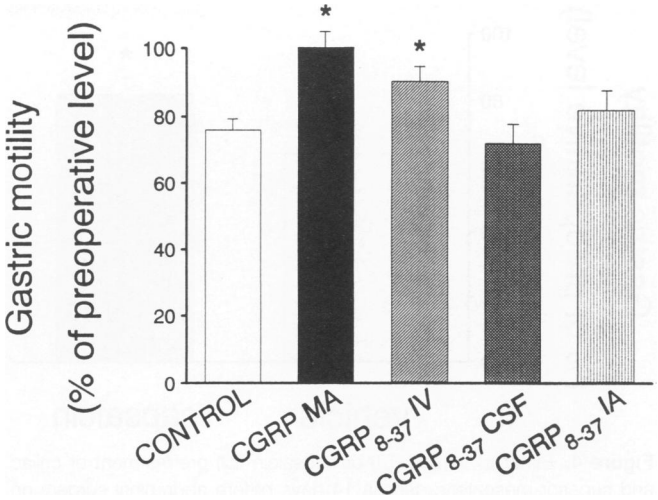

Figure 3. Effect of vehicle (□), CGRP monoclonal antibody (MA, 2 mg intravenous, ■), and $CGRP_{8-37}$ (10 nmol/kg/hr intravenous, ▨; 6.7 nmol into the cerebrospinal fluid, ▩; 10 nmol/kg/hr intra-arterially close to the stomach, □) on postoperative gastric corpus motility. The preoperative gastric corpus motility was set at 100%. The values represent the area under the curve of the 1st hour after abdominal surgery ± SEM.

total gastric corpus motility (tonic MI at 0 to 60 minutes for vehicle, 77 ± 4%; CGRP monoclonal antibody, 100 ± 4% [$p < 0.01$ *vs.* vehicle]; $CGRP_{8-37}$, 86 ± 4% [not significant *vs.* vehicle]). However, the recovery of phasic contractions from abdominal surgery was less by the CGRP monoclonal antibody or $CGRP_{8-37}$ treatments than was the recovery of gastric tone. For the recovery of phasic contractions from postoperative gastric ileus, significant improvements could only be shown in the $CGRP_{8-37}$ treatment group (phasic MI at 0 to 60 minutes for vehicle, 76 ± 21%; CGRP monoclonal antibody, 106 ± 23% [not significant *vs.* vehicle]; $CGRP_{8-37}$, 140 ± 20% [$p < 0.05$ *vs.* vehicle]).

The return of regular phasic contractions of the stomach after abdominal surgery seemed to be more rapid after CGRP monoclonal antibody or CGRP antagonist treatment. However, this was not statistically significant (saline, 11.4 ± 2 minutes; CGRP monoclonal antibody, 6.9 ± 2.7 minutes; $CGRP_{8-37}$, 6.6 ± 2.4 minutes).

Experiment 2: Effect of CGRP Antagonist Through the Splenic Artery or the Cisterna Magna on Abdominal Surgery-Induced Inhibition of Gastric Corpus Motility

There were no significant differences in gastric corpus motility after abdominal surgery with CGRP receptor antagonist administered through the splenic artery or the cisterna magna compared with vehicle (total MI at 0 to 60 minutes for vehicle intravenously, 76 ± 4%; $CGRP_{8-37}$ intra-arterially, 82 ± 6% [not significant *vs.* vehicle]; vehicle into cisterna magna, 75 ± 8% [not significant *vs.* vehicle].

Experiment 3: Effect of Capsaicin Pretreatment on Celiac and Superior Mesenteric Ganglia on Abdominal Surgery-Induced Inhibition of Gastric Corpus Motility

The total MI of gastric corpus motility calculated for 1 hour after the abdominal surgery was significantly improved in the capsaicin pretreatment group (total MI at 0 to 60 minutes for vehicle pretreatment, 64 ± 7%; capsaicin pretreatment, 82 ± 5%; $p < 0.05$ *vs.* vehicle pretreatment). The first significant improvement of capsaicin pretreatment compared with vehicle pretreatment occurred in the 25- to 30-minute period after abdominal surgery (total MI at 25 to 30 minutes for vehicle pretreatment, 68 ± 8%; capsaicin pretreatment, 91 ± 7%; $p < 0.05$ *vs.* vehicle pretreatment, Fig. 4).

Experiment 4: Effects of CGRP on Gastric Corpus Motility

Administration of CGRP (1 to 100 pmol intravenously) decreased the gastric tone and amplitude of phasic contractions in a dose-dependent manner. Phasic contractions were inhibited more than the gastric tone with doses of CGRP of 20 pmol or more. The maximal decrease of gastric corpus motility (total MI), gastric tone, and phasic contractions was achieved with a CGRP dose of 20 pmol. Higher doses were not significantly more effective (Table 3 and Fig. 5).

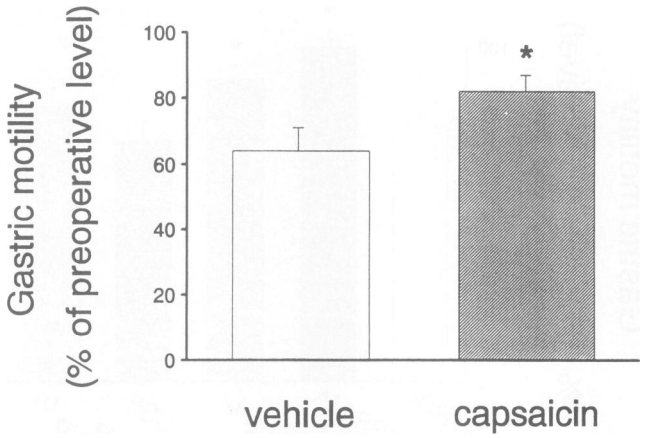

Figure 4. Effect of vehicle (□) or capsaicin (▨) pretreatment of celiac and superior mesenteric ganglia 14 days before abdominal surgery on postoperative gastric corpus motility. Preoperative gastric corpus motility was set at 100%. The values represent the area under the curve of the 1st hour after abdominal surgery ± SEM.

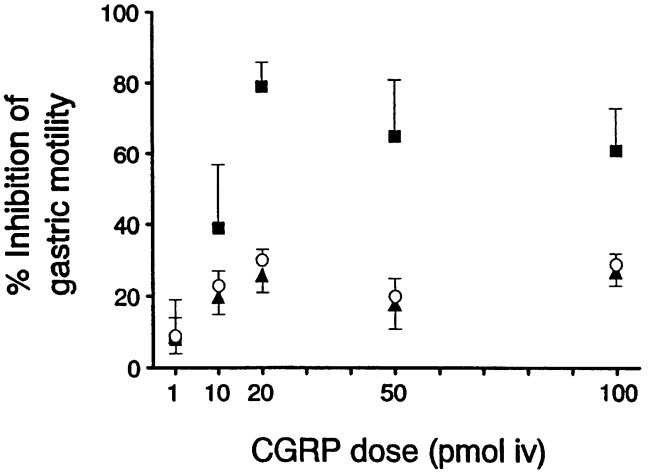

Figure 5. Effect of intravenous CGRP on gastric corpus motility. Gastric corpus motility before CGRP administration was set at 100%. The values represent the gastric corpus motility of 2-minute segment (total area under the curve, ○; phasic contractions, ■; gastric tone, ▲) ± SEM.

DISCUSSION

The present study demonstrates that abdominal surgery causes a marked and sustained decrease in gastric corpus motility, in part, through a neural pathway involving capsaicin-sensitive spinal afferent neurons and CGRP. Our data were obtained in a model placing a recording catheter into the stomach of anesthetized rats. It has to be kept in mind that preparatory surgery and the presence of a recording catheter could influence gastric corpus motility. However, gastric corpus motility was standardized after preparatory surgery so that we were looking at changes relative to a baseline recording that was the same in all rats. A recovery period of 90 minutes was allowed after preparatory surgery; other studies have allowed as little as 20 minutes.[23] Furthermore, evaluation of gastric corpus motility is not possible without placing a recording device into the stomach or electrodes on the serosal surface of the stomach. Despite this pitfall, recording of gastric corpus motility and its components of gastric tone and phasic motor activity have been shown to be important determinants of gastric emptying,[25] and recording of gastric corpus motility is an established model to evaluate gastric motor function.[9,12,23,24,26] Thus, our results provide important insight into the mechanisms and pathways by which abdominal surgery inhibits gastric motor function to produce postoperative gastric ileus.

It has been shown previously that abdominal surgery inhibits gastric emptying[13] and gastrointestinal transit[11] in rats and that capsaicin-sensitive pathways are in-

Table 3. EFFECTS OF CGRP ON GASTRIC CORPUS MOTILITY

Time* (min)	CGRP 1 pmol (n = 13)			CGRP 10 pmol (n = 12)			CGRP 20 pmol (n = 7)			CGRP 100 pmol (n = 14)		
	Total†	Tone‡	Phasic§	Total	Tone	Phasic	Total	Tone	Phasic	Total	Tone	Phasic
0-2	91 ± 4	91 ± 3	92 ± 11	77 ± 4	80 ± 3	61 ± 18	70 ± 3	74 ± 3	21 ± 7¶	71 ± 3	76 ± 4	39 ± 12¶
2-4	92 ± 3	93 ± 4	74 ± 11	82 ± 5	85 ± 5	78 ± 16	75 ± 3	78 ± 3	40 ± 8‖	76 ± 2	81 ± 5	58 ± 11
4-6	97 ± 4	98 ± 5	70 ± 10	94 ± 5	97 ± 5	89 ± 13	92 ± 3	96 ± 3	43 ± 6¶	94 ± 3	98 ± 8	90 ± 16
6-8	98 ± 4	100 ± 4	79 ± 9	101 ± 4	106 ± 5	85 ± 13	100 ± 4	102 ± 3	85 ± 20	103 ± 4	109 ± 8	101 ± 13
8-10	92 ± 5	95 ± 5	72 ± 10	102 ± 3	107 ± 4	85 ± 12	104 ± 4	105 ± 3	125 ± 47	107 ± 4	112 ± 9	136 ± 21

Results are expressed as percent of gastric corpus motility before CGRP administration (mean ± SEM).
* Time periods after CGRP administration.
† Total = area under the curve.
‡ Tone = area under the curve of gastric tone.
§ Phasic = area under the curve of phasic contractions.
‖ $p < 0.01$ *versus* tonic.
¶ $p < 0.001$ *versus* tonic.

volved. Capsaicin is the pungent substance in red peppers of the genus Capsicum. When given either systemically or locally, it produces a functional ablation of neurons with primary afferent C fibers and depletes the terminal fields of these neurons of its neuropeptides, such as substance P and CGRP.[27] The present study extends previous findings by demonstrating, through selective ablation of the spinal afferent innervation to the gastrointestinal tract, that it is the visceral spinal afferent innervation that is partly mediating the postoperative gastric ileus. Capsaicin pretreatment of the celiac and superior mesenteric ganglia blocked by 50% the postoperative gastric corpus motility inhibition, the same amount as systemic capsaicin pretreatment blocked postoperative inhibition of gastric emptying.[13]

The present study also demonstrated that CGRP partly mediates inhibition of gastric corpus motility in response to abdominal surgery. Immunoneutralization of CGRP or CGRP receptor blockade significantly hastened the recovery of gastric motility to preoperative levels. CGRP is contained in spinal afferents terminating in the wall of the gastrointestinal tract.[14,15,28] Both central and peripheral terminal fields of sensory neurons can release CGRP in response to stimulation.[28–31] CGRP could be released into the systemic circulation and may act as a hormone.[32,33] In our model, increased plasma levels of CGRP, released from cecal afferents during manipulation, could inhibit gastric corpus motility by acting on CGRP receptors on gastric smooth muscle cells.[34,35] However, infusion of the CGRP receptor antagonist into the splenic artery close to the stomach failed to improve postoperative gastric corpus motility. Thus CGRP is unlikely to be acting through the circulation on gastric smooth muscle cell CGRP receptors.

CGRP could also be released from spinal afferent neurons as part of an intestinointestinal inhibitory reflex. In the celiac and superior mesenteric ganglia, CGRP-containing afferent fibers have been found to synapse with efferent sympathetic neurons[36] and to form dense terminallike plexuses encircling many of the ganglionic cells.[37] Therefore, CGRP-containing elements in the prevertebral ganglia might represent the afferent limb of an existing peripheral intestinointestinal reflex arch.[24,38] Both spinal afferents and CGRP have been shown to be part of an intestinointestinal inhibitory reflex.[24,38–40] Thus, abdominal surgery could induce CGRP release from spinal afferents in the celiac and superior mesenteric ganglia, thereby activating inhibitory spinal efferents.

CGRP release could also be part of a spinal or supraspinal intestinointestinal reflex, which has been shown to exist.[39] The highest concentrations of CGRP in the brain are found in the medulla oblongata, and CGRP receptors have been identified at various sites in the brain stem.[15,41] Injection of the CGRP receptor antagonist into

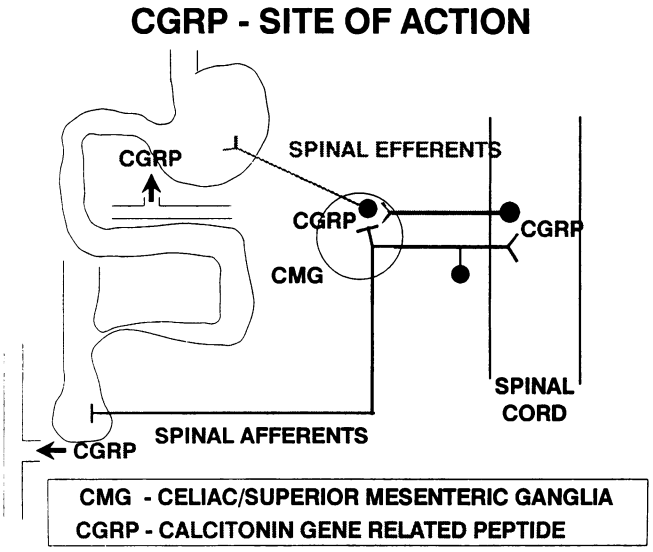

Figure 6. Possible sites of action of CGRP released from spinal afferent neurons by abdominal surgery. CGRP could either be released at the cecum, the celiac and superior mesenteric ganglia, or the dorsal horn of the spinal cord. For additional comments, see the discussion section.

the cerebrospinal fluid through the cisterna magna failed to improve postoperative gastric ileus. This is in accordance with our finding that intravenous CGRP monoclonal antibody was effective in improving postoperative gastric ileus because antibodies do not cross the blood–brain barrier. Possibly, other neuropeptides, such as corticotropin-releasing factor, might be involved in the transmission of a supraspinal intestinointestinal reflex.[42] Therefore, at present, the evidence favors a role of CGRP and spinal afferents in a reflex through the celiac and superior mesenteric ganglia.

CGRP has been shown to delay gastric emptying[16,17] and to produce a sustained relaxation of longitudinal muscle from rat fundus *in vitro*.[43] We investigated the effect of CGRP on gastric corpus motility *in vivo*. Administration of CGRP caused a dose-dependent decrease of gastric corpus motility. Phasic contractions were decreased more strongly than was gastric tone, thus resembling the pattern of abdominal surgery-induced decrease in gastric corpus motility.

To summarize our experiments, we found that spinal afferents play a major role in the inhibition of gastric motility induced by abdominal surgery. Our results support the idea that CGRP could be released from the spinal afferents at the celiac and superior mesenteric ganglia level. However, we cannot exclude the possibility that CGRP acts as a neurotransmitter in the dorsal horn of the spinal cord (Fig. 6). CGRP probably does not act as a hormone through the blood circulation directly on CGRP receptors on gastric smooth muscle cells or on CGRP receptors in the brain stem. Intravenous CGRP inhibited gastric corpus motility, which resembled ab-

dominal surgery-induced inhibition of gastric corpus motility.

At this point, it is impossible to determine whether our findings have a clinical correlation. Our data demonstrated an important sensory mechanism that may contribute to postoperative ileus in patients. Blockade of sensory input during or after surgery may be a useful clinical approach in the reduction of postoperative gastric ileus. This has to be addressed by future studies.

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