Responses of celiac and cervical vagal afferents to infusions of lipids in the jejunum or ileum of the rat

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Responses of celiac and cervical vagal afferents to infusions of lipids in the jejunum or ileum of the rat. Am. J. Physiol. Regulatory Integrative Comp. Physiol. 278: R34–R43, 2000.—Multiunit celiac and single-unit cervical recordings of vagal afferents were performed before and during infusions of fatty acids, triglycerides, or saline into either the ileum or jejunum of the rat. In multiunit recordings, lipids increased activity of vagal afferents to a greater extent than saline. The greatest increases in vagal afferent activity resulted from infusions of linoleic acid, conjugated linoleic acid, or oleic acid. The triglycerides, corn oil or Intralipid, were less effective than the fatty acids in affecting vagal afferent activity. Ileal pretreatment with the hydrophobic surfactant Pluronic L-81 significantly attenuated the response of celiac vagal afferents to ileal infusion of linoleic acid. Single-unit recordings of cervical vagal afferents supported the multiunit data in showing lipid-induced increased vagal afferent activity in ~50% of ileal units sampled and 100% of a limited number of jejunal units sampled. These data demonstrate that free fatty acids can activate ileal and jejunal vagal afferents in the rat, and this effect can be attenuated by pretreatment with a chylomicron inhibitor. These data are consistent with the view that lipid-induced activation of vagal afferents could be a potential substrate for the inhibitory effects of intestinal lipids on gastrointestinal function, food intake, and body weight.

fatty acids; triglycerides; safety

GASTROINTESTINAL FUNCTION and food intake are affected by the presence of lipids in the small intestine. Infusion of lipids in the duodenum has been shown to suppress short-term food intake, suppress body weight gain, inhibit gastric secretions, and reduce total daily energy intake in the rat (5, 11, 22, 25). The rate of basal electrical activity of the gastric antrum in the cat is decreased after infusions of long-chain lipids, but not short-chain lipids, in the duodenum (13). Acute infusion of lipids in the ileum inhibits gastric emptying, inhibits food intake, and delays the transit of a meal through the stomach and small intestine in the rat and dog (3, 4, 10, 14, 17). These outcomes suggest that methods to control the release of intestinal lipids in humans could provide important clinical benefits in terms of controlling appetite and potentially body weight.

The specific mechanisms underlying each of these actions of intestinal lipids are not well understood. It is likely that they differ as a function of intestinal segment and/or that multiple, independent mechanisms may contribute to the effects of infusions of lipids within an intestinal segment (11). However, evidence from several studies indicates that the integrity of vagal afferents is important for many of these effects of lipids on gastrointestinal function. Celiac vagotomy abolishes the suppression of short-term food intake produced by infusion of oleic acid in the duodenum of the rat (22). Capsaicin treatment of the cervical vagus eliminates the inhibitory effect of duodenal infusions of 5% lipid emulsions on gastric secretions, but not 10 or 20% lipid emulsions (11). The inhibitory effect of duodenal infusions of long-chain lipids on basal electrical activity of the gastric antrum in the cat is eliminated by bilateral vagotomy (13).

There is only limited evidence that lipids activate vagal afferents with receptive fields in the small intestine. Direct evidence derives from the study of Melone (12), who found two classes of lipid-sensitive vagal afferents in the cat with receptive fields in the duodenum and jejunum. One class responded preferentially to administration of either glycerol or short-chain fatty acids, and a second class responded preferentially to long-chain fatty acids. Indirect evidence derives from studies showing that perivagal capsaicin pretreatment markedly attenuates the increase in c-Fos expression normally observed in the nucleus of the solitary tract, area postrema, and paraventricular nucleus after duodenal infusions of Intralipid in the rat (15).

Collectively, these data are consistent with the view that lipid-induced activation of vagal afferents may contribute to the effects of lipids on gastrointestinal function and caloric intake. At the present time, there is no direct electrophysiological evidence of lipid-induced activation of vagal afferents with receptive fields in the ileum or jejunum of the rat. The purpose of the following experiments was to determine if vagal afferents respond to localized infusions of lipids in either the jejunum or ileum of the rat.
METHODS

Subjects

Male Sprague-Dawley rats were obtained from Harlan in Pratville, AL. Rats were housed in plastic cages under a 12:12-h light-dark cycle. Food and water were available on an ad libitum basis. All rats weighed between 250 and 350 g at the time of testing. All studies were approved by the Animal Care and Use Committee at the University of Alabama at Birmingham.

Apparatus

Vagal afferents were recorded monopolarly using a silver-silver chloride electrode. Action potentials were displayed on a storage oscilloscope after initial amplification through a low-noise amplifier. In studies of celiac vagal afferents, multiunit potentials were recorded from whole nerve and discriminated from noise with a conventional window discriminator. In studies of cervical vagal afferents, single-unit potentials were recorded from fine filaments of nerve bundle and isolated using an analog delay circuit (BAK DDIS-1). All data were saved on a computer.

General Surgical Procedures

Each rat initially received an intraperitoneal administration of 50 mg/kg of pentobarbital sodium (Nembutal, Abbott Labs, North Chicago, IL). Catheters were inserted into the trachea for artificial ventilation, left femoral artery for recording of arterial blood pressure, and left femoral vein for continuous administration of anesthesia. The rats were then paralyzed with pancuronium bromide (0.4 mg/h), artificially ventilated (60 breaths/min), and maintained on continuous administration of anesthesia. The rats were then isolated using an analog delay circuit (BAK DDIS-1). All data were saved on a computer.

Procedure

1. Baseline unit activity was recorded for 100 s before infusion of a test substance and served as the control period. The substance was then infused at a rate of ~0.03 ml/s, and activity was recorded for an additional 600 s. Infusion volume was 1 ml and was followed by a 1 ml air flush at a rate of ~0.03 ml/s. Air flushes were used to move the test infusate remaining in the infusion catheter into the lumen and also to move the test infusate further along the length of tissue such that the 25 cm length was coated.

2. In some of the experiments, linoleic and oleic acid were tested in both the ileum and jejunal segments. In most cases, however, this was not possible. For example, if an increase in nerve activity produced by a compound did not return to baseline levels after repeated saline flushes, then an experiment was terminated and a second infusion was not attempted. After each test, the compound was thoroughly evacuated and repeatedly flushed with saline.

A final experiment was conducted to evaluate whether the effect of linoleic acid in activating celiac vagal afferents depended on uptake and subsequent transport by chylomicrons. In this experiment, 300 μg of either Pluronic L-81 (1 ml) or vehicle (1 ml) were administered in the ileum 15 min before testing with linoleic acid (1 ml) in the ileum. The general procedures for administration of these substances were similar to those described above with the exception that procedures for flushing the substances ensured that the infusion of linoleic acid only reached the tissue previously occupied by the Pluronic L-81 or vehicle. It should be noted, however, that this resulted in "pushing" the previously administered Pluronic L-81 or vehicle to a new region of the ileum during the recording period. After the test of the ileum, linoleic acid was administered into the jejunum as described previously. This was done to determine whether ileal administration of Pluronic L-81 affected the response of celiac vagal afferents to linoleic acid administration in the jejunum.

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Experiment 2: Cervical vagal afferent recordings. Single-unit responses of left cervical vagal afferents were recorded during bolus intestinal infusions of either 1) linoleic acid (60% linoleic acid–30% oleic acid–10% nonspecific fatty acids), 2) linoleic acid–phosphatidylcholine emulsion (20% linoleic acid–70% sterile water–8% glycine–1% phosphatidylcholine–1% taurocholic acid), or 3) phosphatidylcholine vehicle (90% sterile water–8% glycine–1% phosphatidylcholine–1% taurocholic acid).

Baseline unit activity was recorded for 100 s before infusion of the test substance and served as the control period. The substance was then infused and activity was recorded for an additional 500 s. Infusion volumes varied between 1 and 3 ml.

In one set of experiments, units with receptive fields located in the ileum were tested with both linoleic acid–phosphatidylcholine emulsion and phosphatidylcholine vehicle. After each test, the compound was thoroughly evacuated and the tissue was repeatedly flushed with saline. In a second set of experiments, units with receptive fields located in either the ileum or jejunum were tested with linoleic acid.

Drugs

Fatty acids were obtained from Sigma, St. Louis, MO. Intralipid was obtained from Abbott Labs, North Chicago, IL. Pluronic L-81 was obtained from BASF, Parsippany, NJ. A 0.03% solution of Pluronic L-81 was made by dissolving 30 mg in 100 ml of phosphate-buffered saline (pH 6.4). Pluronic vehicle was phosphate-buffered saline. The vehicle for the linoleic acid–phosphatidylcholine emulsion was made by dissolving phosphatidylcholine, sodium taurocholate, and glyc erin in water (90% sterile water–8% glycine–1% phosphatidy lcholine–1% taurocholic acid; pH 7). Linoleic acid (20% vol/vol) was then added and mixed by sonication for 2 min (pH 4.0).

Data Analysis

Neuronal activity was normalized to reduce variability resulting from differences in background activity. Specifically, raw data were collected for each recording as the number of discharges occurring in 1-s bins, i.e., discharges per second. The first 100 s of each recording session were control data and reflected spontaneous activity in the absence of any manipulation. In the statistical analyses, these 100 s of data were converted to z scores by first determining the mean number of discharges per second for these 100 s. The mean was subtracted from the number of discharges in each 1-s bin and divided by the standard deviation. This provided a z score for each 1-s bin during the first 100 s.

A treatment was then administered at 100 s, and the number of discharges per second was recorded during the experimental period. In the statistical analyses of the experimental data, the number of discharges occurring in each 1-s bin was subtracted from the mean discharges per second obtained during the control period and then divided by the standard deviation of the control period to provide a z score. Thus, if the experimental treatment had no effect, then one would expect that the z scores would be zero. Alternatively, if the number of discharges per second was increased by the experimental treatment, then one would expect the z scores to increase above zero. Conversely, if the number of discharges per second was decreased by the experimental treatment, then one would expect the z scores to decrease below zero.

z Scores for each recording were grouped, and mean z scores were calculated. In the majority of studies, comparisons involved repeated contrasts between the mean of the 100-s control period with the mean of each successive 100-s experimental period. Multiple comparisons were corrected using either Dunnett’s table or Bonferroni’s correction (24). In the studies of Pluronic L-81, a between-group ANOVA was performed. Alpha was 0.05 in all analyses. The designation of n in the results indicates the number of individual rats in a group.

RESULTS

Experiment 1: Multiunit Studies of Celiac Vagal Afferents

Ileum: free fatty acids. LINOLEIC ACID. Linoleic acid infusions (n = 11) in the ileum resulted in a robust increase in celiac vagal afferent activity, and group mean z scores are shown in Fig. 1A. Contrasts on means collapsed over each 100-s time block after the infusion indicated that vagal afferent activity was significantly greater than control activity during each successive 100-s block (t values [10] range from 5.55 to 8.09).

CONJUGATED LINOLEIC ACID. Conjugated linoleic acid infusions (n = 8) in the ileum produced an increase in celiac vagal afferent activity, and group mean z scores are shown in Fig. 1B. Contrasts on means collapsed over each 100-s time block after the infusion indicated that vagal afferent activity was significantly greater than control activity during each successive 100-s block ([100–400 s; t values [7] range from 2.93 to 4.49].

OLEIC ACID. Oleic acid infusions (n = 10) in the ileum also resulted in a robust increase in celiac vagal afferent activity, and group mean z scores are shown in Fig. 1C. Contrasts on means collapsed over each 100-s time block after the infusion indicated that vagal afferent activity was significantly greater than control activity during each successive 100-s block (t values [9] range from 3.02 to 4.96).

Jejunum: free fatty acids. LINOLEIC ACID. Linoleic acid infusions (n = 10) in the jejunum produced an increase in celiac vagal afferent activity, and group mean z scores are shown in Fig. 2A. Contrasts on means collapsed over each 100-s time block after the infusion indicated that vagal afferent activity was significantly greater than control activity during the first four successive 100-s blocks ([100–500 s; t values [9] range from 3.28 to 5.98].

CONJUGATED LINOLEIC ACID. Conjugated linoleic acid infusions (n = 8) in the jejunum resulted in an initial increase in celiac vagal afferent activity that was not sustained over time, and group mean z scores are shown in Fig. 2B. Contrasts on means collapsed over each 100-s time block after the infusion indicated that vagal afferent activity was significantly greater than control activity during the first two successive 100-s blocks ([100–300 s; t values [7] range from 2.84 to 6.67].

OLEIC ACID. Oleic acid infusions (n = 9) in the jejunum also resulted in an increase in celiac vagal afferent activity, and group mean z scores are shown in Fig. 2C. Contrasts on means collapsed over each 100-s time block after the infusion indicated that vagal afferent activity was significantly greater than control activity during the first two successive 100-s blocks ([100–300 s; t values [9] range from 3.28 to 4.96].
activity was significantly greater than control activity during the first four successive 100-s blocks [100–500 s; t values (8) range from 2.87 to 5.29].

Ileum: triglycerides. Corn oil infusions (n = 8) in the ileum resulted in minimal increases in celiac vagal afferent activity, and group mean z scores are shown in Fig. 3A, top. Contrasts on means collapsed over each 100-s time block after the infusion indicated that vagal afferent activity was significantly greater than control activity only during the first 100-s block [100–200 s; t(7) = 5.06].

INTRALIPID. Intralipid infusions (n = 8) in the ileum resulted in no changes in celiac vagal afferent activity. Group mean z scores are shown in Fig. 3A, bottom. Contrasts on means collapsed over each 100-s time block after the infusion indicated that vagal afferent activity did not significantly differ from control activity in any block.

Jejunum: triglycerides. Corn oil infusions (n = 8) in the jejunum resulted in increases in celiac vagal afferent activity. Group mean z scores are shown in Fig. 3B, top. However, contrasts on means collapsed...
over each 100-s time block after the infusion indicated that vagal afferent activity did not significantly differ from control activity in any block.

**INTRALIPID.** Intralipid infusions (n = 8) in the jejunum resulted in no changes in celiac vagal afferent activity. Group mean z scores are shown in Fig. 3B, bottom. Contrasts on means collapsed over each 100-s time block after the infusion indicated that vagal afferent activity did not significantly differ from control activity in any block.

**Ileum: vehicle.** Saline infusions (n = 8) in the ileum resulted in no changes in celiac vagal afferent activity. Group mean z scores are shown in Fig. 4A. Contrasts on means collapsed over each 100-s time block after the infusion indicated that vagal afferent activity did not significantly differ from control activity in any block.

**Jejunum: vehicle.** Saline infusions (n = 8) in the jejunum resulted in virtually no changes in celiac vagal afferent activity. Group mean z scores are shown in Fig. 4B. Contrasts on means collapsed over each 100-s time block after the infusion indicated that vagal afferent activity was significantly greater than control activity during the first 100-s block [t(7) = 3.27].

**Pluronic L-81.** To evaluate whether the effect of linoleic acid in activating vagal afferents depended on transport by chylomicrons, 300 µg of either Pluronic L-81 (n = 12) or vehicle (n = 12) was administered in the ileum 15 min before testing with linoleic acid. Infusions of either Pluronic L-81 or vehicle had little or no effect on vagal afferent activity (data not shown). Figure 5A shows that pretreatment with Pluronic L-81 significantly attenuated the normal response of celiac vagal afferents to linoleic acid. An ANOVA indicated a significant effect of treatment, F(1,22) = 4.83, a significant effect of time after administration, F(6,132) = 7.30, and a significant treatment × time interaction, F(6,132) = 3.56. Between-group comparisons on means collapsed over each 100-s time block after the infusions indicated that vagal afferent activity was significantly reduced in Pluronic L-81 rats compared with vehicle rats during all 100-s time periods except 200–300 s [t values (22) range from 3.59 to 5.87].

Figure 5B shows the effect of pretreatment infusion of Pluronic L-81 in the ileum on responses of celiac vagal afferents to infusion of linoleic acid in the jejunum. An ANOVA indicated no significant effect of treatment, F(1,19) = 2.96, a significant effect of time after administration, F(6,114) = 9.35, and no significant treatment × time interaction, F(6,114) = 1.32. Thus, although the graphs in Fig. 5 give the appearance that...
Fig. 4. Group mean z scores of neural discharges before and during infusions of saline in ileum (A) or jejunum (B).

Fig. 5. Group mean z scores of neural discharges before and during infusions of linoleic acid in ileum (A) or jejunum (B) after prior administration of either Pluronic L-81 or vehicle in ileum.
ileal infusion of Pluronic L-81 influenced the vagal afferent response to jejunal infusion of linoleic acid, the ANOVA indicates that this was not statistically significant.

Experiment 2: Single-Unit Studies of Cervical Vagal Afferents

Ileum and jejunum. LINOLEIC ACID-PHOSPHATIDYLCHOLINE EMULSION. Ten ileal units were tested with the linoleic acid-phosphatidylcholine emulsion. Five of ten units (50%) responded with increased activity, and we were able to test four of these five units with the phosphatidylcholine vehicle alone. Group mean z scores of these data are presented in Fig. 6. The five units that failed to respond to infusions of linoleic acid-phosphatidylcholine emulsion were not tested further, and their data were not analyzed.

Figure 6A shows that these units responded immediately to linoleic acid-phosphatidylcholine emulsion and that unit activity remained elevated relative to the control period for the entire testing period of 10 min. Contrasts on means collapsed over each 100-s time block after the infusion indicated that vagal afferent activity was significantly greater than control activity during each successive 100-s block (t values (4) range from 3.46 to 9.00). Figure 6B shows that the same units failed to respond to phosphatidylcholine alone. A repeated-measures ANOVA indicated no significant changes in vagal activity and no post hoc contrasts were significant.

LINOLEIC ACID. Four units located in the jejunum were tested with linoleic acid. All of these jejunal units (100%) responded with increased activity, and group mean z scores are shown in Fig. 7. Figure 7 shows that linoleic acid resulted in a marked increase in activity of these jejunal units and a pattern of response similar to that observed previously. Contrasts were not performed on these data because of small sample size. Four units located in the ileum were tested with linoleic acid. Two of four ileal units (50%) responded with increased activity with a pattern of activity similar to the jejunal units. An example of the raw data for one of these units is shown in Fig. 8.

DISCUSSION

Previous studies have shown that infusions of lipids in the duodenum, jejunum, or ileum produce satiety-like effects (3–5, 10, 11, 22, 25). Some of these studies also provided data consistent with the view that lipid-induced activation of vagal afferents may contribute to these outcomes (11, 13, 22). Therefore, the present study tested a variety of free fatty acids, triglycerides, and saline for their capacity to alter activity of jejunal and ileal vagal afferents in the rat.

The free fatty acids, linoleic acid and oleic acid, produced the greatest increase in multiunit activity of celiac vagal afferents compared with all other test compounds. The magnitude and duration of increases in celiac vagal activity produced by these two fatty acids were generally comparable when infused within an intestinal segment, but the duration of responses was routinely greater with ileal versus jejunal infusions. Ileal infusions resulted in significant increases in multiunit activity lasting the entire 600 s of recording, whereas jejunal infusions resulted in significant activity lasting for only 400 s of the 600-s recording period.
We cannot be certain that the duration findings truly indicate the ileum is more responsive to these lipids than the jejunum, because it is not known whether comparable numbers of units were recorded from ileal and jejunal tissue with the multiunit recording procedure. However, the vast majority of recordings involved use of the same nerve within the same animal during ileal and jejunal lipid infusions. Furthermore, Hardcastle et al. (8) reported a similar outcome when using glucose infusions in either the ileum or jejunum during recordings of afferent discharges of unidentified mesenteric nerves. However, the greater effectiveness of ileal infusions for stimulating vagal activity appears inconsistent with behavioral studies of intestinal lipid infusions in human and rat, which show greater potency with proximal sites (duodenum and jejunum) compared with distal sites (ileum) of administration (23, 25). However, our data are relevant to stimulation of a fixed amount of tissue and it is not clear that this was true of the behavioral studies. Alternatively, it may be the case that a greater vagal signal does not necessarily translate into a greater behavioral effect.

Infusions of the triglycerides, corn oil or Intralipid, had mixed effects. Corn oil infusions resulted in increases in multiunit celiac vagal afferent activity in both the ileum and jejunum, but these increases failed to achieve statistical significance. In contrast, Intralipid was clearly without effect in either the ileum or jejunum. The generally greater effectiveness of free fatty acids compared with triglycerides is consistent with a report that oleic acid was more potent in reducing food intake than triolein (25). However, infusions of triglycerides in the ileum have been shown to engage the ileal brake (2, 23). It is possible, therefore, that triglyceride administration in the distal intestine uses a nonvagal afferent mechanism to produce this outcome. However, a more likely explanation is that little absorption of triglycerides occurred. Triglycerides are not readily hydrolyzed into their appropriate monoglyceride and free fatty acid components in the distal small intestine because of lower enzymatic actions and/or pH gradients. The present infusions also were made at sites distal to those at which pancreatic enzymes and bile salts enter the small intestine, and...
the test region was flushed with saline and occluded relative to proximal sites by virtue of the infusion catheter insertion points. Infusions of saline were without effect in either the ileum or jejunum.

The single-unit recordings of cervical vagal afferents with receptive fields located in either the jejunum or ileum produced results similar to those obtained in multunit recordings. All of the single units were selected on the basis of their responsiveness to mechanical stimuli. Linoleic acid or linoleic acid-phosphatidylcholine emulsion infusions produced robust increases in single-unit activity in ~50% of ileal units, whereas phosphatidylcholine vehicle infusions were without effect in all cases that were tested. Linoleic acid also produced robust increases in single-unit activity of four of four units tested with receptive fields in the jejunum.

Our study was not intended to determine if these ileal and jejunal vagal afferent units in the rat had response properties similar to the duodenal vagal afferents described by Melone (12) in the cat. However, it is our informal view that they are not similar. None of the 40 duodenal and jejunal units studied by Melone (12) in the cat responded to mechanical, osmotic, or chemical stimuli, other than lipids. In our single-unit studies, however, all units were chosen on the basis of responding to mechanical stimuli and ~50% of ileal and 100% of jejunal units that we tested responded to lipid infusions. Furthermore, Cervero and Sharkey (6) used an in vitro recording preparation of the distal ileum of the rat (21) to record 82 units; 85.5% responded to both mechanical and chemical stimuli, 11.9% responded only to mechanical stimuli, and 2.6% responded only to chemical stimuli. Thus 97.4% of these ileal units responded to mechanical stimuli. If one assumes that many of these mechanically sensitive units were of vagal origin, then it would seem unlikely that the two classes of lipid-sensitive, but mechanically insensitive, vagal units described by Melone (12) are representative of the rat ileum. Finally, although the multunit celiac recording technique did not allow us to determine whether units responding to lipid infusions also had mechanical sensitivity, nerve bundles were chosen initially on the basis of their robust response to mechanical stimuli. However, a clear examination of this issue requires further research.

The data obtained from the Pluronic L-81 experiment support the view that lipids are transported via chylomicrons before activating vagal afferents. Specifically, pretreatment of the lumen of the ileum with Pluronic L-81 significantly attenuated the vagal afferent response to infusion of linoleic acid in ileum, but not the jejunum. An alternative hypothesis, however, is that the ability of Pluronic L-81 to diminish the effect of fatty acids on afferent activity is not due to inhibition of chylomicra secretion, but rather to an unknown action of this surfactant.

These data raise several intriguing issues that require consideration. Specifically, where is the location of vagal afferent terminals that respond to lipids, what is the signal for activation of vagal afferent terminals, and what are the transduction mechanisms involved in activating vagal afferents? Anatomic tracing studies from the rat suggest that the vagal afferents are located in the postluminal site, because presently no evidence exists showing that vagal afferent terminals penetrate the basal lamina into the epithelial cell layer of the duodenum of the rat (1). Instead, vagal afferent fibers are closely associated with fibrocyte-like cells both in the villous and cryptal lamina propria (1). Our Pluronic L-81 data are consistent with a postluminal site of action, perhaps the lamina propria. The literature also suggests many possible ways in which lipids might directly or indirectly exert an effect on vagal afferents. These include (1) direct activation by chylomicrons (20) or (2) chylomycin-induced release of other activating substances, such as apolipoprotein A-IV (9, 19) or release of serotonin and actions on 5-HT4 receptors located on primary vagal afferents (3). In addition, other substances have been implicated in mediating ileal brake effects, including norepinephrine, peptide YY, enteroglucagon, neuropeptide, and cholecystokinin (2, 10, 18, 25). It is even possible that lipids might directly modulate K+ channels as has been reported for taste receptor cells (7). Each of these views merits further examination given the potential use of lipid administration in humans to induce satiety and control body weight. In summary, these are the first studies demonstrating lipid-induced activation of vagal afferents after infusions in the distal small intestine.

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