Differential effects of selective vagotomy and tropisetron in aminoprivic feeding

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Dixon, Kimberly D., Fred E. Williams, Raymond L. Wiggins, Jason Pavelka, James Lucente, Larry L. Bellinger, and Dorothy W. Gietzen. Differential effects of selective vagotomy and tropisetron in aminoprivic feeding. Am J Physiol Regulatory Integrative Comp Physiol 279: R997–R1009, 2000.—Both total subdiaphragmatic vagotomy (TVAGX) and serotonin3 receptor blockade with tropisetron or ondansetron attenuate amino acid-imbalanced diet (Imb) anorexia. Total vagotomy is less effective than tropisetron in reducing Imb-induced anorexia and also blunts the tropisetron effect. With the use of electrocautery at the subdiaphragmatic level of the vagus, we severed the ventral and dorsal trunks as well as the hepatic, ventral gastric, dorsal gastric, celiac, and accessory celiac branches separately or in combination to determine which vagal branches or associated structures may be involved in these responses. Rats were prefa a low-protein diet. On the first experimental day, tropisetron or saline was given intraperitoneally 1 h before presentation of Imb. Cuts including the ventral branch, i.e., TVAGX, ventral vagotomy (above the hepatic branch), and hepatic + gastric vagotomies (but not hepatic branch cuts alone) caused the highest (P < 0.05) Imb intake on day 1 with or without tropisetron. The responses to tropisetron were not affected significantly. On days 2–8, groups having vagotomies that included the hepatic branch recovered faster than sham-treated animals. Because the hepatic and gastric branches together account for most of the vagal innervation to the proximal duodenum, this area may be important in the initial responses, whereas structures served by the hepatic branch alone apparently act in the later adaptation to Imb.

amino acid; diet; amino acid-imbalanced diet; amino acid deficiency; rat; food intake; body weight; vagus; serotonin

INGESTION OF AN AMINO ACID-IMBALANCED DIET (Imb) triggers a rapid feeding depression in rats (reviewed in Refs. 14, 18, 31). In the presence of a serotonin (5-HT) agonist, the anorectic response to Imb is exacerbated (15). Blockade of the 5-HT3 receptor with tropisetron or ondansetron attenuates this anorectic response (17, 22) on the first experimental day (day 1). Intraperitoneal injections of quaternized tropisetron, which does not cross the blood-brain barrier, have an effect similar to the nonquaternized form (20), suggesting a peripheral site for this effect of tropisetron. Moreover, total subdiaphragmatic vagotomy (TVAGX) attenuates the feeding depression associated with Imb diets, although not as well as tropisetron (37), showing involvement of the vagus. A peripheral site of action for tropisetron in this model is also supported by the observation that tropisetron and TVAGX are not additive in ameliorating Imb anorexia.

Peripheral injections of 5-HT cause a greater reduction of food intake in TVAGX than in sham-operated rats (13), indicating that vagal components can modify the peripheral effect of 5-HT in food-intake suppression. In support of this finding, an intact vagal system is required to observe the maximal effect of tropisetron on Imb intake (37). It is not yet known which branches of the vagus participate in the anorectic/aversive responses to Imb or the role of 5-HT therein.

The vagus innervates major portions of the gastrointestinal system and is important in the control of feeding. In the rat, at the level of the diaphragm, the vagus is composed of a ventral and a dorsal trunk. Below the diaphragm, the ventral trunk separates into the hepatic, accessory celiac, and ventral gastric branches, whereas the dorsal trunk separates into the celiac and dorsal gastric branches (21, 28). Gastrointestinal innervation patterns have shown that the gastric branches serve the stomach and proximal duodenum, the hepatic branch serves the proximal duodenum, and the celiac and accessory celiac branches serve more distal portions of the intestine (5).

Preliminary findings in our laboratories suggest that the ventral and dorsal trunks may play very different roles in the anorectic responses to Imb. As noted above, the ventral trunk contains the hepatic branch, and although cutting the hepatic branch does not affect Imb intake on day 1, there may be a role for the hepatic branch in mediating the adaptive phase of the responses to Imb that occurs over the next few days (2, 4).

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Total liver denervation, including fibers that pass through the liver, does not affect the initial attenuation of feeding with Imb nor does it impair the effectiveness of tropisetron (2). However, more recent evidence suggests that cutting the hepatic branch alone can accelerate the adaptive phase of the responses to Imb over several days (4). Also, after a few days on a lysine-deficient diet, responses to infusion of the limiting amino acid lysine into the hepatic portal vein cause a 100-fold increase in the firing rate of hepatic branch neurons (36). Thus the role of the hepatic branch in the anorectic response is not fully elucidated. Adding to the complexity of the problem, Berthoud and Neuhuber (6) have suggested that although the hepatic branch goes to and through the liver, it may innervate other structures such as the bile ducts, pancreas, and duodenum. The role, if any, of the other subdiaphragmatic branches of the vagus in the rat’s response to Imb diets is unknown. Therefore, in the present studies, we used selective partial vagotomies to evaluate the roles of the several vagal branches in Imb intake and in the responses to 5-HT3 blockade with tropisetron in the initial and adaptive phases of the aminoprivic model.

The major findings of these studies are 1) confirmation that a hepatic branch cut alone can accelerate adaptation to Imb over several days, i.e., phase 3 (14) of the feeding responses and 2) innervation of the proximal duodenum and/or distal stomach by the hepatic branch together with at least one of the gastric branches (5) appears to be important in the early learning phase (phase 2) of the anorectic response on the first day of exposure to Imb, which occurs after recognition of the deficiency (phase 1). From the responses measured, neither initial recognition of the deficiency nor the responses to tropisetron appeared to be affected by the treatments used in these experiments.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats were purchased from Harlan Sprague Dawley (Houston, TX) or from Simonsen Laboratories (Gilroy, CA). All animal protocols were approved by the appropriate institutional Animal Use and Care Committee and followed National Institutes of Health Guidelines. Rats were housed individually in stainless steel cages in the vivarium at 22°C on a 12:12-h light-dark cycle. In addition to room lighting, two 25-W red lightbulbs were kept on at all times to facilitate food intake measurements during the dark phase. To allow adaptation to the vivarium, the rats were fasted for 24 h and then subjected to various combinations of partial subdiaphragmatic vagotomies. Before surgery, the rats were anesthetized, as previously described, with either ketamine and xylazine (3) or with a mixture of ketamine, xylazine, and acepromazine, plus subcutaneous atropine to prevent respiratory distress (37). After surgery, the incisions were closed with the use of sutures and wound clips. All animals received an intramuscular injection of 10 mg/kg of penicillin G procaine (10 mg/ml, VEDCO, St. Joseph, MO) and were kept warm under a heat lamp during recovery from anesthesia.

Dietary Treatments

After surgery, the rats were fed a milk-based liquid diet (Carnation sweetened condensed milk, Nestle, Glendale, CA) that was diluted with deionized water, 2:1 vol/vol, for 3 days. After the liquid diet, animals in experiment 1 and experiment 2, trials 1b, 1c, and 2c received a 17% casein-based gel diet (all of the diets are described in detail in Refs. 17, 37). This was given fresh every day for 5 or 6 days. In experiment 2, trials 1a, 2a, and 2b, the animals were given an isoleucine-corrected diet in gel form, also for 5 or 6 days. These liquid and gel diets were used to allow recovery of gastrointestinal function after the various vagotomies.

Next, the rats were switched to a dry powdered low-protein basal diet for a 10-day prefeeding period (17, 37). The basal diet contained purified l-amino acids as the protein source with isoleucine as the growth-limiting amino acid. The Imb was the same as the basal diet, with the addition of a mixture of all of the indispensable amino acids except for isoleucine, which was the growth-limiting amino acid. The corrected diet was the same as Imb, but it was corrected with an additional 1.0% of isoleucine to bring the amino acid profile into physiological balance. When amino acids were added, the carbohydrate fraction was adjusted proportionately. To aid gastrointestinal clearance in the vagotomized animals, fiber was not included in any of the defined diets.

Food-Intake Measurements

Starting at lights out (0 h) for the last 3 days on basal diet, cumulative intake, corrected for spillage, was measured at 3, 6, 9, 12, and 24 h. These data served as basal-baseline control values for each rat. After this, the rats were presented with Imb, and intakes for day 1 were recorded at the times listed above; cumulative intake for the first 24 h served as day 1 intake for comparison with later daily food intake measures. Daily Imb intakes, corrected for spillage, were recorded for the next several experimental days (from day 2 to day 7 or 8) depending on the experimental protocol. When used, the corrected diet was offered after the completion of Imb feeding, and intake of the corrected diet was also measured daily.

Experiment 1: Subdiaphragmatic Truncal Vagotomies

This experiment followed a 4 × 2 design with four subdiaphragmatic surgical conditions and two drug conditions. The surgeries performed were 1) sham, 2) a TVAGX above the hepatic branch on the ventral trunk and above the celiac branch on the dorsal trunk (cuts 1 and 2 in Fig. 1) following the method of Ritter and Taylor (30), 3) a unilateral ventral cut above the hepatic branch (cut 1 in Fig. 1), or 4) a unilateral dorsal cut above the celiac branch (cut 2 in Fig. 1). When the proper branch was visualized and isolated, it was severed by electrocautery. Both the ventral trunk and the hepatic branch were isolated and cauterized independently for the ventral trunk cut group. In the sham operation, the experimental surgery was replicated with all branches of the vagus left intact and only touched with the tip of a cotton swab, moistened with saline. Body weights of the groups at the time of surgery were similar (P > 0.10, nonsignificant): sham-saline 260 ± 5.4 g, TVAGX-saline 243.6 ± 4.3 g, ventral cut-saline 252.3 ± 5.0 g, dorsal cut-saline 249.5 ± 7.8 g.
nucleus of the vagus nerve. Each surgical group, and saline was given to the other half of a dose of 9 mg/kg ip, as determined in previous dose-response studies. 8-Methyl-8-azabicyclo[3.2.1]oct-3-ol Indole-3-yl-carboxylate (Tropisetron) was used to reduce saliva production. The two drug conditions were sham-saline 264.9 ± 4.2 g, ventral trunk cut-saline 262.4 ± 4.2 g, sham-tropisetron 259.3 ± 4.2 g, and ventral cut-tropisetron 257.2 ± 4.2 g. After surgery, the animals were fed as described in Dietary Treatments. Food intake was recorded at the intervals described above during the last 3 basal-baseline days. Body weights after the last basal-diet day were again similar (P < 0.38, nonsignificant): sham-saline 315.6 ± 4.3 g, TVAGX-saline 299.6 ± 5.4 g, ventral trunk cut-saline 305.6 ± 6.0 g, dorsal trunk cut-saline 306.6 ± 6.5 g, sham-tropisetron 315.7 ± 4.3 g, TVAGX-tropisetron 305.2 ± 5.9 g, ventral trunk cut-tropisetron 309.6 ± 6.3 g, dorsal trunk cut-tropisetron 313.6 ± 5.1 g. On the day the Imb was to be introduced, 1 h before lights out, the basal-diet food cups were removed and each rat received an intraperitoneal injection. The two drug conditions were 1) saline (0.9% NaCl) given in a volume of 1 ml/kg body wt, and 2) tropisetron (endo-8-Methyl-8-azabicyclo[3.2.1]oct-3-ol Indole-3-yl-carboxylate hydrochloride, Research Biochemicals, Natick, MA) given in a dose of 9 mg/kg ip, as determined in previous dose-response studies (17, 22). Tropisetron was administered to one-half of each surgical group, and saline was given to the other half of the animals. At lights out (0 h), all rats received a food cup containing Imb, and then interval (day 1) and daily consumption (days 2–7) were measured. On day 8, the diet was changed to the corrected diet, and daily food-intake measurements were continued through day 12. After verification of surgeries, the group sizes were: sham-saline n = 6, sham-tropisetron n = 6, TVAGX-saline n = 6, TVAGX-tropisetron n = 6, ventral cut-saline n = 6, ventral cut-tropisetron n = 6, dorsal cut-saline n = 6, and dorsal cut-tropisetron n = 6.

Experiment 2: Selective Partial Vagotomies

Trial 1: ventral branch vagotomies including the hepatic branch. Trial 1A. The surgeries performed were 1) sham, 2) hepatic branch cut (illustrated as cut 3 in Fig. 1), 3) hepatic branch cut plus accessory celiac cut (cuts 3 + 4 in Fig. 1), 4) hepatic branch cut + ventral gastric branch cut below the accessory celiac branch (hepatic + ventral gastric cuts: cuts 3 + 5 in Fig. 1), 5) TVAGX, 6) ventral cut, or 7) unilateral ventral cut below the hepatic branch (ventral-B cut), including the accessory celiac and ventral gastric branches (cuts 4 + 5 in Fig. 1). The ventral-B cut was included to test all possible combinations of ventral branches. The body weights of the groups were similar (P > 0.10, not significant) at the time of surgery: sham 265.1 ± 3.08 g, hepatic branch cut 272.9 ± 3.63 g, hepatic + accessory celiac branches cut 270.0 ± 3.55 g, hepatic + ventral gastric branches cut 263.4 ± 3.82 g, TVAGX 268.7 ± 3.33 g, ventral cut 266.5 ± 3.71 g, and ventral-B cut 263.1 ± 2.86 g. After surgery, the animals were fed as described under Dietary Treatments.

On the last basal-diet day, the average group weights differed, P < 0.01 (sham 284.9 ± 4.4 g, hepatic branch cut 290.4 ± 5.1 g, hepatic + accessory celiac cut 290.3 ± 4.1 g, hepatic + ventral gastric branch cuts 283.6 ± 5.9 g, TVAGX 263.0 ± 5.2 g, ventral trunk cut 285.4 ± 4.4 g, and ventral-B cut 282.9 ± 5.1 g). The difference was due to the TVAGX group, which weighed less than the sham group (P < 0.01). After verification of nerve transection, the following group sizes remained: sham n = 7, hepatic branch cut n = 8, hepatic + accessory celiac branch cuts n = 16, hepatic + ventral gastric branch cuts n = 14, TVAGX n = 11, ventral cut n = 11, and ventral-B cut n = 10.

Trial 1B. The surgeries were 1) sham, 2) TVAGX, and 3) hepatic + ventral gastric branch + dorsal trunk cuts. The dorsal trunk cut was also used in this experiment, because we wanted to verify that the dorsal trunk cut would not alter the effects seen with cuts of the hepatic and ventral gastric branches. Cuts of the dorsal branch in experiment 1 had indicated that this trunk by itself, containing the celiac and dorsal gastric branches, has no effect on the intake of Imb. Body weights at the time of surgery were 1) sham 286.0 ± 3.1 g, 2) TVAGX 279.9 ± 2.7 g, and 3) hepatic + ventral gastric branch + dorsal trunk cuts 282.9 ± 4.0 g (P > 0.10, nonsignificant). There were no significant differences for food intake at any interval among the groups during the basal-diet prefeeding period (P > 0.10, not significant). Body weights did differ among the groups at the end of the prefeeding period due to the sham group's weight being significantly higher than the other two groups: sham 340.3 ± 3.0 g, TVAGX 313.8 ± 5.2 g, and hepatic + ventral gastric branch + dorsal trunk cut 310.1 ± 4.0 g, P = 0.0003. After verification of the surgeries, the group sizes were: sham n = 6, TVAGX n = 8, and hepatic + ventral gastric branch + dorsal trunk cuts n = 9.

Trial 1C. The surgeries were 1) sham, 2) TVAGX, and 3) hepatic + dorsal gastric branch (cuts 3 + 7 in Fig. 1). The dorsal gastric branch was cut in this experiment, because we wanted to learn whether the dorsal gastric branch cut would...
have effects similar to those seen in trial 1b with the ventral gastric branch when combined with the hepatic branch cut. Body weights at the time of surgery were 1) sham 228.9 ± 11.8 g, 2) TVAGX 220.6 ± 13.0 g, and 3) hepatic + dorsal gastric branch cuts 236.0 ± 11.8 g (P > 0.10, nonsignificant).

There were no significant differences for food intake at any interval among the groups during the basal-diet prereading period (P > 0.10, not significant). Body weights also did not differ among the groups at the end of the prereading period: sham 331.6 ± 9.8 g, TVAGX 319.6 ± 6.1 g, and hepatic + dorsal branch cut 331.1 ± 5.8 g, P > 0.10, not significant. After verification of the surgeries, the group sizes were: sham n = 5, TVAGX n = 4, and hepatic + dorsal branch cuts n = 4.

**Trial 2:** selective ventral vagotomies sparing the hepatic branch. Trials 2a and 2b were conducted at different times, but they were identical except that in trial 2a the rats were given surgical treatments and saline injections only. In trial 2b, they were given the same surgeries, but they were injected with tropisetron rather than saline. Body weights were measured daily during both of these trials. Trial 2c was done to confirm the results of the operations made in previous trials.

**Trial 2a.** The surgeries performed were 1) sham, 2) ventral gastric branch cut (cut 1 in Fig. 1), 3) dorsal gastric branch cut below the celiac branch (cut 7 in Fig. 1), 4) celiac + accessory celiac cuts (cuts 4 and 6 in Fig. 1), and 5) ventral- B + dorsal trunk cuts [bilateral vagotomies below the hepatic branch (BILAT-B) cuts 2, 4, and 5]. The body weights of these groups were similar on the day of surgery 1) sham 232.6 ± 2.5 g, 2) ventral gastric branch cut 232.9 ± 3.4 g, 3) dorsal gastric branch cut 224.9 ± 1.8 g, 4) celiac + accessory celiac cut 231.3 ± 4.7 g, and 5) ventral-B + dorsal trunc cut 231.4 ± 2.2 g, P > 0.10, nonsignificant.

Cumulative consumption of the basal diet by the groups differed at 3 h, P < 0.01, due to the ventral gastric (6.1 ± 0.3 g) and celiac + accessory celiac branch cuts (6.1 ± 0.5 g) groups that consumed more (P < 0.05) basal diet than did the sham group (5.1 ± 0.3 g). Basal-diet intakes of the dorsal gastric branch cut (5.4 ± 0.2 g) and BILAT-B cut (5.0 ± 0.2 g) groups did not differ from the sham group. Cumulative basal-diet intakes for 0–6, 0–9, 0–12, and 0–24 h did not differ among the groups (data not shown). On the last basal-diet day, the body weights of the groups differed, P < 0.001, due to the BILAT-B cut group, which weighed less than the other groups (P < 0.05): sham 279.6 ± 5.7 g, ventral gastric branch cut 267.8 ± 2.7 g, dorsal gastric branch cut 270.8 ± 3.6 g, celiac + accessory celiac cuts 269.8 ± 5.3 g, and BILAT-B cut 255.9 ± 9.8 g. After verification of the surgeries, the following group sizes remained 1) sham n = 10, 2) ventral gastric branch cut n = 13, 3) dorsal gastric cut n = 18, 4) celiac + accessory celiac cut n = 10, and 5) BILAT-B cut n = 17.

**Trial 2b** was a repeat of trial 2a, except that the rats were injected with tropisetron as described in experiment 1. The body weights were similar among the groups (P > 0.10, nonsignificant) on the day of surgery 1) sham 211.8 ± 2.4 g, 2) ventral gastric branch cut 213.0 ± 4.2 g, 3) dorsal gastric cut 204.0 ± 3.0 g, 4) celiac + accessory celiac cut 211.6 ± 4.7 g, and 5) BILAT-B cut 213.0 ± 3.2 g. Cumulative consumption of basal diet by the groups was similar at all time points, with the exception of the 12-h measurement when the BILAT-B cut-tropisetron group consumed less than the sham-tropisetron group. This also occurred in trial 2a in the saline-treated groups having those two surgeries. On the last basal-diet day, before the rats were presented with Imb, the saline-treated groups having those two surgeries. On the last day of trial 2c, the groups were then injected with tropisetron rather than saline. Body weights were measured daily during both of these trials. Trial 2c was done to confirm the results of the operations made in previous trials.
Statistical Analysis

For all food-intake measurements, intake of Imb is presented as a percentage of each rat’s basal diet-baseline intake (% basal intake) so that each rat served as its own control. After verification of nerve transections, data for each trial were subjected to one- or two-way ANOVA (for the effects of surgery or surgery and drug where appropriate) for each of the intervals on day 1. Data for the 24-h measurements on day 1 and subsequent days were analyzed by repeated-measures ANOVA. Post hoc tests (Fisher’s protected least-significant means or Duncan’s tests) were used to determine differences among group means. Significance was assumed at \( P < 0.05 \). Data were analyzed with the use of SAS, 6.12 (SAS Institute, Cary, NC) or ABstat, release 6.51 (Anderson-Bell, Parker, CO) on the laboratory computers.

RESULTS

Experiment 1: Subdiaphragmatic Truncal Vagotomies

Effects of surgery and tropisetron—day 1. The first day on Imb (day 1) the cumulative 24-h intakes of the groups differed significantly (Fig. 2). As expected, all animals reduced their Imb intake relative to their basal diet-baseline intake; values for all eight groups ranged from 38.8 to 55.1% of their basal diet-baseline intake. Also, as expected, tropisetron increased Imb intake on day 1. During the first 3 h, there was a significant drug effect \(( P < 0.04)\) with the usual reduction of Imb intake attenuated in all tropisetron-treated groups. By 6 h, the overall effect was still due to drug-treated groups, as the tropisetron effect for all of the groups remained significant \(( P < 0.001)\) at 6, 9, and 12 h. By 24 h, all tropisetron-treated groups had similar Imb intakes (70–75% of basal-diet baseline).

After 3 h, the sham-saline and dorsal trunk cut-saline groups’ cumulative consumption of Imb diet stabilized at ~40% of their basal-baseline intake, showing the lack of effect with dorsal trunk cuts (see ∆ in Fig. 2). However, there was a significant \(( P < 0.05)\) surgery \( \times \) tropisetron interaction at 9, 12, and 24 h. Notably, at 9 h, both the TVAGX-saline and ventral trunk cut-saline groups (○ and □, respectively) were consuming more of Imb (significance of the surgery effect, \( P < 0.02)\) than the dorsal trunk cut-saline and sham-saline groups (□ and △ in Fig. 2). These significant differences continued at the 12- and 24-h measurements. By 24 h, the ventral trunk cut-saline and TVAGX-saline groups were also eating more (61 and 58%, respectively, \( P = 0.002)\) Imb than the sham-saline group that ate 41% of baseline, by the end of day 1. Intake of Imb by the ventral trunk cut-saline and TVAGX-saline groups was increased to a level that did not differ from that of the tropisetron-treated groups, and it remained higher than the saline-treated sham and dorsal trunk cut groups throughout day 1.

The adaptation phase of the responses to Imb—days 2–7. There were significant differences among the surgical groups that extended throughout all 7 days on Imb \(( P < 0.003, \text{Fig. 3A})\) and persisted (albeit in reversed order of increasing food intake) after the diet was changed to the corrected diet for days 8–12 \(( P < 0.0001, \text{Fig. 3B})\). On day 2 of Imb feeding, there was a residual drug effect \(( P < 0.004)\) such that the TVAGX-tropisetron and ventral trunk cut-tropisetron groups ate significantly \(( P < 0.03)\) more than their respective saline groups (Fig. 3A). There were no significant drug effects after day 2. On days 3, 4, and 6, both ventral cut groups’ and both TVAGX groups’ consumption of Imb was similar and significantly \(( P < 0.04)\) elevated over all of the saline groups, showing accelerated adaption to Imb. On days 5 and 7 also, Imb intakes of the TVAGX-saline and ventral trunk cut-saline groups were significantly greater than those of the sham-saline group, \( P < 0.05)\ (\text{Fig. 3A}). The tropisetron-treated dorsal trunk cut and sham groups remained similarly low (\text{Fig. 3A}).

Effects of surgery and tropisetron on corrected diet intake—days 8–12. After the animals were switched to the corrected diet, all groups increased their food intake as expected, with a moderate compensatory hyperphagia; there were no differences among the groups on day 8 (\text{Fig. 3B}). However, for days 9–12, there were significant surgical effects \(( P < 0.003)\) with the groups reversed from the results with Imb on days 2–7 (compare \text{Fig. 3, A and B}; note different ranges of values on the ordinates). Post hoc testing revealed that on day 12, the sham-saline group was still eating the most of the corrected diet (112.9% of basal-diet intake), and the TVAGX-saline and ventral trunk cut-saline groups were eating the least (87% of basal diet, \( P = 0.001;\) and 94% of basal diet, \( P = 0.002, \text{respectively})\). This
Experiment 1: Selective Vagotomy and Tropisetron

**Trial 1A.** Over the 7-day measurement period on Imb, the TVAGX group had the greatest Imb intake, and the ventral-B cut group had the lowest Imb intake (data not shown). These differences were reflected in body weight differences.

The data for each rat's body weight on days 1–7 were transformed to a percentage of that rat's body weight on the last day of basal-diet feeding, and then daily comparisons among the groups were made. On days 1–3, the body weights of all the groups were similar. Group differences in body weights became apparent (P < 0.02) over the last 4 days that the rats were given Imb. During days 3–5, an increasing trend in body weight gain began to emerge among the groups that was reflective of their Imb consumption. As expected from experiment 1, by day 4 the TVAGX group weighed more (P < 0.01) than the sham group. The weight of the TVAGX group continued to diverge from the sham group over days 5–7. A trend was also apparent, starting on day 4, for the ventral trunk cut and the hepatic + ventral gastric branch cut groups to gain more weight than the sham group. This difference became significant for both of these groups on days 6 and 7. By day 6, the body weights of the TVAGX group were significantly (P < 0.01) increased over all groups except the ventral trunk cut group, in which the body weights did not differ from the hepatic + ventral gastric branch cut group. These results suggested that the ventral trunk effects in Imb anorexia required the hepatic and gastric branches, but not the accessory celiac branch, and that other combinations of cuts among the branches of the ventral trunk were ineffective.

**Trial 1B.** When the Imb diet was fed on day 1, significant differences were seen after 3 h (P < 0.005, Fig. 4A). For the 6- through 24-h measurements, cumulative Imb intakes for the TVAGX group were greater (all P < 0.05) than those of the sham group. The group having the combined hepatic + ventral gastric branches + dorsal trunk cuts also consumed significantly more Imb diet than the sham group at 12 h (P < 0.02), with trends toward significance as early as 6 h (P < 0.07) and in the cumulative data for 24 h (P < 0.06). Notably, the Imb intake for the group having combined hepatic, ventral gastric, and dorsal cuts did not differ significantly from the TVAGX group at any time measured, and it was significantly elevated over the sham group (P < 0.05), although only at 12 h as noted (Fig. 4A). This is consistent with the observations for the hepatic + ventral gastric branch cut group in trial 1A and ventral trunk vagotomy seen in experiment 1.

Significant differences among the surgical groups persisted over the next 7 days (P = 0.02, Fig. 4B). On day 2, the intake of Imb increased in all groups, with the TVAGX group still having the greatest Imb intake, differing significantly from the sham group, P < 0.05. By day 3, the TVAGX group's intake was greater than both of the other two groups, P < 0.05. On day 5, there was an increase in Imb intake for both of the vagotomized groups; both consumed more of the Imb than the sham group, P < 0.002 and P < 0.003, respectively. There were no differences among the surgical groups for Imb intake on days 4, 6, or 7.

Experiment 2: Selective Subdiaphragmatic Vagotomies

**Trial 1:** ventral vagotomies including ablation of the hepatic branch. **Trial 1A.** Over the 7-day measurement period on Imb, the TVAGX group had the greatest Imb intake, and the ventral-B cut group had the lowest Imb intake, and the ventral-B cut group had the lowest Imb intake, with the result that their need for a compensatory hyperphagia was not as great. There was a reciprocal effect may be due to the fact that these groups did not decrease their intake of Imb diet as severely, with the result that their need for a compensatory hyperphagia was not as great. There was a significant residual tropisetron effect in the TVAGX group on day 9 only (P < 0.02), but there were no other drug effects on the intake of corrected diet through day 12.

**Experiment 2:** Selective Subdiaphragmatic Vagotomies

Fig. 3. Experiment 1. A: 24-h Imb intake on days 1–7 as a percent of basal diet-baseline intake. Symbols are the same as in Fig. 2. Selective vagotomy groups are indicated in the legend and defined in Fig. 2; overall F(3,38) = 19.12, P = 0.0001. *Significant effect of surgery over time (days × surgery), F(5,220) = 2.27, P = 0.005. †Significant effect of tropisetron (effect of drug over days 1–7), F(6,220) = 9.85, P < 0.0001, on day 2, P = 0.004; ‡significant tropisetron and *surgery interaction, P < 0.05. B: effects of selective vagotomies on intake of the corrected diet in experiment 1. Twenty-four-hour corrected diet intakes on days 8–12 are given as a percentage of basal-diet baseline. Symbols are the same as in Fig. 3A. *Effects of surgery, F(3,40) = 10.82, P < 0.003. Note the different range of values on the ordinate showing the expected compensatory hyperphagia on the corrected diet.
As seen in experiment 2, trial 1a with the TVAGX and hepatic + ventral gastric branch cuts, significant differences were also noted for body weights (expressed as % basal-baseline) over days 1–7 ($P < 0.01$). The TVAGX group weighed more than the shams on days 4–7 ($P < 0.05$); hepatic (HV) + ventral gastric branch (VGBX) + dorsal trunk cut group (HV + VGBX) > sham, $P = 0.02$. 24-h Imb intakes on days 1–7 are expressed as a percentage of basal-diet baseline. Symbols are the same as in Fig. 2. Selective vagotomy groups are indicated in the legend. Effect of surgical group, $F_{2,17} = 5.25$, $P < 0.02$. TVAGX group significantly $>$ sham group, $P < 0.05$; hepatic + ventral gastric branches + dorsal trunk cuts (HV + VGBX) significantly $>$ sham, $P < 0.05$.

As seen in experiment 2, trial 1c with the Imb diet was fed, there were no differences for the 0- to 3-h period on day 1, but significant differences were seen beginning in the 0- to 6-h period ($P < 0.05$, Fig. 4A), which were due to the TVAGX group. For the 6- through 24-h measurements, cumulative Imb intakes for the TVAGX group were greater (all $P < 0.05$) than those of the sham group. Imb intake for the group having the combined hepatic + dorsal gastric branch cuts was intermediate as they consumed slightly more Imb diet than the sham group (e.g., by 6 h: hepatic + dorsal group 5.3 ± 0.9 g vs. sham group 4.6 ± 0.4 g), and this increase persisted throughout the first experimental day. However, this observation did not reach statistical significance. Notably, however, Imb intake as a percentage of basal baseline for the group having combined hepatic and dorsal branch cuts did not differ significantly from the TVAGX group during the 0–6, 0–9, or the 6- to 24-h measurements. Thus the hepatic + dorsal gastric branch cut group was similar to the hepatic + ventral gastric branch group of trial 1b (Fig. 4) in which the effects of partial vagotomies sparing the celiac branches did not differ from TVAGX in ameliorating Imb anorexia.

Trial 2: selective ventral vagotomies sparing the hepatic branch. Trials 2a and 2b were done separately, but the data for day 1 from the two trials are presented together in Fig. 6 to allow comparison with experiment 1.

**TRIAL 2A: EFFECTS OF SURGERY.** On day 1, cumulative Imb intakes after saline injections, expressed as a percent of basal baseline, differed significantly, $P < 0.001$, among the surgical groups at 3, 6, 12, and 24 h (open symbols in Fig. 6). This was due to the BILAT-B cut-saline group ($\square$) whose 3-, 6-, 12-, and 24-h cumulative Imb intakes were significantly greater than those for the sham group ($\star$). TVAGX group significantly $>$ sham group, $P < 0.05$. Hepatic Ventral Gastric branches + dorsal trunk cuts (HV + VGBX) significantly $>$ sham, $P < 0.05$. 24-h Imb intakes on days 1–7 are expressed as a percent of basal-diet baseline. Symbols are the same as in Fig. 2. Selective vagotomy groups are indicated in the legend. Effect of surgical group, $F_{2,16} = 13.42$, $P < 0.002$. TVAGX group significantly $>$ sham group, $P < 0.05$; hepatic + ventral gastric branches + dorsal trunk cuts (HV + VGBX) significantly $>$ sham on day 2 only, $P < 0.05$.
treated groups, \( P > 0.10 \), nonsignificant. In trial 2a, the BILAT-B cut-saline group’s Imb intake was significantly less than the other groups on day 1. Therefore, it is interesting that in trial 2b, tropisetron increased Imb intake in the BILAT-B cut group (Fig. 6) to a level that did not differ from the other tropisetron-treated groups. Over the next 7 days (days 2–8), the consumption of Imb by the five tropisetron-treated groups was similar (group effect, \( P > 0.10 \), nonsignificant; data not shown). Body weights differed among the tropisetron-treated groups over the 8 days they were eating Imb, \( P < 0.01 \), due to the BILAT-B cut group. Interestingly, in view of the lower body weight in the BILAT-B cut group after eating the basal diet, post hoc analysis showed that when eating Imb on days 3 through 8, the BILAT-B cut-tropisetron group’s body weight was significantly (\( P < 0.01 \)) greater than the sham-tropisetron group (data not shown).

**Trial 2c: BILAT-B cuts and dorsal trunk vagotomies: effect of surgery.** On day 1, the cumulative Imb intakes of the saline-treated groups did not differ (effect of surgery; \( P > 0.10 \), nonsignificant; data not shown) at any interval. Beginning on day 2, the BILAT-B cut-saline group’s 24-h Imb intake, expressed as a percentage of basal-diet baseline, was higher than the other saline-treated groups. This significant (\( P < 0.05 \)) difference continued over days 4–6, during the period of adaptation to Imb (repeated-measures effect of surgery: \( P < 0.008 \)). By day 4, the BILAT-B cut-saline group was consuming 83.7% of its basal diet-baseline intake, which was significantly more than both sham groups. This result is consistent with the body weight data from trial 2a, but it differs from the Imb intake data in that trial.

**Effect Of Tropisetron**

The drug effect over time was significant (\( P < 0.001 \)) due to the effect of tropisetron on day 1. Again, the sham-tropisetron and dorsal trunk cut-tropisetron groups similarly increased their cumulative Imb intake above the saline-treated groups during the 6- to 24-h intervals (\( P < 0.003 \)) as expected, data not shown. On day 2, when the tropisetron effects were no longer seen, the sham-tropisetron group decreased its Imb intake to 29.8% of its basal-baseline intake, which was not different from that for the sham-saline group. The sham-tropisetron group’s Imb intake was significantly lower than all the other groups on day 3 (\( P < 0.03 \)). This is occasionally seen, in our experience, if the animals eat a great deal of Imb on day 1 for any reason. Apparently, when the drug effects are no longer seen and the animals do recognize the effects of Imb, they seem to tolerate it less well for a day or so. By day 5, the sham-tropisetron group’s Imb intake was no longer depressed, and there were no differences among the tropisetron-treated groups throughout the remaining days.
Summary Of The Effects Of Total And Selective Vagotomies

As outlined in Table 1, increased Imb intakes and body weights (taken during Imb feeding) were seen with the following cuts: TVAGX, ventral trunk, hepatic + ventral gastric branch, and hepatic + ventral gastric branch + dorsal trunk. Cuts of the dorsal gastric + hepatic vagal branches produced an intermediate result in which the Imb data did not differ significantly from either the sham group or the TVAGX group. No changes in body weights or food intakes were significantly from either the sham group or the TVAGX group. No changes in body weights or food intakes were seen on day 1 with cuts that did not include at least the hepatic and one of gastric branches. Increased adaptation result in which the Imb data did not differ significantly from either the sham group or the TVAGX group. No changes in body weights or food intakes were seen on day 1 with cuts that did not include at least the hepatic and one of gastric branches. Increased adaptation result in which the Imb data did not differ significantly from either the sham group or the TVAGX group.

Effect Of Surgeries On Initial Imb Intake

As noted above, TVAGX above the hepatic branch enhances intake of an Imb diet after day 1 on the diet (37). We observed an equivalent increase in Imb intake in rats within the first 6 h of experiment 1 after either TVAGX or the surgeries that included ablation of the hepatic and at least one of the gastric branches. The data for the groups having TVAGX, ventral trunk cut, hepatic + ventral gastric branch cuts, hepatic + ventral gastric branch + dorsal trunk cuts, and hepatic + dorsal gastric branch cuts in the selective vagotomy experiment were very similar (experiment 2, trials 1a–1c). These results suggest that the hepatic and gastric branches are the crucial aspects of the vagus nerve during this period of the responses to Imb on day 1, and they support our observation that the crucial fibers in the ventral trunk travel through the hepatic and ventral gastric branches and do not require the accessory celiac connection. The data also indicate that if only one of the critical connections is severed, the other

<table>
<thead>
<tr>
<th>Surgical Ablation</th>
<th>Fig. 1 Illustration</th>
<th>Day 1 Imb Intake</th>
<th>Adaptation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVAGX</td>
<td>1+2=3+4+5+6+7</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Dorsal trunk</td>
<td>2=6+7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ventral trunk</td>
<td>1=3+4+5</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Hepatic branch</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic + accessory celiac branches</td>
<td>3+4</td>
<td>0</td>
<td>↑</td>
</tr>
<tr>
<td>Hepatic + ventral gastric branches</td>
<td>3+5</td>
<td>0</td>
<td>↑</td>
</tr>
<tr>
<td>Hepatic + dorsal gastric branches</td>
<td>3+7</td>
<td>0</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Ventrab-B</td>
<td>4+5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ventral trunk</td>
<td>1=3+4+5</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>TVAGX</td>
<td>1+2=3+4+5+6+7</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Hepatic + ventral gastric + dorsal trunk</td>
<td>3+5+6+7</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>TVAGX</td>
<td>1+2=3+4+5+6+7</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Hepatic + dorsal gastric branch</td>
<td>3+7</td>
<td>0</td>
<td>↑</td>
</tr>
<tr>
<td>Accessory celiac + celiac branches</td>
<td>4+6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BILAT-B*</td>
<td>4+5+6+7 (3 spared)</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>Dorsal gastric branch</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dorsal trunk*</td>
<td>2=6+7</td>
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</tr>
<tr>
<td>Ventral gastric branch</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Numbers are for vagal branch lesions as indicated in Figure 1. Sham surgeries were done in each trial, but they are not included in the table. Effects of lesion are shown as arrows: ↑, increased imbalanced diet (Imb) intake on day 1 or increased adaptation, as seen in increased intake over days 3–5; ↓, decreased intake on day 1; 0, no change in Imb intake. TVAGX, total subdiaphragmatic vagotomy; BILAT-B, bilateral vagotomy below the hepatic branch.
pathway carries sufficient information for the normal anorectic response to Imb. It should also be noted that the combination of ventral gastric + dorsal gastric branch cuts had no effect. Only when the hepatic branch and at least one of the gastric branch pathways were both disrupted was the animal’s feeding response to the Imb ameliorated. Importantly, other combinations of cuts (Table 1) were ineffective on either body weight or Imb intake. These findings suggest that, during the initial responses to Imb on day 1, the specific combination of the hepatic branch and the gastric branches and their innervated structures, including the distal stomach and the proximal duodenum (5), may play a previously unappreciated role in the aminoprivic model. We conclude that the distal stomach and/or the proximal duodenum are the important gastrointestinal structures in the responses to Imb.

The effects of TVAGX as well as of the selective cuts used in these experiments appeared between 3 and 6 h, consistent with a role in phase 2, development of the conditioned taste aversion, rather than phase 1, the initial recognition phase, which occurs during the first 3 h (14). If the information about dietary amino acids that are absorbed at the level of the proximal duodenum is important in the early development of a learned aversion to Imb, it appears that the hepatic branch plus at least one of the gastric branches may cooperate to carry that information.

Among results for selective cuts of the ventral branch below the hepatic branch in experiment 2, the BILAT-B cut groups, in which only the hepatic branch was intact, displayed reduced body weight after surgery, even before eating Imb. This suggests that there were metabolic disturbances induced by removal of all the vagal branches except the hepatic branch. This implicates an inhibitory effect caused by the loss of the other vagal branches that may feed back onto the hepatic afferents and is blocked by 5-HT 3 antagonism (8). Antagonism of 5-HT 3 receptors with tropisetron blocks cisplatin-induced emesis in the ferret (9). Still, whether the conditioned taste aversion to Imb is mediated by gastrointestinal malaise, the increased intake of Imb after TVAGX on day 1 is not as great as the increased Imb intake seen after tropisetron, and there are temporal differences in the aversive responses after the two treatments (12). Tropisetron also consistently attenuates Imb anorexia in intact animals to ~80% of low-protein diet baseline, a 30% increase over controls, as do both of the selective 5-HT 3 antagonists ondansetron and MDL 72,222 (17, 22). Moreover, both tropisetron and MDL 72,222 block the conditioned taste aversion to saccharin after ingestion of saccharin-containing Imb diets (35). Although tropisetron also has effects at the 5-HT 1 receptor that may be seen before 6 h (discussed in detail in Ref. 12), it seems clear that the effects of Imb involve the 5-HT 3 receptor, at least between 6 and 24 h when the conditioned taste aversion develops, i.e., phase 2.

In the present studies, we asked which transections of the vagal nerve branches would interfere with the effectiveness of tropisetron. Observations by Washburn et al. (37) and Pavelka et al. (26) show a significant blunting of the tropisetron effect in the TVAGX group during day 1. In the present study, a trend was revealed consistent with these results, showing that at 6 h the tropisetron effect was blunted by TVAGX and at 9 h by the dorsal trunk cut. However, we were unable to replicate this decreased tropisetron effect in a separate group of dorsal trunk-lesioned rats (trial 2c) and by 24 h, the TVAGX group was responding maximally to tropisetron in that trial. The effectiveness of tropisetron was not blunted either by the celiac + accessory celiac cut or the individual dorsal trunk lesion. Therefore, we suggest that the dorsal trunk of the vagus does not serve alone as an important mediator of tropisetron action. Individual and combi-
nation cuts of the hepatic branch, the accessory celiac, and the ventral gastric branch also did not reduce the tropisetron effect, and thus the ventral trunk also may not act alone in mediating the action of tropisetron in this model. Apparently, both the ventral and dorsal trunk are required for the maximum tropisetron effect.

It should be noted that in the absence of subdia-
phragmatic vagal fibers, even where we did see a blun-
ting of the response to tropisetron, the drug still signif-
icantly increased Imb intake. Therefore, tropisetron may also be acting at extraglinal sites, centrally or peripherally, as reported by Daughters et al. (11). Possible alternative pathways for tropisetron's peripheral action include enteric neurons (19) and splanchnic fibers. Splanchnic nerves contain afferent and efferent fibers that are known to influence feeding behavior (34); these nerves may also be involved in the rat's response to Imb. Bilateral cuts of the greater splanchnic nerve did not blunt the tropisetron effect, and they did not increase Imb intake (25). However, Pavelka et al. (26) showed that ventral vagal trunk cuts (including hepatic branch cuts) combined with splanchnicectomy decreased the tropisetron effect on Imb intake similar to the results of the ventral trunk cut in experiment 1. Also, the ventral-B cut, which spares the hepatic branch, combined with splanchnicectomy eliminated the tropisetron effect at 3 h, attenuated it at 6 h, and had no effect at 12 or 24 h, whereas ventral-B cuts without splanchnicectomy did not alter the tropisetron effect at any time point in the present study (experiment 2, trial 2b). Although cisplatin-induced emesis is reduced by vagotomy in ferrets, surgeries combining vagotomy and splanchnicectomy abolish emesis (23). Splanchnectomy alone do not inhibit cisplatin-induced emesis (23). Therefore, neural information carried by the splanchnic nerves together with the ventral vagal trunk, for which anatomic evidence has been provided (7), may explain why vagotomy alone does not attenuate Imb anorexia as effectively as tropisetron.

Adaptation To Imb Diets

After the drug effects had diminished on day 2, both TVAGX and groups in which the hepatic branch was ablated had elevated Imb intake. The hepatic branch has been implicated in increasing adaptation to Imb diets on days 3–7; partial and total liver denervations by Bellinger et al. (2, 4) accelerate the adaptation to Imb during that period. The body weight data for the hepatic + gastric branch cuts and the ventral trunk-lesioned groups of trials 1a-1c exhibited similar patterns of adaptation. In addition, because a transaction of the celiac and accessory celiac branches (experiment 2, trials 2a and 2b) did not affect Imb adaptation, but the hepatic + gastric branch or ventral trunk cuts did, similar to the results of Bellinger et al. (4), the increased adaptation seems likely to be due to the loss of the hepatic branch. It is clear that the elimination of the dorsal trunk alone had no effect on Imb adaptation (experiment 1, experiment 2, trial 2c). Results for the longer-term effects in the BILAT-B cut groups (in which the hepatic branch was spared, but the accessory celiac and ventral gastric branches and the dorsal trunk were eliminated) were mixed, but we did not see consistent increases in adaptation in this group with an intact hepatic branch. Taken together with previous results (4), the data presented here support a role for the hepatic branch alone in the adaptation phase of the responses to Imb.

In summary, the Imb model (also known as the aminopovic model) depends on vagal innervation for the full expression of its anorectic effects. The post-ingestive responses to Imb do not seem to require either the dorsal trunk or the accessory celiac branch of the ventral trunk. At least one of the gastric branches and the hepatic branch apparently can work together to mediate phase 2 of the initial Imb anorexia. These two vagal branches mediate impulses arising at the level of the proximal duodenum, as demonstrated by Berthoud et al. (5), and this area of the gastrointestinal tract responds more vigorously to amino acids than either to glucose or isosmotic saline (32). Further work is indicated to determine whether this area of the gastrointestinal tract plays a hitherto unrecognized role in the aminopovic model. We cannot presume that these branches are the only ones to carry fibers that respond to Imb. As noted above, the dorsal gastric branch may be able to substitute for the ventral gastric branch in this model, although combinations of the hepatic and both gastric branches were somewhat more effective. Indeed, the many branches of the vagus are so diffusely distributed throughout the abdominal viscera that complex interactions are inevitable. Nonetheless, the loss of certain vagal fibers, especially the hepatic branch and the gastric branches, that innervate the proximal duodenum (5) did appear to diminish the aversion to Imb, although the hepatic branch may have a unique role in the later adaptation phase of the responses to Imb. In contrast, the effect of tropisetron appears to be mediated by extravaginal as well as vagal structures.

Perspectives

In past years, the central nervous system has been thought to be the exclusive mediator of the responses to Imb. Carotid infusions and central injections of the limiting amino acid restore food intake in animals ingesting Imb (reviewed in Refs. 14, 31). The presence of 5-HT₃ receptors in the anterior piriform cortex and amelioration of Imb anorexia by central injections of 5-HT₃ antagonists (16) give further evidence for a central mechanism. The present studies provide support for peripheral mechanisms involved in the Imb response as well and further indicate that the hepatic and gastric branches mediate at least some aspects of this function. These results impli-
cate the distal stomach and proximal duodenum in the initial aversive responses to Imb. The results of previous studies with the hepatic branch support its role in the adaptive phase. Still, full restoration of food intake has not yet been achieved by manipula-
tion of vagal systems, suggesting that central mechanisms remain important. In the wild, where animals rely on nutrient information to secure appropriate diets for maintenance of energy and growth, the presence of multiple systems provides an adaptive advantage. Further studies of the interactions among central and peripheral systems are needed to reveal the site(s) for integration of these systems.

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