Vagal involvement in dietary regulation of nutrient transport

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Bates, Sarah L., Keith A. Sharkey, and Jon B. Meddings. Vagal involvement in dietary regulation of nutrient transport. Am. J. Physiol. 274 (Gastrointest. Liver Physiol. 37): G552–G560, 1998.—In omnivores, gradual alterations in dietary nutrient composition are observed. To efficiently absorb dietary nutrients these animals alter intestinal nutrient transporter expression to match the pattern of nutrient intake. This often involves reprogramming the crypt cell to express greater numbers of the relevant transport system. The aim of this study was to determine whether vagal afferents are involved in this adaptive process. Guinea pigs were habituated to a low-carbohydrate diet and then switched to a high-carbohydrate diet. The resultant increase in glucose transporter expression was assessed by determining rates of glucose transport in jejunal brush-border membrane vesicles. Ablation of vagal afferents was accomplished by application of capsaicin to exposed cervical vagi and confirmed using Fast blue tracer studies. We found that animals in which vagal afferents were ablated with capsaicin were unable to alter rates of glucose transport in response to an increase in dietary carbohydrate. This suggests that vagal afferents are involved in this adaptive process. These findings support a role for the vagus nerve in regulating intestinal transport function, which may be important to consider in clinical disease that involves the vagus nerve.

Glucose transport; adaptation; vagus; vagal afferents; capsaicin

One of the more interesting capabilities of the small intestine is its ability to adapt nutrient transport systems to match altered dietary composition. This feature is most evident in omnivores in which it probably arose as a response to the dietary realities these animals face. Over short periods of time, the intestine of an omnivore may encounter nutrients that are high in protein or carbohydrates. Under these circumstances, the small intestine must either maintain large numbers of transport systems waiting to absorb whatever comes along or have the ability to alter the expression of epithelial transport systems.

It appears that the latter solution has been adopted by many species. These animals appear to have evolved a sophisticated mechanism to sense luminal contents and to alter epithelial transport in response to this. The existence of these mechanisms has been confirmed over the last few years in a series of elegant experiments (7, 8). Through the use of glucose transport as a model system, it is now clear that the presence of glucose is sensed in the diet, this information is processed in an unknown location, and a resulting decision is communicated to the small intestinal crypts. Within the developing crypt enterocyte there is a response to either up- or downregulate the number of sodium-dependent glucose transporters (7). The net result 3–4 days later, as these crypt cells mature and move onto the villus epithelium, is a mucosa now suited for absorption of the prevailing dietary composition. Presumably, this is one of the explanations for rapid turnover of the intestinal epithelium. If rapid turnover did not occur, adaptation to dietary intake would be difficult and slow.

For this mechanism to function three components are required. The first component is the effector compartment, which has already been clearly identified as the intestinal crypt (7). Second, a site to sense luminal contents is mandatory, and third, an integrative site must exist to make decisions regarding alterations in dietary composition. Furthermore, these three compartments must communicate in some manner, presumably either by hormonal or neural mechanisms. Because the location of the latter two compartments is presently unclear, we decided to investigate this system by analyzing the potential contribution of the nervous system as a communication pathway.

The existence of vagal glucoreceptors has been recognized for many years. Several different populations of mucosal receptor have been claimed as quality-specific chemoreceptors based on specific responses to stimuli. Receptors sensitive to luminal perfusion with glucose have been described with C fiber afferents in the vagus (20). These receptors are not spontaneously active but generate a persistent discharge when glucose or other carbohydrates are perfused through the alimentary tract. Hardcastle et al. (11) demonstrated that actively transported hexoses in rat ileum increased afferent nerve discharge in ileal mesenteric nerves. In addition, almost 20 years ago, MeI (20) demonstrated that luminal glucose in the distal ileum of the cat prompted action potentials in vagal afferent neurons. These neurons were termed “vagal glucoreceptors,” but their ultimate function was never established. Finally, recent work has suggested more direct vagal involvement in nutrient transport. Nassar et al. (21) have recently reported alterations in jejunal alanine uptake after either vagotomy or application of capsaicin to the cervical vagus.

Therefore, we generated the following hypothesis: information regarding dietary nutrient composition, ultimately destined for use in intestinal adaptation, is passed to an integrative center via vagal afferents. The decision reached by the integrative center is then sent to the crypt region for implementation.

To test this hypothesis, we used capsaicin to selectively ablate vagal afferent fibers (13). If the hypothesis was correct, we predicted that under these conditions animals would be unable to adapt to changing dietary nutrient composition. Guinea pigs were selected for...
study, because they form tight brush-border membrane vesicles suitable for studies of transport, and much previous work with the enteric nervous system has been performed with this species.

METHODS

Animals. Male guinea pigs, weighing 300–350 g (~4–5 wk of age), were purchased from Charles River (St. Constance, QC, Canada). They were allowed 1 wk to acclimate to the housing facility at the University of Calgary. During this time they were kept on a 12:12-h light-dark cycle and allowed free access to food and water. All experiments were approved by the Animal Care Committee of the University of Calgary.

Enterocyte migration. Enterocyte migration rates were determined using previously described methods (23). Briefly, bromodeoxyuridine (BrdU) was injected intraperitoneally (80 mg/kg) and allowed to incorporate into the DNA of dividing crypt cells. Animals were killed either 1, 3, 4, or 5 days later, and the midjejunum was isolated and fixed in Zamboni’s fixative. BrdU was detected with immunohistochemical techniques, using a primary anti-BrdU antibody (Sigma Chemical, St. Louis, MO) and a secondary anti-mouse immunoglobulin G Cy3 conjugate (Sigma Chemical). To determine migration rates in capsaicin-treated animals, BrdU was injected immediately after capsaicin ablation (see below) and only the 4-day time point was studied, as this appeared to correlate with the enterocyte turnover time for control animals (see RESULTS).

Capsaicin ablation. After an overnight fast, guinea pigs were anesthetized with halothane. The carotid arteries were exposed by a midline incision in the neck, and the vagus nerve was freed from each artery for a distance of ~1 cm. A small piece of paraffilm was placed under each nerve, thus isolating the surrounding tissue and preventing the spread of capsaicin. A small ball of cotton wool was placed on top of each nerve, and 50 µl of a 32.8 mM solution of capsaicin (Sigma Chemical) in a 90% paraformal-10% Tween 80 solution was placed on each cotton ball (24). The capsaicin was left in contact with the nerve for 30 min. The cotton ball was then removed, and the area was carefully and thoroughly rinsed with sterile saline. Vehicle-treated animals were managed in an identical fashion except that only vehicle was applied to the cotton wool.

Preparation of brush-border membrane vesicles. Brush-border membrane vesicles were prepared from the jejenum after an overnight fast. Guinea pigs were anesthetized with an intraperitoneal injection of somnotol (0.5 mg/kg pentobarbital sodium). A section of the small intestine, 10 cm beyond the ligament of Treitz to approximately the midlength point of the small intestine, was rapidly removed and the animal was killed by exsanguination. The section was rinsed with ice-cold saline and slit lengthwise. The mucosa was collected by scraping the luminal surface with a glass slide. The scrapings were homogenized with a Waring blender in 150 ml homogenizing buffer [30 ml of 10 mM tris(hydroxymethyl)-ammonomethane-HCl, 250 mM mannitol (pH 7.1), and 120 ml distilled water]. One milliliter of this homogenate was incubated with 1.5 ml of 1 M CaCl₂ for 20 min, and the preparation was centrifuged at 3,000 g for 15 min in a Sorval SS-34 rotor at 4°C. The pellet was discarded, and the supernatant was spun at 27,000 g for 30 min at 4°C. The resulting pellet was resuspended in 50 ml of final vesicle buffer [340 mM mannitol, 100 mM KCl, and 15 mM N-2-hydroxyethylpiperazine-N’-2-ethanesulfonic acid (HEPES), pH 7.5] and homogenized with a glass Teflon homogenizer for six strokes. The homogenate was again centrifuged at 27,000 g for 30 min, and the final pellet was resuspended in ~1 ml final vesicle buffer with a syringe and a 25-gauge needle for 15 strokes. The volume of this final vesicle buffer was variable to ensure that the protein concentration of the vesicle preparation fell within 9–14 mg/ml as determined by the Lowry protein assay (18). This final membrane preparation was immediately frozen in liquid nitrogen. An aliquot of the final preparation was tested for sucrase activity. This activity was compared with the activity in the homogenate, and the purity of the preparation was determined. Sucrease activity was determined using the modified colorimetric assay of Dahlqvist (3). Throughout the course of these experiments sucrase activity of the final membrane preparations was 13.68 ± 0.43-fold greater than the starting homogenates. This did not vary regardless of the treatment group.

Glucose transport analysis. Glucose transport into brush-border membrane vesicles was analyzed using a rapid filtration technique over a 5-s time course. Previous experiments have demonstrated that in this system the uptake rate is linear over 8–10 s (14). Therefore, the first 5 s of transport may be used to approximate the initial uptake rate. Briefly, the vesicles were incubated with the radiolabeled glucose tracer in the presence of an inwardly directed sodium gradient. All experiments were performed under voltage clamped conditions by the addition of valinomycin (1 mg/ml ethanol; Sigma Chemical) in the presence of 100 mM KCl inside and outside the vesicles. The amount of valinomycin added corresponded to 1% of the total membrane volume. Temperature (37°C), pH (7.5), and ionic strength of all solutions were kept constant over the study.

Brush-border membrane vesicles were thawed but maintained at 4°C until transport, at which time they were warmed to 37°C. Transport was initiated by rapidly mixing 10 µl of vesicles with 50 µl of a buffer containing a variable concentration of mannitol ranging from 0 to 100 mM, 15 mM HEPES, 100 mM KCl, 120 mM NaCl (pH 7.5), 4 mM D-[3H]glucose (DuPont NEN, Boston, MA), and a variable concentration of unlabeled D-glucose ranging from 0 to 100 mM. Transport was stopped by rapid dilution of the reaction mixture with 4 ml ice-cold stop solution containing 100 mM mannitol, 15 mM HEPES, 100 KCl, and 120 NaCl (pH 7.5). The final solution was rapidly filtered through a 0.45-mm filter (Millipore/Continental Water Systems, Bedford, MA), washed three times with 2 ml of stop solution, and counted in a liquid scintillation counter (Beckman Instruments, Palo Alto, CA). The protein content of each membrane sample was determined, and glucose uptake into the vesicles was expressed as picomoles D-[3H]glucose taken up per minute per milligram of protein.

Kinetic analysis of glucose transport was performed using a previously described method (19). Rates of glucose transport were calculated assuming that the cold substrate behaves as a competitive inhibitor of tracer flux and that the rate of tracer uptake will obey the modified Michaelis-Menton equation. 
\[ V_T = \frac{\left[ I_{\text{max}} T \right]}{K_m + T + C} + K_d \]
In this relationship, \( V_T \) represents the rate of labeled glucose uptake, \( T \) represents the tracer concentration, \( C \) represents the concentration of unlabeled substrate, \( I_{\text{max}} \) represents the maximal transport velocity, \( K_m \) represents the concentration at which half-maximal transport rates are achieved, and \( K_d \) represents the nonspecific component of glucose uptake. This method of kinetic analysis has been described, and its advantages over other conventional approaches have been elucidated (19).

Sucrase analysis. Sucrase activity was assayed in all experimental animals. At the time of brush-border membrane isolation, a 5-cm length of jejunum was isolated from the gut,
and the mucosa was scraped as was done for the brush-border membrane preparation. Scrapings were suspended using a 5-ml syringe and a 25-gauge needle and frozen at −20°C. Samples were analyzed for sucrase activity using the modified colorimetric assay of Dahlqvist (3).

Effect of capsaicin ablation on dietary regulation. We investigated whether functional ablation of vagal afferents altered dietary regulation of glucose transport and/or sucrase activity. “High-” and “low-” carbohydrate diets, designed for guinea pigs and meeting their basic nutrient requirements, were purchased from Purina Mills Test Diets (Richmond, IN). The precise composition of these diets is shown in Table 1. The primary difference was that the high-carbohydrate diet contained 55% carbohydrate by weight compared with 1.9% in the low-carbohydrate diet.

After acclimatization, during which they were given regular laboratory chow (43.3% carbohydrate by weight), animals were habituated to the low-carbohydrate diet. This involved a gradual introduction of the diet over 2–3 wk, mixed with regular chow. Throughout the diet manipulation, weights were monitored to ensure that the animals were thriving.

Guinea pigs were adapted to and maintained on the low-carbohydrate diet for 2 wk. One-half of the animals then underwent capsaicin treatment of their cervical vagi as described above (capsaicin-treated group), and the other one-half received vehicle (vehicle control group). After a 2-wk recovery period, one-half of the capsaicin-treated group and one-half of the control group were transferred to the high-carbohydrate diet, while the other animals remained on the low-carbohydrate diet. Ten days after the change in diet, the animals were killed and measurements of glucose uptake and sucrase activity were performed as described.

One additional experiment was performed in this group. Fast blue was used to verify that a population of vagal afferents was functionally ablated. This was done by the methods described above using the commercially available program, Systat version 5.0 (Evanston, IL). Comparisons among multiple groups were analyzed using a one-way analysis of variance followed by Tukey’s test for multiple comparisons when significance (P < 0.05) was indicated. The Student’s t-test was applied to comparisons restricted to two groups. In all groups, a minimum of 10 animals were used and for membrane transport quintuplicate determinations were made at eight different substrate concentrations.

**RESULTS**

Acute effects of capsaicin. As a preliminary experiment to decide whether the vagus nerve had any regulatory control over rates of jejunal glucose transport, we studied the acute effects of capsaicin application, an acute massive stimulation, followed by an irreversible loss of function of capsaicinsensitive afferents (13). If the vagus nerve were involved in regulating transport, we might have expected an alteration in rates of brush-border membrane transport during either the acute stimulation or the time period in which neuronal signaling was diminished.

The first problem to overcome in performing this experiment was the time course to be studied. The end points of this study were first, the rate of glucose transport into villus jejunal brush-border membrane vesicles, and second, sucrase activity. Because the latter measurement is also primarily a reflection of the mature villus enterocyte, experimental timing was critical. The neural signal, which might be received from the acute effect of capsaicin application, was expected to be received in the crypt, while the measurements to be performed by necessity involved the mature villus enterocyte. Therefore, we wished to study these crypt enterocytes when they had matured into villus enterocytes. To do this we first measured enterocyte turnover rates in both control and capsaicin-treated animals as described. In both groups we found that by 4 days, BrdU-labeled crypt enterocytes had almost reached the tip of the villus (Table 2). By 5 days the leading edge of BrdU staining was above the villus tip. Thus enterocyte migration rate was not altered by capsaicin treatment, and crypt enterocytes reached the villus tip in just over 4 days in both animal groups. Therefore, we selected two time points for study: 4 and 10 days post-capsaicin application. The former corresponds to the acute effect of capsaicin and the latter to the state of reduced neural signaling with 2.5 villus turnovers after application.

The kinetic parameters of glucose transport across the microvillus membrane after treatment with either vehicle or capsaicin are depicted in Fig. 1. It was apparent that the maximal rate of sodium-dependent glucose uptake, \( J_{\text{max}} \), into vesicles from capsaicin-
treated animals was elevated compared with their controls (i.e., vehicle treated) at day 4 (Fig. 1A). It was also apparent that maximal rates of glucose transport were substantially lower 4 days after surgery than at day 10. This would appear to be an acute effect of surgery. Importantly, at day 10, when the acute stimulatory effect of capsaicin should no longer be present, there was no difference in maximal rates of glucose uptake between capsaicin- and vehicle-treated animals. Throughout the experiment, there were no differences observed in either $K_m$ or $K_d$ (Fig. 1, B and C).

The acute effects of capsaicin treatment on jejunal sucrase activity are shown in Fig. 2. Sucrease activity is expressed in units of enzyme activity per milligram of mucosal protein. In contrast to the results obtained for glucose transport, capsaicin did not alter sucrease activity either 4 or 10 days after application.

Dietary adaptation experiments. We had two concerns regarding these experiments. The first was that either a dietary or a surgical group might not ingest equivalent amounts of food and therefore our results might reflect inadequate intake. To evaluate this we weighed all animals twice weekly over the course of these experiments. Weight gain was linear in all groups, averaging 6 g/day, and did not differ between any group. These data strongly argue against a marked variation in intake between groups. Our second concern was the adequacy of capsaicin to ablate vagal sensory afferents. To assess this, an additional experiment was performed.

One week after surgery, capsaicin- and vehicle-treated animals were given a single intraperitoneal bolus of Fast blue, as described in METHODS. Seventy-two hours later the animals were perfused, and both the nodose ganglia and brain stem were removed for fluorescence microscopy with quantitation of positively stained cell bodies. These data are shown in Table 3.

Not shown in Table 3 is the observation that cell body staining in the dorsal motor nucleus of the vagus in the brain stem was equivalent in both groups. These cells are the cell bodies of vagal efferent fibers, and this finding demonstrated that equivalent uptake and trans-
curves as described in METHODS.

Table 3. Fast blue positive staining

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Fast Blue-Positive Cells, no./nodose ganglion</th>
</tr>
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<tbody>
<tr>
<td>Vehicle</td>
<td>291.3 ± 30.2</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>80.0 ± 18.6*</td>
</tr>
</tbody>
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Data are means ± SE. *P < 0.05 compared with vehicle-treated group.

Figure 4 shows the results for the same experiment performed in those animals in which cervical vagi were treated with capsaicin. There is a dramatic difference from the data shown in Fig. 3. Rates of glucose uptake were identical and by necessity so were the derived kinetic parameters. In these animals, with capsaicin-treated cervical vagi, no adaptation to altered nutrient composition was evident.

Figure 5 shows jejunal sucrase activity found in these animals. For both vehicle- and capsaicin-treated animals, increasing dietary carbohydrate was associated with an increase in the activity of this enzyme.

**DISCUSSION**

For animals with varying dietary nutrient composition, the ability to regulate digestive and absorptive processes in response to luminal nutrient composition is important and is seen in many different species (6, 15–17). Adaptation to dietary nutrients can take place over several different time scales, and the mechanisms involved differ. In this report we have concentrated on a specific type of adaptation that involves reprogramming of the crypt cell in response to dietary alterations (7, 8). Previous work has demonstrated that rapidly switching animals from a low- to a high-carbohydrate-containing diet induces a change in nutrient transporter expression in the crypt cell. Because the ultimate effect of this alteration is only apparent after the crypt cell has migrated onto the villus, this adaptive response takes several days to become evident. This is in contrast to other forms of intestinal adaptation that can take place over a time scale of minutes to hours (2, 4, 5, 22). The aim of this study was to determine whether vagal afferents were involved in the regulation of this longer process.

In considering this scenario, several predictions seemed reasonable. First, we knew from previous experiments that the effector component of this pathway resides in the intestinal crypts (7). Ultimately, a change is made in the stem cells of this region and enterocytes with altered numbers of transporters are produced. However, at the very least, two more components must exist for this system to function efficiently.

Luminal nutrient composition must be sampled at some point. Without information regarding the composition of luminal nutrients such an effector system is useless. Also, there must be an integrative center that accumulates the sensory information. Finally, these three centers, sensing, integrative, and effector, must communicate with each other. Because the intestine is a large organ, it is unlikely that all communication occurs by paracrine actions. Therefore, we are left with the hypothesis that the communication pathways are either hormonal or neural. Hormonal regulation of nutrient transport has been demonstrated previously (12, 27); however, these are often acute effects.

The majority of vagal fibers are afferent and carry information from the gut to the brain. Furthermore, there is evidence that luminal nutrients can stimulate neural pathways. Luminal perfusion with glucose has been described to activate C fiber afferents in the vagus.
Glucose in the distal ileum produces action potentials in vagal afferent neurons. Therefore, it appeared reasonable to hypothesize that vagal afferents carry sensory information regarding luminal nutrient composition and that these pathways were important to the ability of the intestine to regulate nutrient transport systems.

We used capsaicin application to the cervical vagi as a tool to selectively ablate primary afferents arising from the gut and then tested whether animals could adapt to altered dietary nutrient content. The cell bodies of these primary afferent nerves reside in the nodose ganglia, whereas the efferent cell bodies are found in the dorsal motor nucleus of the vagus in the brain stem. After capsaicin application, vagal efferent pathways remained intact as demonstrated by our experiments with Fast blue. This neuronal dye was injected intraperitoneally and travels up vagal fibers to stain cell bodies. In these experiments, staining of the efferent fiber cell bodies in the dorsal motor nucleus of the vagus was the same in animals treated with capsaicin or vehicle. However, in the same animals, a 70% reduction of staining was apparent in the nodose ganglia of the capsaicin-treated group, whereas there was no reduction seen in the vehicle-treated group (Table 3). These data demonstrate that capsaicin, given in this manner, selectively ablates vagal afferent fibers.

One mechanism by which altered rates of transport can occur over time is by replacing the villus epithelium with a more immature cell type. Crypt cells have fewer glucose transporters than mature villus tip cells, and isolating the brush-border membrane from these cells produces dramatically lower observed rates of transport. This did not occur in these experiments. Crypt cell migration rates were identical in control and capsaicin-treated animals (Table 2). Furthermore, it is interesting to note that 4 days after the acute effect of capsaicin application, basal rates of glucose transport were greater than those observed in control animals exposed to vehicle alone (Fig. 1). The reduction in glucose transport observed in the control animals appeared to be secondary to the anesthesia and surgery required for exposing the cervical vagus. The application of capsaicin significantly blunted this reduction. This time point coincides with the acute neuronal discharge induced by capsaicin reaching the crypt region and suggests an acute neuronal effect on the programming of the crypt cell, independent of dietary change. These results differ from those observed by Nassar et al. (21), in which an increase in alanine absorption, determined by in vivo perfusion, was observed 1–2 wk after capsaicin application to the rat cervical vagus. In our experiments, we observed no difference in rates of glucose transport into isolated vesicles 10 days after treatment. Whether these differences are due to the animal species

Fig. 3. Dietary adaptation in vehicle-treated animals. A: rates of glucose transport into brush-border membrane vesicles isolated from animals switched from a low-carbohydrate diet to either a low- or high-carbohydrate diet. Animals were killed 10 days after switching to second diet. Data represent rates of uptake of labeled glucose as a function of increasing concentration of cold, competing glucose. B and C depict the kinetic parameters $J_{\text{max}}$ and $K_{\text{m}}$, respectively, derived from these curves. The significant difference in the curves shown in A was completely accounted for by the increased maximal rate of transport, $J_{\text{max}}$. Data represent means ± SE. *P < 0.05 vs. low-carbohydrate diet.
The most important finding in this study is apparent from consideration of Figs. 3 and 4. Guinea pigs treated with vehicle, and therefore having intact vagal afferents, were able to appropriately increase their ability to absorb glucose when changed from a low- to a high-carbohydrate diet (Fig. 3). This increase in the rate of glucose transport was completely explained by an increase in the maximal transport rate of this sugar, suggesting an increased number of transport sites in the brush-border membrane. No change in transporter affinity was evident. In distinct contrast, animals that received capsaicin, with a resultant reduction in vagal afferents, demonstrated no adaptation to the same alteration in dietary nutrient composition (Fig. 4).

We conclude from these experiments that functional vagal afferents are a necessary prerequisite for adaptation to occur. However, the location of the integrative center remains unclear. A reasonable hypothesis would be that this resides within the CNS and information regarding luminal nutrient composition is transmitted to the CNS via vagal afferents. Whether the vagal afferents themselves are the sensor is at present unclear and cannot be answered by these experiments.

Previous studies have examined Fos protein expression in the CNS after intestinal nutrient perfusion (29). Both lipid and glucose significantly increased the number of immunopositive cells. Therefore, a population of neurons in the brain stem is activated in response to intestinal nutrients. In view of our results, it is tempting to speculate that these cells may be involved as an integrative center and determine the ultimate intestinal response to dietary nutrient alterations. However, our experiments do not eliminate the possibility that a vagal axonal reflex is responsible for the observed

Fig. 4. Dietary adaptation in capsaicin-treated animals. Data are presented in a manner identical to that of Fig. 3. A: rates of glucose uptake in these animals were identical, irrespective of which diet they were placed on. This was confirmed by the calculated kinetic parameters, which were also identical (B and C). After capsaicin application, no adaptation to a high-carbohydrate diet, in terms of glucose transport, was observed.
dietary adaptation. Such a reflex involves transmission of a signal down the bifurcating terminal endings of a neuron. These reflexes are independent of signal transmission to the brain stem and could also account for our findings.

The second major finding of these studies was that dietary regulation of sucrase activity was not regulated by the same mechanisms important in the regulation of glucose transport. Although animals treated with capsaicin could not increase rates of intestinal glucose transport when placed on a high-carbohydrate diet, they were clearly still able to upregulate sucrase activity (Fig. 5). This is perhaps not surprising when consideration is given to previous studies examining regulation of sucrase activity. Feeding a carbohydrate-rich diet increases the immunoreactive amount of sucrase as well as its synthetic rate (28). High-protein or high-lipid diets appear to reduce sucrase activity (9, 10), while medium-chain triglycerides enhance sucrase activity (26). These effects may be mediated by pancreatic proteases, which degrade brush-border bound sucrase. Alpers (1) has demonstrated a reduced turnover rate of sucrase in rats after ligation of the pancreatic duct.

From these considerations it is apparent that regulation of both sucrase activity and glucose transport is complex, and a discordance between them is not surprising. However, what remains clear is that a signal involved in transporter adaptation is carried by vagal afferents. If signals concerning sucrase adaptation are carried by similar pathways, they are not of the same importance as those involved in transporter adaptation. Other mechanisms can override them.

In summary, this study has demonstrated that vagal afferents are involved in the ability of the guinea pig intestinal brush border to adapt to changing dietary nutrient conditions. Before extending these results to the intact organ, it is important to recognize that a blation of vagal afferents will almost certainly affect numerous variables important in the control of intestinal absorption. However, these findings may be of relevance to human conditions in which vagal damage occurs. In patients with vagotomies or metabolic diseases associated with autonomic neuropathy, such as diabetes, mild malabsorption is not uncommon. Although the data presented here do not address these issues directly, it is tempting to speculate that a previously unrecognized defect may be an inability of these patients to adapt to changing dietary nutrient composition.

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