Amino acids in the rat intestinal lumen regulate their own absorption from a distant intestinal site

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Mourad FH, Barada KA, Khoury C, Hamdi T, Saadé NE, Nassar CF. Amino acids in the rat intestinal lumen regulate their own absorption from a distant intestinal site. Am J Physiol Gastrointest Liver Physiol 297: G292–G298, 2009. First published June 18, 2009; doi:10.1152/ajpgi.00100.2009.—Intestinal nutrient transport is altered in response to changes in dietary conditions and luminal substrate level. It is not clear, however, whether an amino acid in the intestinal lumen can acutely affect its own absorption from a distant site. Our aim is to study the effect of an amino acid present in rat small intestinal segment on its own absorption from a proximal or distal site and elucidate the underlying mechanisms. The effect of instillation of alanine (Ala) in either jejunum or ileum on its own absorption at ileal or jejunal level was examined in vivo. The modulation of this intestinal regulatory loop by the following interventions was studied: tetrodotoxin (TTX) added to Ala, subdiaphragmatic vagotomy, chemical ablation of capsaicin-sensitive primary afferent (CSPA) fibers, and IV administration of calcitonin gene-related peptide (CGRP) antagonist. In addition, the kinetics of jejunal Ala absorption and the importance of Na⁺-dependent transport were studied in vitro after instilling Ala in the ileum. Basal jejunal Ala absorption [0.198 ± 0.018 μmol·cm⁻¹·20 min⁻¹ (means ± SD)] was significantly decreased with the instillation of 20 mM Ala in the ileum or in an adjacent distal jejunal segment (0.12 ± 0.015; P < 0.0001 and 0.138 ± 0.014; P < 0.002, respectively). Comparable inhibition was observed in the presence of proline in the ileum. Moreover, basal Ala absorption from the ileum (0.169 ± 0.025) was significantly decreased by the presence of 20 mM Ala in the jejunum (0.103 ± 0.027; P < 0.01). The inhibitory effect on jejunal Ala absorption was abolished by TTX, subdiaphragmatic vagotomy, neonatal capsaicin treatment, and CGRP antagonist. In vitro studies showed that Ala in the ileum affects Na⁺-mediated transport and increases Kₘ without affecting Vₘₐₓ. Intraluminal amino acids control their own absorption from a distant part of the intestine, by affecting the Na⁺-mediated Ala transporter, through a neuronal mechanism that involves CSPA and CGRP.

control of amino acid absorption; intestinointestinal reflex; enteric nervous system

The presence of nutrients in the lumen of the gastrointestinal tract (GI) triggers reflexes that optimize their processing by coordinating and controlling GI motility, blood flow, secretion, and absorption. Feedback inhibition of gastric secretary and motor function together with stimulation of pancreatic secretion, gallbladder contraction, and relaxation of the sphincter of Oddi are examples of these control mechanisms observed during the intestinal phase of a meal.

The signals that elicit reflexes in response to the passage of nutrients in the lumen are not entirely known, but the existence of reflexes implies the activation of “sensors” or special cells that can detect the presence of nutrients (21, 45). It has been demonstrated that these sensors not only are located in the gut wall but may also exist in extraintestinal sites (21, 45). For example, glucose ingestion stimulates CCK release from the proximal small intestine (27), which may lead to a decrease in hexose absorption and thus reduces excessive increase in plasma glucose concentration during a meal (28). On the other hand, the presence of glucose or maltose in the ileum induces an increase in jejunal glucose absorption (16).

Similarly, it has been shown that intestinal transport of amino acids and peptides is upregulated by their presence at high concentrations in the intestinal lumen (51). In addition, protein deprivation or semistarvation induces an increase in nutrient transport (36). On the other hand, prolonged total starvation leads to a reduction in nutrient transport as a result of decreased intestinal mass (2, 36). These adaptive changes usually take place over days (18, 20).

The end products of protein digestion are absorbed at different rates along the jejunoileal axis, with small peptides being absorbed mostly in the jejunum and free amino acids mostly in the terminal ileum (22). Hence a significant amount of amino acids and peptides may reach the distal part of the jejunum and the ileum after even a regular protein load (3, 42, 43). Furthermore, a more significant amount may reach the ileum after a heavy meal or in patients with rapid transit, malabsorption, or proximal small bowel dysfunction, such as those observed with celiac disease.

In experimental situations, responses to the presence of nutrients in the lumen of the GI tract can be studied by infusion of meal nutrients (carbohydrate, lipid, or protein) into the distal or proximal small intestine or the colon (29, 45, 46, 53). In most published studies, amino acid or sugar absorption in a segment of the small intestine, at a given dietary condition, was compared with basal transport in the same segment. However, very little data is available on the acute regulation of amino acid absorption from the small intestine and how the presence of a certain amount of amino acid in one part of the intestine can affect its absorption at a distant site.

The aim of this study is to determine the effect of amino acids present in a small intestinal segment on its own absorption from a proximal or distal site and to try to elucidate the mechanism of this cross talk between different parts of the intestine.

MATERIALS AND METHODS

All animal experiments were approved by the Institutional Review Board-Animal Care Committee and the University Research Board of the American University of Beirut-Lebanon.
Intestinal perfusion for measurement of amino acid absorption. Adult female Sprague-Dawley rats (180–220 g body wt) (n = 5–9 in each group) fasted for 18 h were anesthetized with an intraperitoneal (IP) injection of sodium pentobarbitorne (45 mg/kg) and maintained throughout the experiments by intermittent IP injections (15–30 mg/kg) as necessary. The abdomen was opened through a midline incision and cannulae were inserted into the jejunum (proximally 5 cm distal to the ligament of Treitz and 20 cm distally) and fixed by ligation (test segment) as described previously (40). In addition, an adjacent distal 15-cm segment of jejunum or a 15-cm segment of distal ileum was similarly isolated and cannulated. The intestine was returned to the abdominal cavity and the abdomen was closed. The femoral vein was cannulated for intravenous (IV) administration of saline or drugs. The isolated test segment was perfused in situ at a rate of 0.7 ml/min with PBS containing 1 mM cold alanine (Ala), 10 μCi [14C]Ala, and 15 mg/l phenol red, which was used to correct for any changes in Ala concentrations resulting from water movement (48). In other experiments, proline (Pro) was used instead of Ala. Twenty minutes were allowed to elapse to ensure establishment of a steady state, following which consecutive 20-min collections of the effluent were obtained from the distal cannula for 2 h. During the experiments, rectal body temperature was maintained at 37 ± 0.2°C, through a heating blanket connected to a YSI temperature controller (YSI, Yellow Springs, OH). Heart beats were continuously monitored through a Hellige-Servomed digital monitor (Freiburg, Germany). At the end of the experiments, the animals were killed by an overdose of pentobarbitone and the perfused intestinal segment removed, and its accurate length was documented. The samples of effluent were analyzed immediately or kept frozen at −20°C until analyzed within 2 wk. Aliquots of the initial and effluent solutions were assayed for phenol red concentration and radioactivity content. Absorption was calculated from the rate of disappearance of labeled amino acid from the perfusate solution, taking into account water transport as measured by the change of phenol red concentrations (9, 40, 41).

Effect of intestinal amino acid on jejunal amino acid absorption. Immediately before starting the jejunal perfusion, Ala at different concentrations (10 or 20 mM) in 2.5 ml phosphate-buffered saline (PBS) or PBS alone was instilled in the ileum or in the isolated distal jejunal segment and the cannulae were closed. In addition, a few experiments were repeated after use of 20 mM Ala in Na+−free PBS in the ileum. In further experiments, the effect of 20 mM Pro in PBS instilled in the ileum on jejunal Pro or Ala absorption was also determined.

Effect of jejunal Ala on ileal Ala absorption. The same protocol was followed as above with instillation of either 20 mM Ala in PBS or PBS alone in the jejunum and then measurement of Ala absorption from the ileum.

Time frame for the effect of intestinal Ala on Ala absorption from an adjacent or distant intestinal segment. To study the time it takes for Ala to exert its effect at a distant site, a different protocol was followed in which a proximal jejunal segment was perfused for 1 h with 1 mM Ala as stated above; then 20 mM Ala was instilled in the distal jejunal segment or in the ileum and the rate of proximal jejunal Ala absorption was determined for a further 2 h. In further experiments, the effect of 20 mM glucose or 20 mM mannitol instilled in the ileum instead of Ala was studied.

Effect of intravenously administered Ala on jejunal Ala absorption. To study whether Ala in the systemic circulation can affect jejunal Ala absorption, a proximal jejunal segment was perfused continuously with 1 mM Ala and the effluent collected every 20 min as stated above. Sixty minutes later, an intravenous infusion of Ala (1 mM) dissolved in sterile saline or saline alone was started at a rate of 1 ml/h for 1 h. Jejunal Ala absorption was measured all through the experiment and continued for 1 h after stopping intravenous Ala infusion.

Neuronal blockade by either TTX, capsaicin, or subdiaphragmatic vagotomy. To determine whether the inhibitory effect of ileal Ala on jejunal Ala absorption is neurally mediated, different protocols of neuronal blockade or ablation were used: 1) TTX: TTX at a concentration of 0.2 μmol/l was added to the 20 mM Ala in the ileum (32, 52). 2) Chemical ablation of capsaicin-sensitive primary afferents (CSPA): Rats were injected subcutaneously with capsaicin (50 mg/kg) (in 10% Tween 80, 10% olive oil, 80% distilled water) on the second day after birth. Sham rats received the vehicle injection (47). Fifteen days later, rats were checked for successful ablation by the eye wipe test (26) and were entered in the experimental protocol when they reached the desired weight (180–220 g). 3) Subdiaphragmatic vagotomy: Under anesthesia, the abdominal cavity was explored through a midline incision exposing the intestine, the stomach, and the lower part of the esophagus. With an operating microscope, a subdiaphragmatic vagotomy was performed by isolating and cutting the anterior and lateral branches of the descending vagus nerves. Directly after completion of the surgical procedure, the isolation of the intestinal segments and the perfusions were carried out as described above.

CGRP antagonism. The CGRP antagonist (hCGRP8−37) dissolved in 0.9% saline containing 0.1% BSA was infused at a rate of 1 nmol kg−1 min−1 (1 ml/h) and was started with the Ala perfusion. The specificity of this antagonist was previously demonstrated (7).

Kinetic studies on Ala absorption in vitro. Kinetic studies for the effect of ileal Ala on jejunal Ala absorption was determined in vitro. The same experimental protocol as in the in vivo study was followed for ileal loop isolation and instillation of PBS with or without 20 mM Ala. Forty minutes later, a 15-cm segment of proximal jejunum was removed and placed immediately in oxygenated ice-cold PBS solution. It was freed from its mesenteric and fat attachment, opened along the mesenteric line, and cut longitudinally into 1-cm strips. Isolated jejunal strips were then incubated for 1 min in oxygenated PBS solution containing different concentrations of Ala 0.1−20 mM and 10 μCi labeled [14C]Ala. After incubation, the strips were removed and immediately dipped into ice-cold isotoic mannitol solution. Each strip was blotted with Whatman no. 1 filter paper, its wet weight was determined, and then the strip was extracted in 2 ml of 0.1 M HNO3 for at least 4 h. Aliquots of the tissue extracts and incubation media were counted for their [14C]Ala content in a liquid scintillation counter. From the data obtained, intracellular concentration of Ala was calculated after correction for the extracellular space by using a trace amount of [1H]inulin as an extracellular marker (41). Values of intracellular Ala concentration were plotted against Ala concentration in the incubation medium. The kinetic constants [maximal velocity (Vmax) and Km] for each animal were calculated by Lineweaver-Burk plot (GraphPad Prism 3 software) and then the means of Vmax and Km were compared between the two groups.

Further experiments were performed following the same protocol but the jejunal strips were incubated for 1 min in Na+−free PBS containing the different concentrations of Ala.

Data analysis. The rates of amino acid absorption are expressed in the figures as means ± SD in micromoles per centimeter per 20 min of intestinal segment length at different time intervals (every 20 min) in each group of animals studied. In addition, the mean of amino acid absorption over a 1- or 2-h period was calculated and presented under RESULTS to simplify data presentation. Comparisons between groups were made by paired or unpaired t-test depending on experimental protocols. In multiple comparisons, ANOVA was used followed by Bonferroni post hoc test as appropriate. GraphPad Prism 3 and Instat 3 software were used for statistics and graphics (GraphPad Software, San Diego, CA).

Materials. TTX, capsaicin, and hCGRP8−37 were obtained from Sigma Chemical (St. Louis, MO). Radiolabeled Ala and Pro were obtained from Amersham International (Buckinghamshire, UK). All other reagents were supplied by British Drug House (BDH Chemicals, Poole, UK).

RESULTS

Effect of intestinal Ala on jejunal Ala absorption. Jejunal Ala absorption in the presence of PBS in distal ileum was steady over the 2-h study period ranging from 0.190 to 0.210
μmol·cm⁻¹·20 min⁻¹ (mean ± SD: 0.198 ± 0.018, n = 9) (Fig. 1). This absorption was significantly decreased by the presence of 10 mM Ala in the ileum (0.166 ± 0.012, n = 7; P < 0.002), and the decrease was more pronounced reaching 40% with the presence of 20 mM Ala (0.120 ± 0.015, n = 6; P < 0.0001) (Fig. 1). Instilling 20 mM Ala dissolved in Na⁺-free PBS in the ileum did not produce a significant alteration of its inhibitory effect on jejunal Ala absorption (0.140 ± 0.005, n = 5).

In addition, instillation of 20 mM Ala in a distal jejunal segment resulted in a significant drop in Ala absorption from the proximal segment (0.138 ± 0.014, n = 5; P < 0.002).

**Effect of ileal Pro on jejunal Ala or Pro absorption.** The presence of Pro in the ileum also decreased jejunal Ala absorption by ~25% (0.155 ± 0.010, n = 5; P < 0.0003) (Fig. 2A). This inhibitory effect persisted for at least 2 h. The rate of basal jejunal Pro absorption (0.157 ± 0.007, n = 5) was less than that of Ala but was also significantly decreased in the presence of 20 mM Pro in the ileum (0.132 ± 0.009, n = 5; P < 0.04) (Fig. 2B). This decrease was observed mainly during the second hour of perfusion (29%).

**Effect of neuronal blockade.** TTX added to the 20 mM Ala in the ileum completely abolished the inhibitory effect of ileal Ala on jejunal Ala absorption (Fig. 3A). Acute subdiaphragmatic vagotomy did not affect basal Ala absorption (0.195 ± 0.012, n = 6) but inhibited the effect of ileal Ala on jejunal Ala absorption (Fig. 3B). Neonatal ablation of CSPA resulted in a significant decrease in basal Ala absorption (0.157 ± 0.014, n = 6) but no further drop was observed with the instillation of 20 mM Ala in the ileum (0.155 ± 0.015, n = 6; P < 0.005 compared with 20 mM ileal Ala in sham) (Fig. 4A).

**Effect of CGRP antagonism.** Intravenous administration of the CGRP antagonist at a rate of 1 nmol·kg⁻¹·min⁻¹ had no significant effect on basal Ala absorption but completely abolished the inhibitory effect of ileal Ala on jejunal Ala absorption (Fig. 4B).

**Effect of jejunal Ala on ileal Ala absorption.** Ala absorption from the ileum was less than that from the jejunum (0.169 ± 0.025, n = 5) but was significantly decreased (44%) by the presence of 20 mM Ala in the jejunum (0.103 ± 0.027, n = 5; P < 0.01) (Fig. 5).

**Time frame for the effect of intestinal Ala on Ala absorption from an adjacent or distant intestinal segment.** Jejunal Ala absorption (0.210 ± 0.019, n = 5) was significantly decreased (by 36%) after the introduction of Ala in the distal jejunal segment (0.133 ± 0.019, n = 5; P < 0.002) (Fig. 6). This inhibitory effect was observed immediately and disappeared within 1 h (Fig. 6). Similarly, the inhibitory effect of ileal Ala on jejunal Ala absorption was seen immediately; however, it persisted for at least 2 h (Fig. 6).

On the other hand, instillation of 20 mM glucose or 20 mM mannitol in the ileum did not affect jejunal Ala absorption (glucose: 0.186 ± 0.012 vs. 0.180 ± 0.018, n = 5, and mannitol: 0.195 ± 0.016 vs. 0.184 ± 0.010, n = 5; both P > 0.05).

**Effect of intravenous alanine on jejunal alanine absorption.** Intravenous Ala infusion had no effect on jejunal Ala absorption and was similar to the effect of saline infusion (0.181 ± 0.020, n = 5 and 0.182 ± 0.017, n = 5, respectively) (Fig. 6).

**Kinetic studies on alanine absorption in vitro.** The presence of Ala in the ileum significantly decreased Ala absorption by jejunal strips at different Ala concentrations (Fig. 7A). The V_max in the two groups was similar (PBS in the ileum: 53.9 ± 6.5, n = 10; Ala in the ileum 64.9 ± 5.8 μmol·min⁻¹·g⁻¹ dry wt, n = 13); however, there was a significant difference in
the $K_m$ (22.8 ± 3.5 and 31.6 ± 3.8 mM, respectively; $P < 0.03$), pointing to a change in the affinity of Ala to its transporter (Fig. 7A).

The effect of intraluminal alanine on Na$^+$-dependent and Na$^+$-independent jejunal Ala uptake was also determined. With Na$^+$-free PBS as an incubation medium for jejunal strips, there was no difference in the absorption of Ala between the two groups at different Ala concentrations (Fig. 7B).

DISCUSSION

Our data demonstrate that the presence of Ala in one segment of the small intestine reduces its own absorption from a proximal or distal segment. This phenomenon appears to be neurally mediated through the vagus nerve and involves CGRP as a putative neurotransmitter.

The presence of Ala in the ileum decreases jejunal Ala absorption in a concentration-dependent manner reaching almost 40% at a concentration of 20 mM. This inhibitory effect occurs within a short period of time after instillation of Ala in the ileum and persists for at least 2 h. Many observations were made regarding this inhibitory effect. First, it is not specific for a single amino acid since the same inhibition was seen with Pro, an amino acid that may use the same mucosal transporters. Second, there is cross reactivity between different amino acids, since the presence of Pro in distal ileum inhibited jejunal Ala absorption, although to a lesser extent than Ala itself. Third, this distal to proximal inhibition is paralleled by a proximal to distal one, since the presence of 20 mM Ala in the jejunum significantly decreased the rate of ileal Ala absorption. Fourth, these inhibitory reflexes exist between remote and adjacent intestinal areas, since the presence of 20 mM Ala in a distal segment of jejunum inhibited its own absorption from a proximal segment of the jejunum. Thus there are both feedback and feedforward inhibitory reflexes of Ala on its own absorption. Fifth, this reflex is not induced by circulating amino acids since intravenous infusion of Ala did not inhibit jejunal Ala absorption.

Ala is transported into the small intestine by amino acid carriers, namely, the B0 (SLC6A19), the B0,+ (SLC6A14), ASC (SLC1A5), b0,+ (SLC3A1, SLC7A9), and PAT (SLC36A1) transport systems, via sodium-dependent and sodium-independent mechanisms (4, 12, 22). Furthermore, it is absorbed from both jejunum and ileum with some species difference as to the site of the maximal absorptive capacity. Whereas Ala is better absorbed from the ileum than the jejunum in the rabbit (39), the reverse occurs in rat intestine (5, 34), which may reflect
differences in the availability of amino acid transporters. On the other hand, Pro is essentially transported in the rat intestine by the B and the PAT transport systems (31). Our observation that ileal Pro also reduces jejunal Ala absorption suggests that the signal in the ileum may be a substrate for the same transporter.

Regulation of nutrient transporter activity in response to changing dietary substrate levels in the lumen has been demonstrated in the small intestine in humans and animal models (15, 18, 19). Their upregulation or downregulation take place slowly, i.e., over hours to days, and the mechanism involves a change in the number of transporters at the brush border membrane (i.e., $V_{\text{max}}$) without a change of $K_{\text{m}}$. In addition, this regulation varies for different amino acids. For example, dietary protein restriction resulted in a significant reduction of transport capacity for the nonessential amino acid Ala and an increase in transport capacity for the essential amino acid leucine in sheep and goat intestines (49). By contrast, in our model, the reduction in transport took place quickly (in less than 20 min), a time that is too short to alter the synthesis of new transporters. Although an increased trafficking of the transporters from the brush border membrane to the intracellular compartment could theoretically provide a possible explanation (1), our data point to a change in the $K_{\text{m}}$ rather than in the $V_{\text{max}}$ in the kinetic studies performed in vitro. Thus it seems that there is a change in the affinity of the transporter to its substrate. Whether this occurs through a conformational change of the transporter, induced by the presence of Ala, remains to be determined.

The concentrations of Ala and Pro used in our study are higher than that achieved after a regular meal (3), but the presence of brush border membrane peptidases could create high local concentrations of free amino acids (11) after a high protein intake or under pathological conditions such as dumping syndrome, rapid transit, and malabsorption. Furthermore, this concentration is comparable to what has been used in other studies (9). In general, unabsorbed nutrients reaching the ileum have been reported to increase their absorption in the upper gut. As illustration, the rate of jejunal glucose absorption is increased significantly when either glucose or maltose are present in the lower ileum (16). In addition, unabsorbed fat in the ileum prolongs small intestinal transit time, which serves to increase the absorption of a meal (17). Different effects on
proximal gut function between ileal proteins on one hand, and ileal carbohydrates and fat on the other hand, have been described by others (35). It has been suggested that nutrients in the intestinal lumen can induce or inhibit their own transporter in the intestine depending on whether the nutrient is essential, is toxic at high concentrations, or can be used as a source of energy. Thus uptake of nonessential amino acids used for calories increases with increasing luminal concentration. Our data unravel a different intestinointestinal inhibitory reflex for the control of amino acid absorption, a process that might serve to save energy required for the absorption and/or to control the level of amino acids in the systemic circulation. In addition, the accumulation of one amino acid in the enterocytes may affect the absorption of other more essential amino acids (22) and therefore the described inhibitory reflex may serve to favor the absorption of these essential amino acids. Another possible explanation is that the decrease in one amino acid absorption will save the energy for the production of peptide transporters and thus increase the efficiency of protein and amino acids absorption (1, 22). Furthermore, this reflex may serve to decrease the absorption of cationic amino acids, which use a transport system that functions as an obligatory neutral amino acid exchanger (22).

Although several possibilities can be considered, the mechanism of the inhibitory effect of Ala in the present study can be explained by either humoral or neural reflexes or both. Nutrients in the ileum induce the secretion of neurotensin (NT), enteroglucagon, and peptide YY (PYY) from N and L cells, respectively. Infusion of egg chicken hydrolysate in the isolated, vascularity perfused, rat ileum stimulate glucagon-like peptide-1 (GLP-1), PYY, and NT secretion (17). Both NT and GLP-1 were shown to increase, rather than inhibit, jejunal amino acid absorption (13, 14, 33). PYY is known to enhance intestinal water absorption (10), but its effect on amino acid absorption is not known. Thus it is unlikely that the observed inhibitory effect of Ala on its own absorption is secondary to the release of one of these hormones.

The present study presents several indications for a neural involvement in the inhibitory effect of ileal Ala on jejunal Ala absorption. The presence of TTX with Ala in the ileum abolished this inhibitory effect, suggesting that it requires action potential transmission and therefore the activation of extrinsic and/or enteric neural mechanisms. Indeed, all the major macronutrients have been reported to induce the activation of mucosal afferent nerve fibers (25). For example, infusion of fatty acid in the ileum increased discharges of vagal afferents in the rat. This activation was attenuated by prior treatment of the intestinal mucosa with a local anesthetic or with the sensory autonomic CSPA fibers (50) and are known to play a "local efferent" role by releasing different peptides such as VIP, CGRP, and substance P at the level of the peripheral endings (23, 24, 30, 37). Thus it can be speculated that the presence of nutrients in the small intestine may activate CSPA fibers. Such activation can lead to a local release of neuuropeptides from their peripheral endings (local effector mechanism) in addition to a reflex activation of vagal and sympathetic efferents.

Blocking CGRP mechanisms by IV injection of CGRP antagonist completely abolished this inhibitory effect without affecting basal jejunal Ala absorption. CGRP is widely distributed in the enteric neurons and in primary sensory afferents in the gut (23, 38). Previous results from our group provided direct evidence on the role of CGRP in decreasing jejunal amino acid absorption through direct (intrinsic) and indirect (central) neural mechanisms (7). Thus one might speculate that CGRP release triggered by ileal Ala may inhibit jejunal amino acid absorption through two possible mechanisms: either locally, by the release of CGRP from CSPA peripheral terminals, or centrally, by alteration of the function of vagal preganglionic neurons through CGRP released by the central terminals of CSPA fibers.

In conclusion, it can be speculated that an absorptivorsorptive reflex controls, at least partially, the transport of amino acids in the different intestinal segments by affecting the affinity of the Na"+-dependent transporter to its substrate. This reflex is mediated by intrinsic and extrinsic neural mechanisms and involves vagal CSPA fibers and CGRP as a neurotransmitter.

REFERENCES


