Learned flavor preferences induced by intragastric administration of rewarding nutrients: role of capsaicin-sensitive vagal afferent fibers

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Zafra MA, Molina F, Puerto A. Learned flavor preferences induced by intragastric administration of rewarding nutrients: role of capsaicin-sensitive vagal afferent fibers. Am J Physiol Regul Integr Comp Physiol 293: R635–R641, 2007. First published May 2, 2007; doi:10.1152/ajpregu.00136.2007.—Learned flavor preferences can be established after intragastric nutrient administration by two different behavioral procedures, concurrent and sequential. In a concurrent procedure, two flavored stimuli are offered separately but at the same time on a daily basis: one stimulus is paired with the simultaneous intragastric administration of partially digested food and the other with physiological saline. In sequential learning, the two stimuli are presented during alternate sessions. Neural mechanisms underlying these learning modalities have yet to be fully elucidated. The aim of this study was to examine the role of vagal afferent fibers in the visceral processing of rewarding nutrients during concurrent (experiment 1) and sequential (experiment 2) flavor preference learning in Wistar rats. For this purpose, capsaicin, a neurotoxin that destroys slightly myelinated or unmyelinated sensory axons, was applied to the subdiaphragmatic region of the esophagus to selectively damage most of the vagal afferent pathways that originate in the gastrointestinal system. Results showed that capsaicin [1 mg of capsaicin dissolved in 1 ml of vehicle (10% Tween 80 in oil)] blocked acquisition of concurrent but not sequential flavor preference learning. These results are interpreted in terms of a dual neurobiological system involved in processing the rewarding effects of intragastrically administered nutrients. The vagus nerve, specifically capsaicin-sensitive vagal afferent fibers, would only be essential in concurrent flavor preference learning, which requires rapid processing of visceral information.

vagus nerve; concurrent flavor preference learning; sequential flavor preference learning

FOOD INTAKE IS A MOTIVATED behavior aimed at maintaining the energy homeostasis necessary for the survival of organisms. Besides genetic predispositions for certain foods, food preferences appear to develop largely via learning mechanisms (6, 38, 64). Thus, flavor may become associated with positive postigestive consequences, e.g., a reduction in nutrient deficits or recovery from a vitamin deficiency (6, 14, 38, 62).

Flavor preferences can be induced in the laboratory by two different behavioral procedures, concurrent and sequential taste preference learning. In the concurrent procedure, two different-flavored stimuli are offered at the same time, one paired with simultaneous intragastric administration of a nutrient and the other with physiological saline (PS). In the sequential learning procedure, the two flavored stimuli are presented at alternate sessions (55, 60, 73).

Studies of taste aversion learning (TAL) demonstrated that concurrent TAL requires simultaneous viscerogustatory stimulation, demanding rapid detection and processing of the substances administered into the gastrointestinal cavity. However, this simultaneous administration does not appear to be necessary for sequential TAL (31). Information on nutrients in the gastrointestinal tract can reach the brain by both the neural and humoral pathway. The former allows rapid detection of the visceral stimuli, whereas the latter involves a slower visceral processing (39, 42, 54, 59, 67). It has been demonstrated that the integrity of the vagus nerve is essential in concurrent TAL but does not appear to be relevant in sequential TAL, which allows long intervals between the gustatory and visceral stimuli (2–4, 72).

Little is known to date about the neurobiological mechanisms that mediate nutrient-induced flavor preferences (63). Therefore, the present study was designed to investigate whether the anatomical and functional dissociation observed in TAL might also be found in flavor preference learning induced by intragastric nutrient administration. The specific objective was to determine the influence of vagal afferents in the development of concurrent and sequential flavor preference learning, using intragastrically administered cephalic foods.

The nutrients used in these experiments were partially digested complex foods, which have been reported to be highly rewarding when intragastrically administered in learning experiments (45, 46, 71, 73). These so-called cephalic foods are pumped out of the stomach of donor animals after undergoing the cephalic/nervous phase of digestion (71).

Vagal afferents can be selectively damaged by the perivagal application of capsaicin, a neurotoxin that has no effect on afferents but destroys weakly myelized primary afferent fibers or unmyelinated C-fibers (22, 53), which are both abundant in the vagus nerve (34, 43, 44). The capsaicin was topically applied in the present experiments to produce only localized lesions and avoid the generalized destruction of fibers observed after systemic (intraperitoneal or subcutaneous) administration of capsaicin to neonate or adult animals (22, 24, 51, 53). In this study, capsaicin was applied to the subdiaphragmatic region of the esophagus, thereby preserving intact the vagal fibers originating from the thoracic viscera and located in the cervical vagus nerve.

Previous studies from our laboratory demonstrated that vagal deafferentation with capsaicin induces a transient increase in food intake during 24 h after the surgery (68, 69), suggesting the possible usefulness of this effect as a behavioral index of the efficacy of the perivagal application of capsaicin (68). Therefore, as a test of the afferent vagotomy, the food intake in these experiments was quantified during 24 h after the perivagal application of capsaicin.

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MATERIALS AND METHODS

Subjects

All experiments were performed on adult male Wistar rats from a breeding colony at the University of Granada. Experiment 1 used 24 male Wistar rats (310–350 g each), which were randomly assigned to a capsaicin-treated (n = 9), control (sham procedure) (n = 8), or donor (n = 7) group. Experiment 2 used 19 male Wistar rats (260–300 g each) randomly assigned to a capsaicin-treated (n = 11) or control (sham procedure) group (n = 8). Experiment 2 also included as donors 10 neurologically intact rats from the previous experiment. On arrival at the laboratory, the animals were individually housed in 30 × 15 × 30 cm methacrylate cages (which also served as training chambers during the experiment) with unlimited access to food and water. The lateral sides of the cages were black and opaque; the front and back sides were transparent. The front side had two 1.6-cm holes at the same distance from the center and edges and at the same height above the floor of the cage. These orifices allowed the animal access to spouts attached to cylindrical graduated burettes through which flavors, liquid diet, and water were delivered. The experimental procedures took place during light periods and were conducted in accordance with the Animal Care and Use Committee Guidelines established by Spanish Royal Law 1201/2005. Approval for this study was granted by the Ethical Committee of the University of Granada. In addition, all authors of this paper were granted a license by the Andalusian (Federal State) Government to conduct research with animals.

Surgical Procedure

Perivagal capsaicin treatment. The perivagal capsaicin treatment was performed following a modification of the method published by Raybould and Taché (51). After intraperitoneal administration of 0.15 mg atropine (Sigma, St. Louis, MO), the animal was anesthetized with sodium pentothal (46.3 mg/kg ip sodium thiopental; Abbott Laboratories, Abbott Park, IL). A 3-cm incision was then made along the midline of the abdominal wall, and the esophagus was exposed with extreme care. A paraffin was placed beneath it to minimize the spread of capsaicin (Fluka, 98%) to surrounding tissues. A cotton pledget soaked in capsaicin solution [1 mg of capsaicin dissolved in 1 ml of vehicle (10% Tween 80 in olive oil)] was placed around the esophagus for 30 min. Capsaicin drops were applied every 5 min to keep the esophagus moist. The total amount of capsaicin applied was 1 ml (1 mg/rat). The surgical procedure for control animals was identical except that the esophagus was not handled, that is, they underwent a laparotomy and remained under these conditions for 30 min, but no substance was applied around the esophagus.

Intragastric catheters. In all animals (capsaicin-treated, controls, and donors), two intragastric catheters were implanted into the body of the stomach and routed through the abdominal muscle wall, one on each side of the animal, to the back of the neck. The area was then thoroughly rinsed with saline and dried with sterile swabs. Stitching was made as appropriate to help close the wounds, and a local antiseptic was applied to the wound (Betadine, Viatris Pharm, Madrid, Spain). Finally, both lesioned and control animals were given an intramuscular 0.1 cc dose of penicillin (1,000,000 IU, Penilevel, Spain). Finally, both lesioned and control animals were given an intramuscular 0.1 cc dose of penicillin (1,000,000 IU, Penilevel, Spain). After surgery, the animals were returned to their cages, where solid food and water were available ad libitum. A behavior index of the lesioning effect of the perivagal application of capsaicin was obtained by recording the amount of food consumed during the 24 h after surgery (68).

Experiment 1: Learned Concurrent Flavor Preferences

The aim of experiment 1 was to examine the participation of capsaicin-sensitive afferent vagal fibers in concurrent flavor preference learning. An anatomic and functional dissociation was previously observed in TAL, in which the vagal pathway was only essential in concurrent tasks requiring a rapid processing of the visceral information (2–4, 31, 72). It was hypothesized that the vagal pathway might also be essential for the rapid processing of rewarding nutritive information and that damage to vagal afferents might interrupt concurrent flavor preference learning.

Pretraining period. After 10–12 days for postoperative recovery with food and water available ad libitum, subjects underwent a 3-day pretraining period of water and food restriction. During each pretraining session, all animals were allowed to drink tap water daily from two graduated burettes offered simultaneously (to avoid positional preferences) through the frontal orifices of the cages. Water was offered to the subjects for 10 min on the first day and for 7 min on the last two days. If the animal tended to consume water from only one of the burettes during the first two pretraining days, this burette was removed for the last 3 min of each session to induce the animal to drink from the other burette. On the third pretraining day, practically all animals spontaneously drank from both burettes alternately. At 30 min after removal of the water, the animals were offered 15 g of food (Panlab, Barcelona, Spain).

Donor rats were placed in a different room and trained for 5 days to ingest a liquid diet (Ideal Evaporated whole milk, 50% diluted; Nestlé, Barcelona, Spain); 100 ml of this liquid diet contained 5.75 g of carbohydrates, 3.93 g of fat, and 3.93 g of protein (total energy: 74.37 kcal). The diet was offered for several hours both in the morning and afternoon. During the first two days of the pretraining period, this diet was combined with ~7 g of solid food. During the three remaining days, the animals were only offered a liquid diet. Water was offered for 10 min during the evening of each day, although the animals did not generally consume it.

Behavioral procedure. The experiment began after the 3-day pretraining period, when the capsaicin-treated and control animals had learned to drink alternating between the two burettes. In each trial (7 min), the rats were given a choice of two flavored stimuli offered at the same time [0.5% strawberry (S) and 0.5% coconut (C) extract diluted in water, McCormick, San Francisco, CA]. The position of the burettes containing flavors remained the same throughout the experiment (strawberry on the left side of the animal and coconut on the right). Intake from one 0.1-cc-graduated burette was paired with the simultaneous intragastric injection via catheter of a partially digested liquid diet pumped from the stomach of the donor rats (the food had remained in the stomach of the donor rats for ≥30 min before being pumped out). Intake from the other burette was paired with physiological saline (0.9% NaCl; Apiroserum Laboratory, Instituto de Bio logia y Suero terapia, Madrid, Spain) administered via the other catheter. Both stimuli (liquid diet and physiological saline) were intragastrically and simultaneously injected manually by the experimenter every time the rats drank from the associated burette, at a rate of 1 ml/1 ml of ingested flavor stimulus. To compensate for any natural flavor preferences of the subjects, pairing of the liquid diet was balanced. Thus, half of the animals received the liquid diet when they drank S and received physiological saline (PS) when they drank C, whereas the other half received the liquid diet paired with C, and PS paired with S. An illustration of this procedure was previously published (31). After 60 min, the animals were offered 10 g of food and, later in the evening (i.e., 15 h before the next session), any remaining food was removed. This experimental procedure was repeated over the course of six trials.

Experiment 2: Learned Sequential Flavor Preferences

Studies of TAL showed that vagal afferents were essential in concurrent but not sequential TAL (2–4, 72). Experiment 2 was designed to test the hypothesis that capsaicin-sensitive vagal fibers are not involved in sequential flavor preference learning.
**Pretraining period.** After 14–15 days for postoperative recovery, with food and water available ad libitum, animals underwent a 3-day pretraining period of water and food restriction. The animals had access to a single burette containing tap water during days 1 and 2. The burette position was varied appropriately to avoid the development of positional preferences. On day 3, both burettes were simultaneously presented. Water was offered for 10 min on the first pretraining day and for 7 min on the last 2 days. Each day, at 30 min after removal of the water, 15 g of solid food (Panlab, S.L. Barcelona) was administered, and the experiment continued as described for experiment 1.

**Behavioral procedure.** The experiment began after the 3-day pretraining period, with the animals passing through a four-session cycle (two learning trials) and a final test. In the first and third sessions of this cycle, a flavored stimulus (0.5% strawberry) was offered for 7 min from a graduated burette on the left side of the cage. In one half of the capsaicin-treated and control animals, flavor intake was associated with simultaneous intragastric injection of a partially digested milk from a graduated burette on the right side of the cage. The volume of liquid diet or PS administered was 1 ml/1 ml of flavor stimulus ingested and weighing the stomach of the animals after 12 h of fasting. The Martin, Cheng and Novin procedure (29) was followed, extracting and weighing the stomach of the animals after 12 h of fasting. When the proportion of the weight of the stomach to that of the animal (before fasting) exceeded 0.02, the animal was considered vagotomized, and its data were excluded from the study.

**Vagotomy Test**

To test whether the vagus nerve accidentally suffered complete damage during the surgical intervention, the capsaicin-treated animals underwent a complete vagotomy test after the experiments. Control animals were not tested because the esophagus had not been handled. The Martin, Cheng and Novin procedure (29) was followed, extracting and weighing the stomach of the animals after 12 h of fasting. No animals were vagotomized during the experimental procedure. No animals were vagotomized.

**Data Analysis**

Statistica ver. 5.1 program (Statsoft, Tulsa, OK) was used for all statistical analyses, and P < 0.05 was considered statistically significant. The significance of mean differences among groups was determined by ANOVA. Values are presented as means.

**RESULTS**

**Experiment 1**

Two animals in the capsaicin-treated group were excluded from the statistical analysis: complete vagotomy was detected in one of them, and a catheter became detached during the experiment in the other.

**Postsurgical food intake.** During the first 24 h after surgery, food intake of the capsaicin-treated group was significantly higher than that of the control group (7.98 vs. 3.06). *AJP-Regul Integr Comp Physiol • VOL 293 • AUGUST 2007 • www.ajpregu.org*

**Learned concurrent flavor preferences.** Analysis of the concurrent TAL data using a three-way ANOVA (group × day × substance) showed that the days variable [F(5,65) = 5.87; P = 0.00015], group × substance interaction [F(1,13) = 7.54; P = 0.016] and days × substance interaction [F(5,65) = 3.43; P = 0.008] were significant.

According to subsequent analyses (two-way ANOVA with repeated measures, days × substances), the capsaicin-treated animals did not learn the task, since neither the days × substance interaction [F(5,30) = 1.01; P = 0.42] nor the substance variable [F(1,6) = 0.66; P = 0.44], nor the days variable [F(5,30) = 2.42; P = 0.058] were significant (See Fig. 1A). In contrast, the discriminatory task was learned by the control group, since the days variable [F(5,35) = 4.91; P = 0.0016], the substance variable [F(1,7) = 9.91; P = 0.016], and the days × substance interaction [F(5,35) = 4.71; P = 0.002; Fig. 1B] were significant. These differences were already significant on day 5 [day 1: F(1,7) = 4.53, P = 0.07; day 2: F(1,7) = 3.25, P = 0.11; day 3: F(1,7) = 0.93, P = 0.36, day 4: F(1,7) = 3.55, P = 0.101, day 5: F(1,7) = 9.20, P = 0.019, day 6: F(1,7) = 14.38, P = 0.0067].

**Experiment 2**

Three animals in the capsaicin-treated group and one in the control group were excluded because a catheter became detached during the experimental procedure. No animals were vagotomized.

**Postoperative food intake.** During the first 24 h after surgery, food intake of the capsaicin-treated group was significantly higher than that of the control group (4.27 vs. 2.17). Fig. 1. Mean intake of flavor stimuli paired with predigested liquid diet and physiological saline in capsaicin-treated (A) and control (B) rats of experiment 1.
Learned sequential flavor preferences. Choice test data were analyzed using a two-way ANOVA (group × substance), which showed that no variable was significant in the first choice test, and only the substance variable was significant \[F(1,13) = 12.17; P = 0.0039\] in the second choice test. No significance was found in either choice test for the group variable \[F(1,13) = 0.88; P = 0.36\] or group × substance interaction \[F(1,13) = 0.03; P = 0.86\]. Independent one-way ANOVAs for each group showed a significant effect of substance. Both capsaicin-treated \[F(1,7) = 6.29; P = 0.04\] and nonlesioned control animals \[F(1,6) = 6.18; P = 0.047\] preferred the gustatory stimulus associated with the intragastric administration of predigested liquid food (see Fig. 2).

DISCUSSION

These experiments demonstrate that damage to capsaicin-sensitive vagal afferents (behaviorally confirmed by data on intake during the first 24 h after surgery), that is, to weakly myelinated primary afferent fibers (Aδ) or unmyelinated C-fibers, blocks learning in concurrent taste discrimination tasks when rewarding nutrients are intragastrically administered. In contrast, similar damage had no effect when taste stimuli and their respective intragastric administrations were offered according to a sequential procedure, with capsaicin-treated animals completing the task similarly to intact animals. As shown in Fig. 2, although a tendency to learn was already apparent in the first choice test, acquisition of this learning task was demonstrated in the second choice test (after four trials), when both treated and control animals showed a preference for the flavor associated with intragastric administration of predigested nutrients.

Results obtained from the second experiment in this study ruled out the possibility that the results of experiment 1 might be due to some incapability of capsaicin-treated animals caused by the damage to vagal afferents, since animals with identical damage could learn the task in the sequential paradigm, despite a smaller number of trials with the nutrient-paired flavor (4 vs. 6 trials). Experiment 2 data were comparable with the results of other studies, in which both capsaicin-treated (28) and vagotomized (55, 57) animals were able to associate gustatory stimuli with intragastrically administered macronutrients in sequential paradigms.

An essential difference between concurrent and sequential learning is that the former is only possible when animals can rapidly detect and process visceral stimuli to associate them with their respective gustatory stimuli. Various authors have demonstrated that information from the gastrointestinal tract is transmitted to the brain via two complementary pathways, that is, the humoral and neural systems (39, 54, 59). In concurrent learning, participation of the humoral pathway appears unlikely because the stimuli between which the animals can alternate are only present for a brief time period (7 min), too short for any relevant participation of the humoral system. In fact, postabsorptive factors generated by the presence of foods in the gastrointestinal tract probably do not appear until after the animals have completed their consumption. Indeed, if these humoral signals had been present, they could not have been important; otherwise, the capsaicin-treated animals would have learned the concurrent learning task.

Hence, it appears likely that information can only be transmitted by the neural pathway in concurrent learning. However, sensory information from the gastrointestinal tract can also be transmitted to the brain via vagal and spinal afferent fibers (13, 59), either of which may therefore be responsible. Nevertheless, experiment 1 results suggest that an intact vagal system is essential for concurrent learning (since damage to this system interrupted the learning) and appear to rule out the participation of spinal afferent fibers. This conclusion is compatible with the demonstration by physiological and behavioral studies that spinal visceral afferents are of little importance in nutrition-related processes (12, 19).

The gastrointestinal localization of the vagal receptors that mediate the rewarding effect induced by predigested foods remains to be determined. Given the time requirements imposed by the concurrent task, vagal afferents probably come from the stomach and perhaps also from the first segments of the small intestine, the only ones likely to be reached by the visceral stimulus in such a short time period. In this context, electrophysiological data have confirmed that the gastrointestinal tract is amply innervated by chemosensitive afferents, mostly of a vagal nature (13, 21, 32, 33, 35, 49, 50, 59). These afferents are found in the mucosa of the digestive tract and are sensitive to the pH, osmolarity, and nutrient component of foods, for example, glucose, amino acids, or lipids (20, 32, 33, 49, 50, 59). Whereas pH- and osmolality-sensitive afferents are mostly localized in the first segments of the digestive tract (32, 33, 49, 59), afferents sensitive to different macronutrients have almost exclusively been identified in the small intestine, espe-
cially the proximal part into which the stomach empties after a meal (11, 32, 33, 35, 49, 50, 59). Nevertheless, glucosensitive fibers have also been reported in the antral portion of the stomach (33).

Besides chemosensitive afferents, fibers sensitive to mechanical stimuli are found in the gastrointestinal mucosa. These mechanosensitive vagal fibers almost all act as contact receptors activated by the passage of solid particles through the digestive tract (11, 59). It has therefore been proposed that their main function is to deliver information on characteristics of the food bolus, especially its consistency (13, 21, 32, 33, 49, 50). Nevertheless, it appears unlikely that these fibers are relevant in the present investigation, since not all intragastrically administered foods can induce flavor preferences (47, 48, 56). The above suggests that the induction of preferences may depend more on the chemical properties of nutrients than on characteristics detectable by gastrointestinal mechanoreceptors.

At any rate, the response of vagal afferents to these nutritive stimuli is usually rapid (21, 33, 59); therefore, the vagus nerve appears to have the appropriate properties for detecting and transmitting the presence and characteristics of intragastrically administered nutrients. These gastrointestinal vagal afferents may be activated during the short time period of intragastric administration in the concurrent paradigm (7 min). This is especially likely with the administration of liquid diets, characterized by a significantly faster gastric emptying into the duodenum, which is further accelerated when the nutrients reach the stomach by intragastric administration (25, 26, 37). Thus, between one-third and one-half of liquid food is emptied into the intestine before the end of its intragastric administration (26).

Previous studies demonstrated that some nutrients, e.g., glucose, can be very rapidly absorbed from the gastrointestinal system (61). Although the food administered in the present study was much more complex (evaporated whole milk), we cannot completely rule out activation of the vagus nerve at hepatic level by postabsorptive signals.

It could also be argued that the concurrent task might be established by long-term learning associating the amount of the two flavors consumed with the amount of subsequent nutrient reinforcement received, as reported in other studies (5). However, if this were so, capsaicin-treated animals could be expected to have learned the task, and they did not.

Likewise, because gustatory stimuli associated with intragastric nutrients were always offered to each animal in the same position in our experiments, it could be proposed that learning might have been established by spatial cues rather than by gustatory-olfactory type indexes. In this context, various studies have demonstrated a close relationship between visceral and gustatory information, with a preferential predisposition for the latter to be associated with visceral signals (15, 16, 40, 58). When gustatory cues are absent, animals usually associate the visceral stimulus with olfactory-type information (1). Nevertheless, these results do not rule out the possibility that when neither type of clue (taste or olfactory) is available, animals can learn concurrent conditioning place preference induced by the simultaneous administration of rewarding nutrients (F. Molina and A. Puerto, unpublished results).

In fact, a previous comparison by our group between concurrent TAL and right/left placement aversion learning (using hypertonic sodium chloride) found that the animals learned the task with the former but not the latter procedure (30). Furthermore, when animals that had learned the concurrent TAL task underwent a taste reversal test, they were unable to correctly perform this new task and were also unable to maintain their reinforced position preference, which could be expected if they had learned the task by using spatial cues (30).

To summarize, the present results suggest that, as in TAL, there are two learning modalities with different neurobiological substrates for associating foods with the visceral consequences of their ingestion. The mechanism underlying one of these modalities involves a rapid processing, of a vagal nature, to swiftly detect some characteristics of the ingested nutrients, whereas the other modality is based on a slower mechanism in which vagal afferents appear to play no role.

This anatomic dissociation of the two visceral processing systems has also been observed in other behavioral processes of importance for the survival of the individual. Thus, it has been traditionally accepted that the intake of nutrients is controlled by two neurobiological substrates that inform the brain about the energetic status of the individual. One of these, responsible for short-term satiety (satiation), is a fast-action mechanism involved in the cessation of consumption behavior and is essentially of a vagal nature (41, 52). The other substrate has a more delayed action, participates in long-term satiety, and depends on postabsorptive effects, such as the availability of nutrients, the rate of their utilization, and their storage in adipose tissue (42, 67).

During disease, cytokines released by immune cells are known to act on the nervous system to affect numerous behaviors and processes, for example, food and water intake, body temperature, hypothalamo-pituitary-adrenocortical axis, and activity level of the individual, among others (10, 17, 66). Recent studies showed that cytokines gain access to the nervous system via the humoral pathway (by active transport processes or circumventricular structures) or are peripherally processed via their action on vagal afferents (9, 10, 18).

Dual processing has also been demonstrated in cases of nausea and vomiting, a protective mechanism that removes potentially harmful substances from the alimentary tract (7, 23, 27). Depending on the emetic agent utilized, this mechanism can be abolished by vagotomy (7, 65) or by ablation of the area postrema, a circumventricular structure that serves as a chemoreceptive site to detect emetic toxins in the blood (8, 36).

In conclusion, data obtained in the present and previous studies show that the implication of the vagus nerve in flavor preference learning largely depends on the learning conditions. Thus, when the experimental task demands the rapid detection and processing of substances present in the gastrointestinal tract, using stimuli that can be neurally processed, the vagal afferents appear to be essential. In contrast, when the learning task is characterized by a delayed presentation of the stimuli, as in the sequential paradigm, this neural system does not appear to be necessary, and alternative processing systems may play a role such as the spinal innervation or, more likely, the humoral pathway.

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