Enteral feeding: brain-visceral interactions in the processing of nutrients

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†In memoriam

Abstract

Enteral nutrition is often mandatory, especiallyfor patients in vegetative or minimally conscious state. However, its application is non-viable in certain cases due to various adverse effects. Some of theseare explained by absence of the cephalic phase of digestion,during which exocrine, endocrine, and motor physiological responsesprepare the digestive system to receive, digest, transform and utilizeingested nutrients. These responses result from the stimulation by nutrients of cephalic sensory systems, mainly in the oropharyngeal cavity,and can also be elicited by food-related thoughts or expectations.

The digestive system appearsable torapidly assess the suitability of food and transmitthis information to the brain.The vagus nerve and its brainstem relays in the caudal nucleus of the solitary tract (NST) and parabrachial complex appear to participate in the anatomic pathwayresponsible for this rapid processing. Thus, blockade of the vagus nerve, NST, or external lateral parabrachial region (LPBe) interrupts expression of conditioned taste preferencesinduced by administration of “predigested” food, while LPBe activation by electric stimulation generates similar preferences to those observed after cephalic food administration.

This research may help design enteral diets better adapted to digestive physiology and developpharmacological interventionsagainst adverse effects of enteral nutrition.

Keywords: Enteral nutrition, cephalic phase, rapid processing of nutrients, vagus nerve, gelatinous subnucleus, external lateral parabrachial subnucleus.

1. Introduction

Clinical nutrition refers to practicesfor supplying nutrients to individuals when oral administration is inadvisable, insufficient, or impossible [1]. These areessential to maintain the function of vital organs and systems, minimizing the effects of food deprivation and avoiding nutritional deficiencies [2].In general, these techniques are divided between enteral nutrition, in which liquid diet is directly administered into the gastric or intestinal cavity, and parenteral nutrition, in which nutritional solutions are delivered intravenously [3; Figure 1].

INSERT FIGURE 1 ABOUT HERE

2.- Enteral *versus* parenteral nutrition

Most clinical nutrition specialists report that enteral nutrition has multiple advantages over parental nutrition and should be selected whenever the gastrointestinal tract can be used [3-8]. Parenteral nutrition is more expensive [6,7,9]and is usually more invasive in comparison to enteral nutrition, exposing patients to greater risks [10]. Notably, there are important clinical reasons for preferring the enteral administration route because of the association of parenteral nutrition with severe complications,including thromboembolism, severe metabolic fluctuations, hyper-or hypo-glycemia, hyperlipidemia, blood electrolyte abnormalities, infectious complications [2, 7, 11,12],and, more controversially [13], a greater risk of "bacterial translocation" [12, 14-17].

Bacterial translocation takes place when bacteria usually confined to the digestive tract penetrate the intestinal mucosa and invade the lymphatic system, blood system, and numerous internal organs [16-18]. This event has been described as one of the main causes of septicemia and as a risk factor for the onset and progression of multiple organ failure,characterized by the uncontrolled systemic inflammation of internal organs [14, 16, 18-20]. The main factors proposed as possible triggers for bacterial translocation include intestinal mucosal barrier break(increased mucosa permeability), intestinal microflora alteration (bacterial overgrowth),and immune system impairment [5, 17, 18, 21].These changes are associated with parenteral but not enteral nutrition [21-24].

Under normal conditions, the gastrointestinal mucosa acts as an effective barrier against the migration of microorganisms into the systemic circulation[16, 21, 25]. The integrity of this barrier is determined by the renewal of epithelial cells that compose it and by the number and type of bacteria that it contains[20, 25, 26]. A key stimulus for mucosal cell proliferation and the maintenance of bacterial homeostasis appears to be the presence and availability of nutrients in the intestinal lumen [4-6, 16, 24-27]. The food itself and the hormones released in its presence exert trophic effects on mucosa throughout the gastrointestinal system,from the stomach, small intestine, and colon to the gallbladder and pancreas [5, 24-26]. Both stimuli preserve the intestinal flora [5, 6, 20-22], which in turn critically modulate the immune response by producing the enzymes neededto release immunostimulant nutrients and by activating the secretion of cytokine-like molecules known as bacteriocins [23,25, 28].

Hence, mucosa atrophyis favored when the gastrointestinal system is not used, as in patients receiving parenteral nutrition. This increases the risk of septic complications[12, 20, 25] and compromises intestinal immunocompetence, because the expression and induction of specific immune responses critically depend on the local microenvironment[20, 25, 28]. These problems are less frequently encountered in patients receiving enteral nutrition [9, 12, 20,21].

For these reasons, enteral (rather than parenteral) nutritionis recommended in a wide range of clinical situations, including organ transplantation [11], cancer[29],pancreatitis [3, 30], Crohn'sdisease [31], intestinal resection or inflammation [5], critical disease [3, 6, 7, 9], and the postoperative period [3, 8, 11, 23]. It is also preferred for premature or low-birth-weight infants[12,32], for the elderly, for neurological patients [29, 33-35],for patients with anorexia nervosa [29]and for those with AIDS[36].Nevertheless, enteral nutrition is not free of drawbacks, as discussed below[1,22].

3.- Problems associated with enteral nutrition

There is a consensus among health careprofessionals that the nutritional status of patients is lower in those receiving enteral nutrition than in those fed

orally. Enteral feeding has been associated with several disorders, although it is sometimes difficult to establish whether they are caused by the disease, the specific diet,or by the food administration route[1].

However, regardless of their disease, patients on enteral nutrition often show a series of “secondary” symptoms that can be described as gastrointestinal tract reactions to diet administration, including: pain;discomfort; gastric residual volume; delayed gastric emptying; abdominal bloating and cramps; nausea/vomiting; diarrhea [1, 4, 8, 9, 12, 20, 22, 32,38,39]; metabolic disorders[1,12]; and, when the enteral nutrition is longer term, ulcersand major weight loss [33,34]. In addition, some patients are unable to tolerate enteral nutrition [9, 22], especially pediatric patients [38,39].The causes of these problems have not been fully elucidated, although some psychobiological studies, mainly inanimals, have suggested that they may in part result from the entry of food into the digestive tract in “non-physiological” conditions[40, 41].

4.- Animal models of enteral nutrition: Intragastric feeding

In experimental studies, enteral nutrition is known as intragastric or intraintestinal feeding and also appears to be accompanied by numerous disorders that affect the digestion, absorption, and metabolism of nutrients. One of the first authors to document alterations in animals caused by intragastric feeding was the Russian scientist Ivan Pavlov[42], whose studies masterfully demonstrated the marked importance of the passage of food through oropharyngeal systems for its subsequent digestion [43, 44]. This oropharyngeal stimulation, designated “psychic reflex” by Pavlov, is now known as the cephalic phase of digestion, which comprises a set of autonomic and endocrinalresponses to stimulation by the food of sensory perceptive systems in the head and particularly in the oropharyngeal cavity. Nevertheless, although these cephalicresponses are preferentially initiated by contact with the food, they can also be effectively elicited just by seeing or anticipating it or by thoughts or any learned cues associated with it[40, 42, 44].

Pavlovreported that when food was directly introduced into the stomach, thesecretion of gastric juiceswas delayed and scant, with weak digestive power, contrasting with the rapid and abundant cascade of gastric secretions observedwhen the same nutrients passed through the oropharyngeal cavity after their real or sham intake (in the latter case, when food is orally ingested but extracted through a cannula before reaching the stomach).He concluded that the low gastric juice secretion in enteral nutrition delaysand considerably prolongs digestion [42].

The absence of oropharyngeal stimulation also indirectly delays other digestive secretions. It was reported by Pavlov that intragastricallyadministered food is not accompanied by salivary secretions, whose arrival in the stomach cavity stimulates the release of gastric juices[42]. It has also been demonstrated that the digestion of carbohydrates and fats that starts in the mouth through the action of salivary amylase and lipase continues in the stomach [45-47]. Hence, the absence of saliva delays gastric secretion and hampers the digestion of some nutrients. There is also an indirect effect on the release of pancreatic juices, whose secretion is determined by the level of hydrochloric acid in the stomach [42].

Absence of the cephalic phase impacts on digestion-related substances throughout the digestive system, from the mouth or stomach(e.g., salivary enzymes, hydrochloric acid, gastrin, pepsinogen, immunoglobulins, etc.), as mentionedabove,to the small intestine (bicarbonate ordigestive enzymes), liver, or pancreas (numerous hormones) [for review seereferences 40 and 44]. Many secretions triggered by cephalic stimulation are also specific and adapted to the

nature of the food [42, 48-53]. In other words, food components appear to be identified before they reach the stomach, allowing the digestive system to be specifically prepared for their transformation and utilization [40, 54].

Removal of the cephalic phase affects not only endocrine and exocrine secretions but also gastrointestinal motor activity, with an anticipatory increase in cephalic stimulation[55-58]. The intragastric feeding of experimental animals has also been found to markedly accelerate the outflow of gastric contentsinto the duodenum[59-61], which might be responsible for the discomfort experienced by patients with “dumping syndrome”[59]. This syndrome is observed in humans who have undergone abdominal vagotomy and is characterized by the rapid emptying of gastric contents into the duodenum, producing nausea and epigastric pain [62]. In this regard, the intraintestinal administration of nutrients (fats) was found to significantly damage the intestinal mucosa [60, 63].

Disorders induced by the absence of oropharyngeal stimulation extend to post-absorptive stages [51, 54, 59, 61, 64-67]. In human studies, glucose intolerance (increased blood levels)and reduced blood glucagon levels wereobserved after intragastric glucose administration, but not when this was accompanied by oral sensory stimulation through modified sham feeding [68].It has also been demonstrated that lipolysis is slower with intragastric *versus* oral feeding, leading to higher plasma levels of fatty acids[59].

Responses that are affected by the absence of cephalic stimulation can be observed in other levels of the digestive system and beyond, including postprandial thermogenesis, anticipatory rise in heart rate, increased respiratoryrate in response to eating, and changes in thetransport and intestinal absorption of nutrients and in bile flow and secretin release, among others [46, 69-72].

Taken together, publishedstudies confirm that the cephalic phase not only optimizes food digestion but also intervenes in processes related to nutrient absorption and metabolism. Many of these effects may be secondary to the release of gastrointestinal hormones, whose secretion is stimulated by the anticipation and presence of food in the oropharyngeal cavity [73-76].

5.- Is intragastric feeding“stressful”?

According to the above-reported studies, intragastric or intraintestinal feeding means that the digestive system is not prepared to receive, digest, process, or even appropriately utilize the administered nutrients. They would arrive in the system undernon-physiological,negative conditions, which may in part account for the digestive problems that can often make enteral nutrition non-viable.

Taste learning is one of the behavioral procedures used by scientists to determine whether individuals perceive the food reaching the digestive system as positive or negative. In these learning tasks, two non-nutritionalflavored solutions of water are offered, with the intragastric/intraintestinal administration of a nutritional stimulus being associated with one solution and of an innocuous, non-nutritional stimulus (e.g., physiological saline) with the other. The preference of animals is determined after multiple sessions pairing the taste and visceral stimuli[77-79.]

Studies using this techniquehave demonstrated that the direct administration of complex food into the gastric cavity is a powerful way to establish flavor-conditioned aversions [63, 80, 81].Thus, when rats were subjected to a discriminative flavorlearning task using whole milk as visceral stimulus, theypreferred the flavor associated with physiological saline and strongly rejected the flavor associated with the food, even after a 22-h food deprivation period[77, 80-83]. Similar results were observed with intraintestinal feeding, finding that

association of the intraduodenal administration of fats with the oral intake of saccharose produced a strong rejection of saccharose in subsequent presentations [63].

Results obtained with the enteral administration of natural food markedly contrast with those obtained for the intragastric administration of food subjected to cephalic processing(aspirated from the stomachs of donor subjects shortly after its oral consumption). Unlike observations with natural food, the animals developed a strong preference for the taste stimulus associated with the administration of "predigested" food and rejected the stimulus associated with physiological saline [77, 78, 84, 85].Hence, enterally administered foods are experienced as rewarding/positive when they have undergone oropharyngeal processing, and assistanceof the cephalic phase appears to adapt enteral diets more closely to digestive physiology. According to these data, the digestive system also seems perfectly preparedfor the rapid assessment of the suitability of foods and for the transmission of this information to the central nervous system.

Results of research in animals has prompted numerous clinical studies. Although enteral nutrition was not routine clinical practice until the 1960s, food had long been administered*via* gastric catheters, with the first case being published in 1564 by Matthew Cornax, a Viennese professor and physician. The first reports on gastric function and disorders in individuals fed *via* gastric catheters were presented by Coronel William Beaumont(1833)and the French physician Charles Richet (1879), who described the appearance of reddish blemishes and spots, scabs, and fragments of gastric mucosa, as well as delays in digestion and gastric emptying[86].

One of the most famous studies in this field was published by Wolf and Wolff andknown as "Tom's case". In 1895, at the age of 9 years, Tom underwent gastronomy after accidentally eating boiling food and was only able to consume food *via* gastric catheter for the next 65 yrs. Tom was studied by various authors during this time, and one of the main findings was that digestion was not optimal when the food was deposited directly in the stomach and the intake was wholly unsatisfactory, leading to his malnourishment. However, when he was allowed to taste and chew the food before intragastric administration, at his own request, he gained weight and developed a good appetite[87].Other similar reports in the literature include the case of a 24-yr-old woman presented during the Annual Meeting of the American College of Gastroenterologyin 1950[88] and of a patient with a 29-year history of complete esophageal obstruction andlarge permanent gastrostomy [89],who both acquired the habit of tasting and partially chewing food before intragastric administration.

In summary, these data indicate that the signals produced by food in the oropharyngeal cavity trigger a cascade of exocrine, endocrine, and motor reactions that prepare the digestive system for the reception, digestion, absorption, and metabolism of the food ingested, allowing feeding to be perceived as a satisfactory or rewarding event. When these signals aremissing, a series of noxious consequences can hamper the adequate development of these processes, making the feeding experience negative or "stressful"[40, 41, 44, 59].

It is therefore possible that some of the noxious effects of enteral nutrition can be palliated by administering diets that imitate "cephalic" food in some way. This possibility is currently under investigation in our laboratory.

6.- Transmission pathways of rewarding visceral information to the central nervous system

In general, two distinct procedures can be used to establishflavor learning, designated by our group as concurrent and sequential flavor learning. Two non-

nutritionalflavored stimuli with their respective intragastric administrations are simultaneously offered during a short time period (usually7 min) in concurrent learning, whereas the stimuli are presented in alternating sessions in sequential learning (Figure 2). A key difference between these procedures is that animals must detect and process visceral stimuli very quickly to establish an association in concurrent learning, whereas this can be established in a more delayed fashion in sequential learning[79, 81, 85].

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Using these procedures, and with the aim of being able to palliate the negative effects of enteral nutrition in the future, our group has studied the rapid pathway for processing information related to nutritional stimuli present in the gastrointestinal tract (concurrent learning), especially in the case of suitable or rewarding ("cephalic")foods [78, 84, 85].

Information from the gastrointestinal tract reaches the brain *via*complementary humoral and neural pathways [90]. However, given the aforementioned time constraints of concurrent taste, participation of the humoral pathway in this task appears unlikely, and the neural pathway would be responsible for the transmission of information under these learning conditions [84].

Neuroanatomical and neurophysiological studies have demonstrated that the gastrointestinal tractreceives both vagal and spinal nerve fibers [90], and either may have carried nutritional information to the brain in our studies. However, numerous physiological and behavioral investigations have indicated that spinal visceral afferents arelessimportant in nutrition [91] and appear more related to nociceptive processes[92].For this reason, we have focused on the vagal system in our experiments on the neural substrates involved in transmitting rewarding visceral information to the central nervous system.

Vagal afferents are distributed throughout the digestive system and receive detailed information on the specific nature of the nutrients present in the gastrointestinal lumen *via* interoceptors (chemo-, osmo-, thermo-, and mechanoreceptors) [90, 93, 94]. This takes place directly, through the free diffusion of luminal chemicals across epithelial cells), and also indirectly *via* paracrine messengers released by enteroendocrine cells, which act as sensory transducers ("taste" cells) thatdetect the physical and chemical nature of luminal contents [93, 95-97].Vagal afferents with nutritional information ascend towards the brain in parallel with autonomic motor fibers, forming bundles on both sides of the esophagus and ending in the nodose ganglion, from which central vagal branches extendtowards their first brain relay: the nucleus of the solitary tract (NST)[98, 99].

Our group has investigated the participation of vagal afferents in the rapid transmission of rewarding nutritional information to the brain using capsaicin. We appliedthis neurotoxin around the esophagus,selectively lesioning unmyelinated afferents and weakly myelinated fibers[100], which are both largely present in the vagus nerve [101, 102]. Wefound that information transmission mediated by capsaicin-sensitive vagal afferents is essential in concurrent taste discrimination tasks [84]. Thus, neurochemical interruption of this pathway hampers the establishment of taste preferences induced by the intragastric administration of "cephalic" foods, which is achieved without difficulty by neurologically intact animals.

However, capsaicin-sensitive afferents are not indispensable for the induction oftaste preferences using sequential tasks. In this case, both capsaicin-treated and neurologically intact animals effectively learn the task and show clear preferences for taste stimuli associated with the intragastric administration of predigested nutrients. These results support the idea that information is unlikely

to be transmitted to the brain *via* spinal or humoral mechanisms in concurrent tasks, because capsaicin-treated animals could be expected to learn the task if this was the case, and they did not [84]. Because each flavor is presented with its respective intragastric administration on alternate days inthe sequential modality, long time periods are available for the detection and processing of the visceral stimuli. Hence, neurologically intact animalscoulduse both neural pathways(likely while the food is present in the gastrointestinal tract) and humoral pathways (after the absorption of nutrients), whereas capsaicin-treated animals couldonly use the humoral (and/or spinal) pathway, although this would be sufficient to develop the corresponding taste preference behaviors.

Anatomical, physiological, and immunohistochemical studies have demonstrated that vagal afferents from the upper gastrointestinal tract project towards the intermediate-caudal region of the NST (Figure 3), a gateway for visceral signal processing [103].Thus, various subnuclei of the intermediate-caudal region of the NST (NSTic)show c-fos activity after normal foodintake [104], after intragastric or intraduodenal nutrient administration [105-107], and in situations of gastric[108]and intestinal [109] distension, among others. In many of these cases, NSTic activation is abolished by the chemical or surgical lesioning of vagal afferents[106, 110].

INSERT FIGURE 3 ABOUT HERE

Given the time constraints implicit in the concurrent procedure,the digestive segments most likely to be involved in this learning modality (i.e., responsible for initial detection of the visceral stimulus) would be proximal ones(preferentially the stomach and duodenum). Sensory visceral information is known to be organized topographically in the NSTicwith relative anatomical segregation [98, 99]. For instance, a high density of gastric vagal afferents is concentrated in the lateral portion of the dorsomedial NST ina cell cluster known as the gelatinous nucleus [98, 99, 103, 111-112],whereasafferents from the duodenum and other segments of the small intestineare distributed in different areas of the dorsomedial nucleus, especially in more caudal and medial areas of the intermediate region[98, 99, 109].

Our group recently demonstrated that the gelatinous subnucleus (SolG) participates in the learning of concurrent taste preferences induced by intragastrically administered “cephalic” foods [85]. It therefore appears that the gelatinous nucleus (SolG), alongside capsaicin-sensitive vagal afferents,may participate in the neural pathway that rapidly processes rewarding nutritionalinformation from the upper gastrointestinal tract. This subnucleus almost exclusively concentrates gastric vagal afferents [99, 105, 109, 112]and is a receptor of fine vagal afferents [113], i.e., the type of fibers lesioned by capsaicin [100]. In addition, capsaicin-induced damage of small ganglion cells was found to produce axonaldegeneration in the SolG, among other regions [114].

The NSTic in turn relays visceral information from the gut to the lateral division of the pontine parabrachial complex (Figure 3), especially to its lateral external subnucleus (LPBe). This subnucleus concentrates information from both the stomach and duodenum, receiving a large numberof the afferents projected from the SolG [111, 115, 116]. These anatomical connections allow modification of LPBe activity by electrical stimulation of the vagus nerve and by the intragastric administration of various nutrients [106, 117, 118]. Moreover, the intragastric application of nutrients induces c-fos expression inintermediate-caudal and dorsomedial NST subnucleiand in the LPBe,among other regions [106, 107]. This dual activation has also been observed after the administration of substances that positively or negatively affect food intake, including pharmacological agents such as methyl palmoxirate, 2,5-anhydro-D-mannitol, or dexfenfluramine) and

various hormones (e.g., cholecystokinin, bombesin, or secretin) [119-124]. These effects of neuronal activation and/or intake can also be abolished or attenuated by truncal vagotomy or perivagal capsaicin treatment [106, 119, 123-127].

Our laboratory has also addressed the possibility of the LPBe nucleus being part of the rapid processing pathway of rewarding information related to nutrients present in the upper gastrointestinal tract in our laboratory. Unlike neurologically intact animals, LPBe-lesioned animalsprovedunable to develop taste preferences induced by the intragastric administration of "cephalic or predigested" foods in concurrent taste learning tasks, but both groups were able to learn taste preferences in sequential taste learning tasks [78].

We have also used other procedures to explorethe involvement of the LPBe in rewarding processes, including the induction of taste and place preferences by electrical stimulation of this subnucleus [128]. In addition, large lesions of the LPB, including the external subnucleus,appear to reverse aversive effects of the intragastric administration of natural, non-predigested nutrients, avoiding rejection of the associated taste stimulus and appearing to induce a flavor preference (*versus* water) in late trials of the task [82].

Considered together, these data suggest that the rapid processing of visceral information on rewarding nutrition(in upper gastrointestinal segments) is mediated by a neural pathway that originates peripherally in the vagus nerve and includes NSTic regions (e.g., SolG) and the LPBe [78, 84, 85].In fact, this visceral vagal-NSTic-LPBe information pathway also appears to participate in other physiological processes requiring the rapid transmission of nutritional information. We recently showed that both the vagus nerve [129] and SolG [130]or LPBe [131] are essential in circumstances that require the immediate adjustment of food intake, extracting part of ingested food immediately after ending a meal and finding that approximately the same amount was re-ingested by neurologically intact animals but a much smaller amount by lesioned animals.

The vagus nerve-NSTic-LPBe pathway also proved essential for the rapid transmission of non-nutritional visceral information. We found that the vagus nerve [81] and NSTic [132] or LPBe [133] are necessary for concurrent taste aversion learning but notforsequential TAL.

According to the studies presented in this chapter, organisms have at least two complementary neurobiological systems for the detection and processing of nutritional rewarding visceral information: one that depends on the vagus nerve, NSTic, and LPBe,and another that is independent of this pathway. The former appears to participate when rapid information processing is needed and the latter when there are no time constraints.

7.- Conclusions

Research into the biological mechanisms underlying nutritional behavior is exhilarating, both for the simple pleasure of unravellingthese complex phenomenaand for itspotential importance in numerous clinical fields, including artificial nutrition. As shown in our review, enteral nutrition for any reason and of any type is frequently associated with adverse effects whose causes have yet to be fully elucidated. Studies by our group suggest that at least some of these negative effects may result from the absence of the cephalic phase of digestion. Further investigations of the physiology of this nutritional process are needed to support the design of enteral diets better adapted to digestive physiology and the development of pharmacological strategiesthat counteract its noxious effects.

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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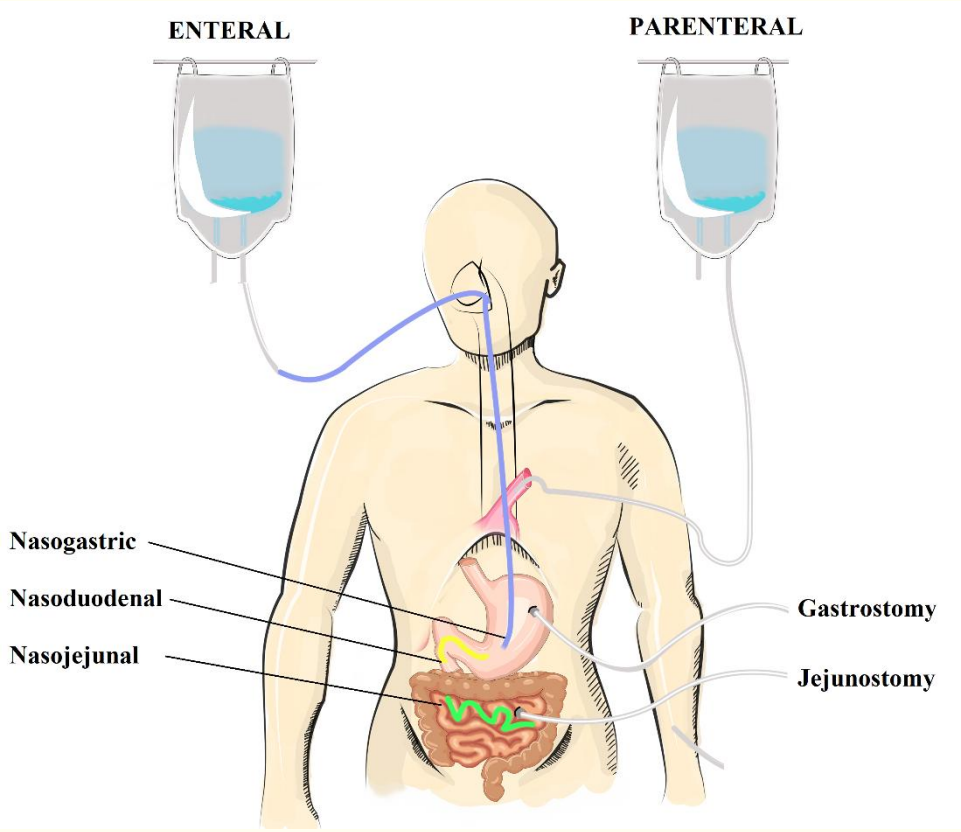

Figure 1. Enteral (nasogastric, nasoduodenal, nasojejunal, gastrostomy,jejunostomy) and parenteral nutrition.

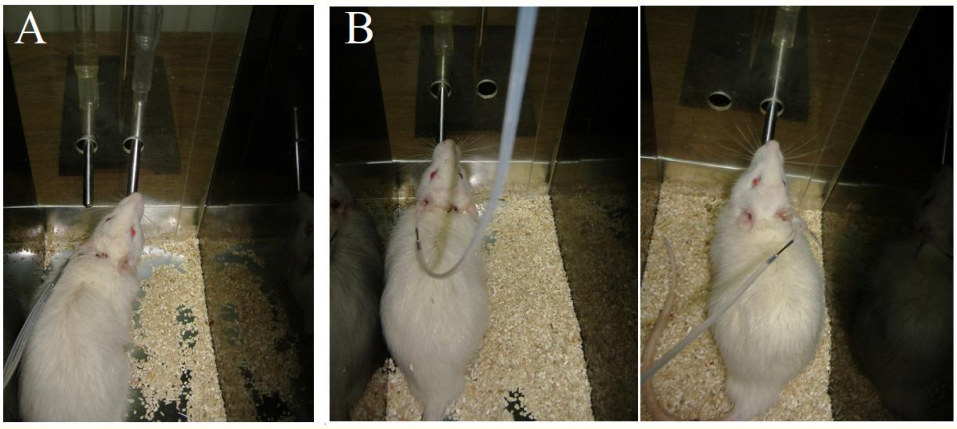

Figure 2. Experimental procedure followed in concurrent (A) and sequential (B) flavor learning. In the former, two flavored stimuli are presented at the same time, one associated with simultaneous intragastric administration of predigested nutrients and the other with saline; in the latter, the two flavored stimuli, with their respective intragastric administrations, are presented in alternatesessions.

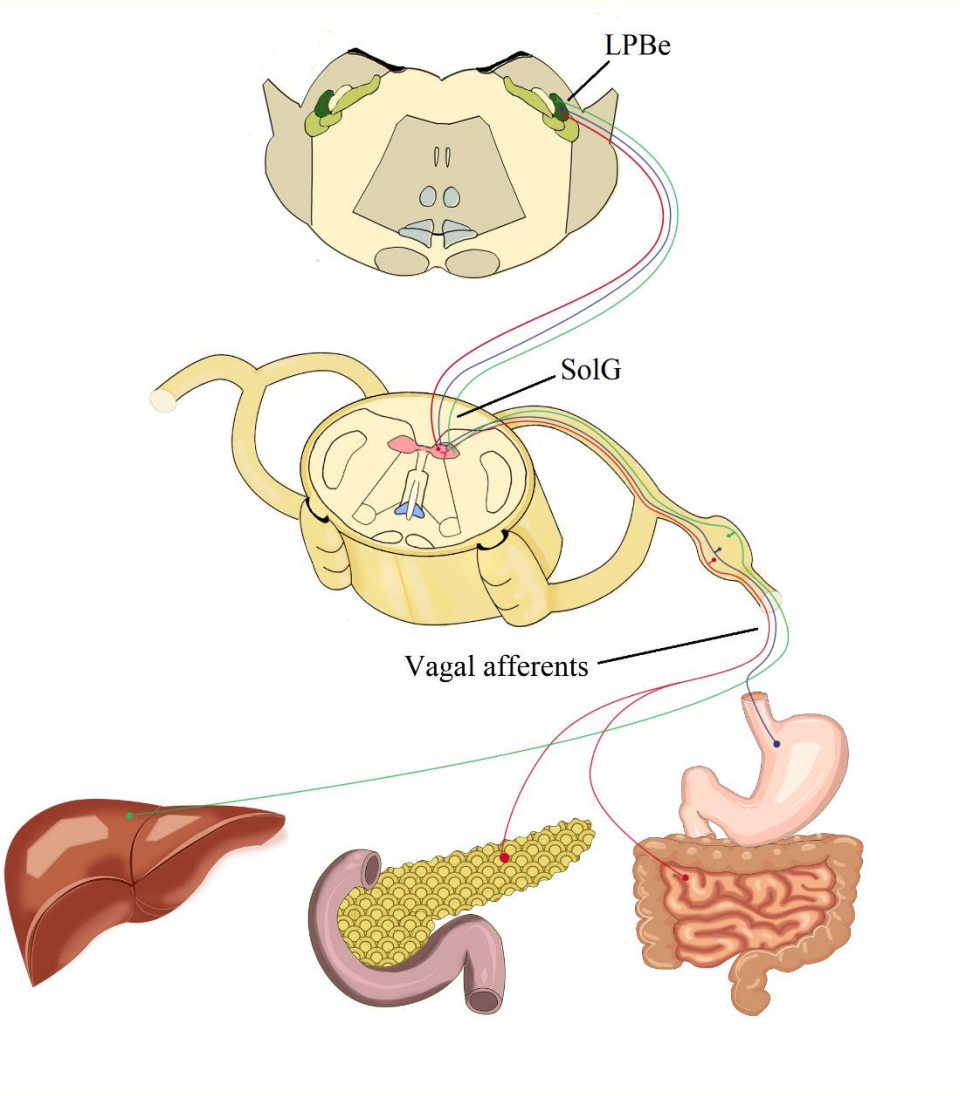

Figure 3. Hypothetical anatomical pathways and nuclei involved in the rapid detection and processing of nutritional rewarding visceral information.