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Enteral Feeding: Brain-Visceral Interactions in the Processing of Nutrients

María Angeles Zafra Palma, Javier Mahía, María J. Simón, Filomena Molina and Amadeo Puerto

Abstract

Enteral nutrition is often mandatory, especially for patients in vegetative or minimally conscious state. However, its application is nonviable in certain cases due to various adverse effects. Some of these are explained by absence of the cephalic phase of digestion, during which exocrine, endocrine, and motor physiological responses prepare the digestive system to receive, digest, transform, and utilize ingested 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 appears able to rapidly assess the suitability of food and transmit this 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 pathway responsible for this rapid processing. Thus, blockade of the vagus nerve, NST, or external lateral parabrachial region (LPBe) interrupts expression of conditioned taste preferences induced by administration of "predigested" food, while LPBe activation by electric stimulation generates similar preferences to those observed after cephalic food administration. This review may help design enteral diets better adapted to digestive physiology and develop pharmacological interventions against 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 practices for supplying nutrients to individuals when oral administration is inadvisable, insufficient, or impossible [1]. These are essential 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 (**Figure 1**; [3]).
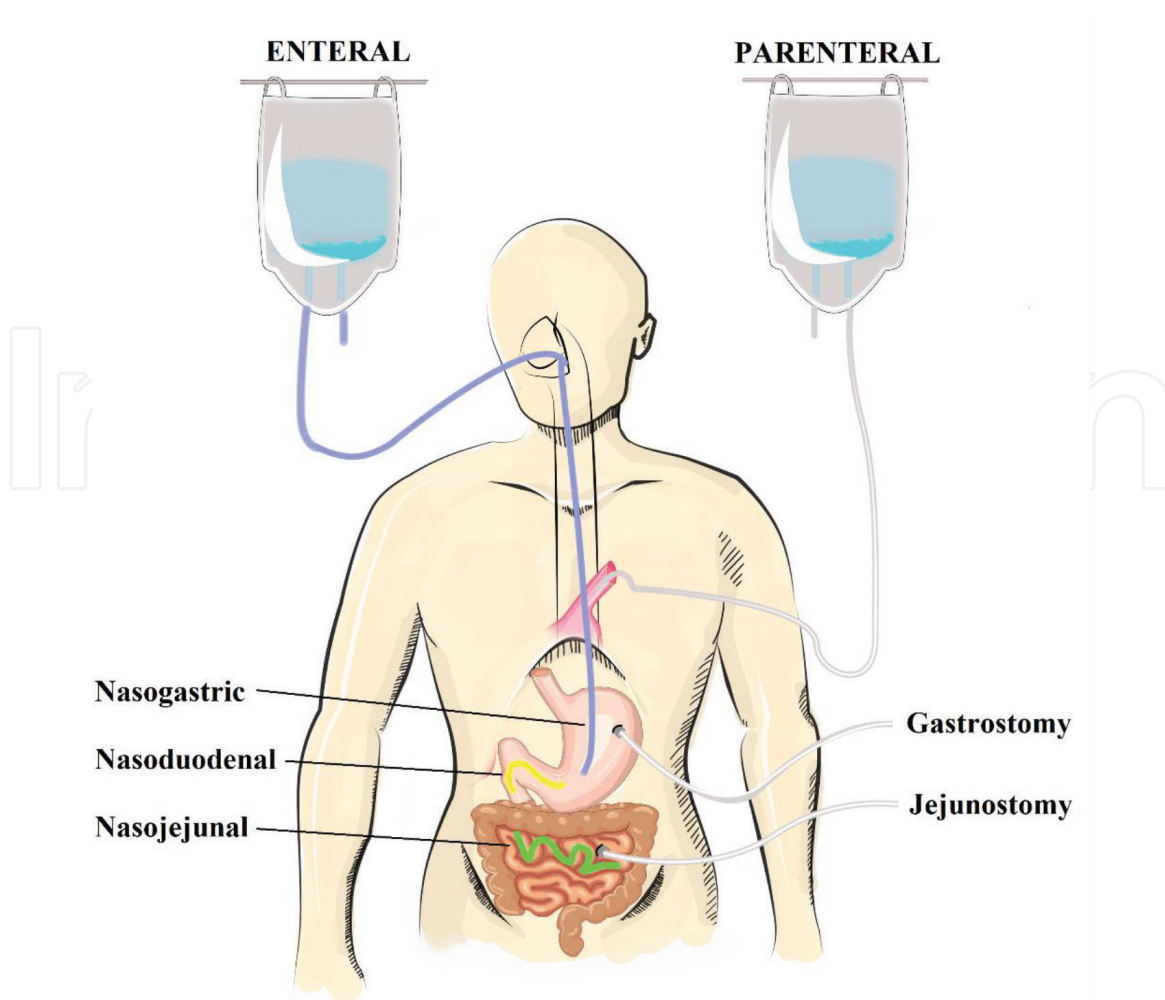
Figure 1.
Enteral (nasogastric, nasoduodenal, nasojejunal, gastrostomy, jejunostomy) and parenteral nutrition.

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 hypoglycemia, 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 needed to release immunostimulant nutrients and by activating the secretion of cytokine-like molecules known as bacteriocins [23, 25, 28].

Hence, mucosa atrophy is 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) nutrition is recommended in a wide range of clinical situations, including organ transplantation [11], cancer [29], pancreatitis [3, 30], Crohn's disease [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-care professionals 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, 33–39], metabolic disorders [1, 12], and, when the enteral nutrition is longer term, ulcers and 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 in animals, have suggested that they may in part result from the entry of food into the digestive tract in "nonphysiological" conditions [40, 41]. The absence of oral stimulation means that the digestive system is not prepared to receive the food (with the appropriate endocrine and exocrine secretions or motor activity changes, etc.), hampering the optimal digestion, absorption, and utilization of the nutrients (see below).

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. In these feeding modalities, meals are directly delivered to the gastric cavity (intragastric feeding) or lower segments of the digestive tube, such as the duodenum or jejune (intraintestinal feeding), generally using a permanently implanted catheter. A physiological variable or function is then studied and compared with results obtained for oral feeding or for sham feeding, in which the food is orally ingested but extracted *via* a cannula before reaching the stomach.

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 endocrine responses to stimulation by the food of sensory perceptive systems in the head and particularly in the oropharyngeal cavity. Nevertheless, although these cephalic responses 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].

The digestive events triggered by cephalic stimulation are mediated by vagal parasympathetic efferents except for salivary secretions, which are partly controlled by sympathetic and nonvagal parasympathetic fibers. These vagal efferents, which are distributed throughout the digestive tube and associated digestive organs (liver, pancreas, and gallbladder), largely originate in the dorsal motor nucleus of the vagus (DMV), which is localized in the caudal medulla oblongata close to the floor of the fourth ventricle and is closely related to the nucleus of the solitary tract, the main structure receiving visceral signals from the digestive system [40–44].

DMV activity is directly or indirectly modulated by centers at upper levels of the nervous system that are responsible for the changes in digestive function that take place during the cephalic phase of digestion. This descending control of the DMV has been reported for such structures as the insular cortex, medial prefrontal cortex, central nucleus of the amygdala, bed nucleus of the stria terminalis, tegmental ventral area, and nucleus accumbens. Many of these signals reach the DMV through relays in hypothalamic regions (posterior hypothalamus and paraventricular nucleus) and brainstem regions (e.g., periaqueductal gray matter or parabrachial nucleus) [40, 44–47].

Pavlov reported that when food was directly introduced into the stomach, the secretion of gastric juices was delayed and scant, with weak digestive power, contrasting with the rapid and abundant cascade of gastric secretions observed when the same nutrients passed through the oropharyngeal cavity after their real or sham intake. He concluded that the low gastric juice secretion in enteral nutrition delays and considerably prolongs digestion [42].

The absence of oropharyngeal stimulation also indirectly delays other digestive secretions. It was reported by Pavlov that intragastrically administered 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 [48–50]. 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 mentioned above, to the small intestine (bicarbonate or digestive enzymes), liver, or pancreas (numerous hormones) (for review, see references [40, 44]). Many secretions triggered by cephalic stimulation are also specific and adapted to the nature of the food [42, 51–56]. 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, 57].

Removal of the cephalic phase affects not only endocrine and exocrine secretions but also gastrointestinal motor activity, with an anticipatory increase in cephalic stimulation [58–61]. The intragastric feeding of experimental animals has also been found to markedly accelerate the outflow of gastric contents into the duodenum [62–64], which might be responsible for the discomfort experienced by patients with "dumping syndrome" [62]. 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 [65]. In this regard, the intraintestinal administration of nutrients (fats) was found to significantly damage the intestinal mucosa [63, 66].

Disorders induced by the absence of oropharyngeal stimulation extend to postabsorptive stages [54, 57, 62, 64, 67–70]. In human studies, glucose intolerance (increased blood levels) and reduced blood glucagon levels were observed after intragastric glucose administration, but not when this was accompanied by oral sensory stimulation through modified sham feeding [71]. It has also been demonstrated that lipolysis is slower with intragastric *versus* oral feeding, leading to higher plasma levels of fatty acids [62].

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 respiratory rate in response to eating, and changes in the transport and intestinal absorption of nutrients and in bile flow and secretin release, among others [49, 72–75].

Taken together, published studies 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 [76–79].

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 under nonphysiological, negative conditions, which may in part account for the digestive problems that can often make enteral nutrition nonviable.

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 nonnutritional flavored solutions of water are offered, with the intragastric/intraintestinal administration of a nutritional stimulus being associated with one solution and of an innocuous, nonnutritional stimulus (e.g., physiological saline) with the other. The preference of animals is determined after multiple sessions pairing the taste and visceral stimuli [80–83].

Studies using this technique have demonstrated that the direct administration of complex food into the gastric cavity is a powerful way to establish flavor-conditioned aversions [66, 80, 84–86]. Thus, when rats were subjected to a discriminative flavor learning task using whole milk as visceral stimulus, they preferred the flavor associated with physiological saline and strongly rejected the flavor associated with the food, even after a 22-h food deprivation period [80, 84–86]. Similar results were observed with intraintestinal feeding, finding that association of the intraduodenal administration of fats or glucose with the oral intake of saccharose or water produced a strong rejection of both in subsequent presentations [66, 80, 81, 86–88].

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 [80, 81, 86–88]. Hence, enterally administered foods are experienced as rewarding/positive when they have undergone oropharyngeal processing, and assistance of the cephalic phase appears to adapt enteral diets more closely to digestive physiology. According to these data, the digestive system also seems perfectly prepared for 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 have prompted numerous clinical studies. Although enteral nutrition was not a 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 [89].

One of the most famous studies in this field was published by Wolf and Wolff and known 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 years. 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 [90]. Other similar reports in the literature include the case of a 24-year-old woman presented during the Annual Meeting of the American College of Gastroenterology in 1950 [91] and of a patient with a 29-year history of complete esophageal obstruction and large permanent gastrostomy [92], who both acquired the habit of tasting and partially chewing food before intragastric administration. Although we have been unable to trace more recent studies of this type, other results obtained in humans have highlighted the importance of cephalic stimulation in nutrition. For instance, oral stimulation with monosodium glutamate (flavor enhancer that improves taste/palatability and augments salivary flow) increased the appetite and weight of elderly patients with problems of taste sensitivity, appetite loss, and weight loss, improving their overall health [93, 94]. Similar findings were reported in neonates with established enteral feeding, whose discomfort was reduced by oral stimulation with glucose [95], and in restrained eaters, whose food intake was increased by the sensory experience of tasting fat [96].

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 are missing, a series of noxious consequences can hamper the adequate development of these processes, making the feeding experience negative or "stressful" [40, 41, 44, 62].

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 establish flavor learning, designated by our group as concurrent and sequential flavor learning. Two nonnutritional flavored stimuli with their respective intragastric administrations are simultaneously offered during a short time period (usually 7 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 [82, 93, 88].

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 [81, 87, 88].

Information from the gastrointestinal tract reaches the brain *via* complementary humoral and neural pathways [97]. 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 [87].
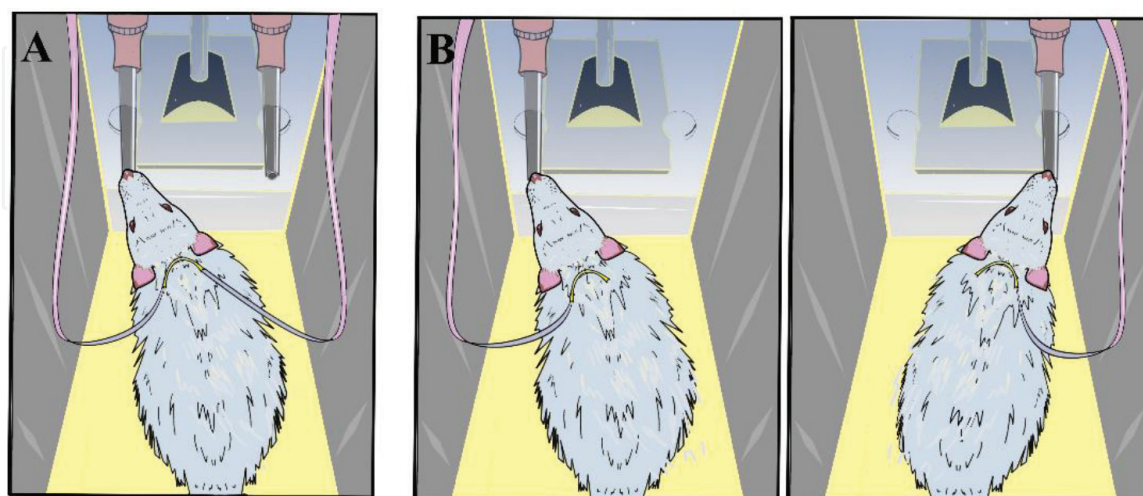

Figure 2.
Experimental procedure followed in concurrent (A) and sequential (B) flavor learning. In the former, two flavored stimuli are presented at the same time; when the animal voluntarily consumes one of these stimuli, it is simultaneously and intragastrically administered with the associated visceral stimulus (e.g., predigested nutrients through an intragastric cannula); when the animal consumes the other stimulus, it is simultaneously and intragastrically administered with the other visceral product (e.g., physiological saline) through a second cannula. The same procedure is followed in sequential learning (B) except that each of the flavored stimuli and their respective intragastric administrations are presented in alternate sessions.

Neuroanatomical and neurophysiological studies have demonstrated that the gastrointestinal tract receives both vagal and spinal nerve fibers [97], 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 are less important in nutrition [98] and appear more related to nociceptive processes [99]. 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 (**Figure 3**) and receive detailed information on the specific nature of the nutrients present in the gastrointestinal lumen *via* interoceptors (chemo-, osmo-, thermo-, and mechanoreceptors) [97, 100, 101]. 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)
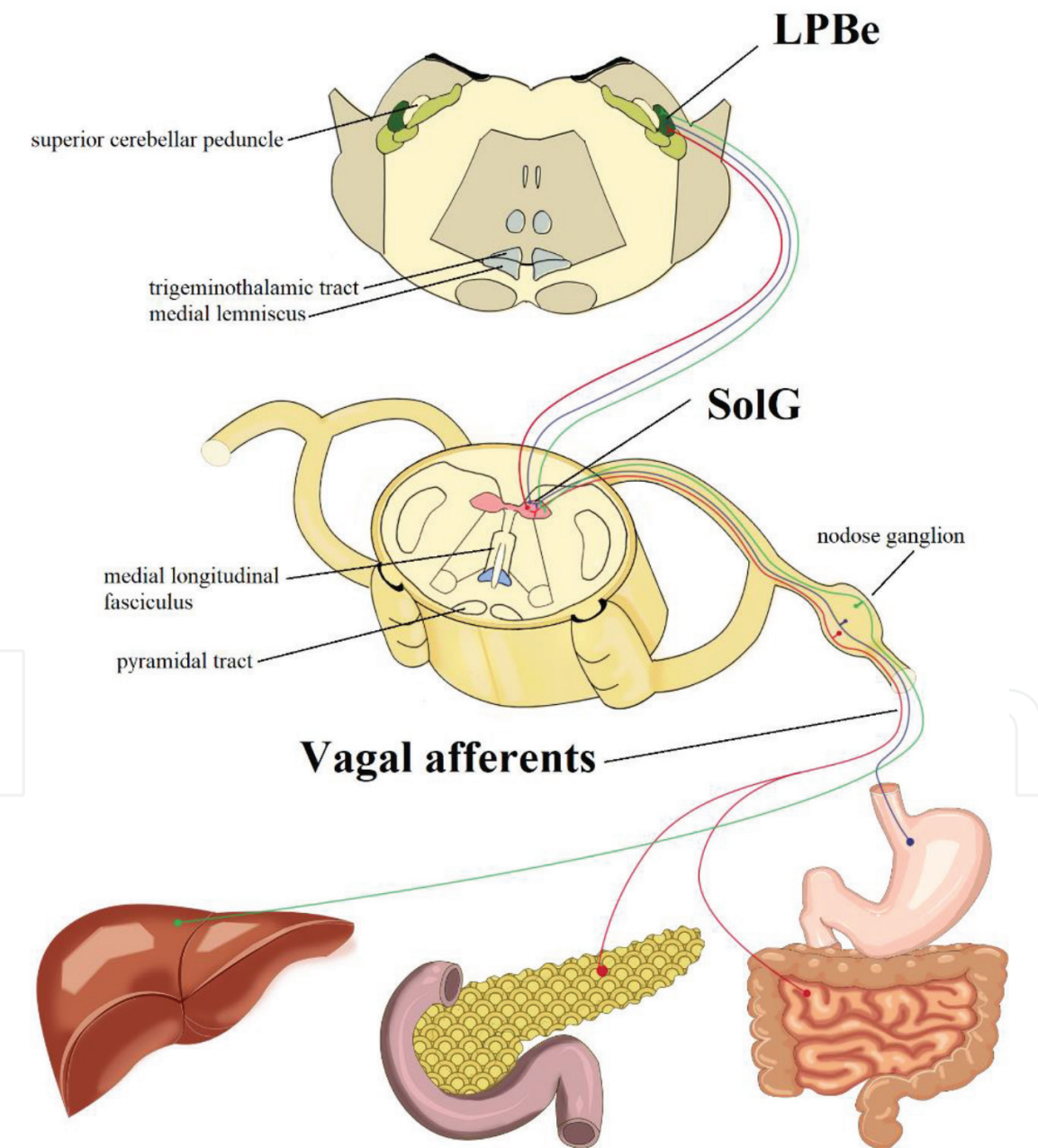

Figure 3.
Anatomical pathways and nuclei involved in the rapid detection and processing of nutritional rewarding visceral information (SolG: gelatinous subnucleus of nucleus of solitary tract; LPBe: external lateral parabrachial subnucleus).

that detect the physical and chemical nature of luminal contents [100, 102–104]. Vagal afferents with nutritional information ascend toward 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 extend toward their first brain relay: the nucleus of the solitary tract (NST) [105–106].

In rats, the NTS is a small-sized bilateral structure that ends in a single midline nucleus caudal to the area postrema (AP), one of the main circumventricular organs of the brain (Y-shaped in horizontal plane). Three regions have been differentiated in the anteroposterior dimension of the NTS: a rostral region that extends from the rostral pole of the nucleus to the point where the medial division contacts the fourth ventricle border; an intermediate band that extends from this last point to the caudal end of the AP; and a caudal division wholly occupied by the commissural subnucleus [105–107]. Most of the subnuclei of the NTS are found in its intermediate region, especially in the medial division (localized medially to the solitary tract, a bundle of fibers that crosses the entire anteroposterior extent of the nucleus) [107].

The NTS is the first relay for a wide range of special and general visceral afferent sensory fibers (oropharyngeal, gastrointestinal, cardiovascular, and respiratory), which are relatively segregated in subnuclei distributed throughout its rostrocaudal dimension. Those originating in the gastrointestinal system largely terminate in subnuclei in the medial division of the intermediate-caudal NTS [105–106].

Our group has investigated the participation of vagal afferents in the rapid transmission of rewarding nutritional information to the brain using capsaicin (8-methyl N-vanillyl-6-nonenamide), the pungent component in red pepper of the genus *Capsicum* (family Solanaceae). When topically applied, capsaicin causes the initial excitation of thinly myelinated Aδ- and unmyelinated C afferent fibers (enhancing the release and inhibiting the reuptake of substance P and other neuroactive peptides from terminals), producing a transient hyperalgesia. This is followed by a refractory period with reduced sensitivity, explaining its clinical application to treat different types of pain. After prolonged or repeated exposure, capsaicin produces a permanent degeneration of these fibers and a persistent desensitization. Therefore, perineural application of this substance provides an important neuropharmacological tool for determining the specific role of an afferent pathway [108].

We applied capsaicin around the esophagus, selectively lesioning unmyelinated afferents and weakly myelinated fibers [108], which are both largely present in the vagus nerve [109, 110]. We found that information transmission mediated by capsaicin-sensitive vagal afferents is essential in concurrent taste discrimination tasks [87]. 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 of taste 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 [87]. Because each flavor is presented with its respective intragastric administration on alternate days in the sequential modality, long time periods are available for the detection and processing of the visceral stimuli. Hence, neurologically intact animals could use 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 could only 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 toward the intermediate-caudal region of the NST (**Figure 3**), a gateway for visceral signal processing [111]. Thus, various subnuclei of the intermediate-caudal region of the NST (NSTic) show c-fos activity after normal food intake [112], after intragastric or intraduodenal nutrient administration [113–115], and in situations of gastric [116] and intestinal [117] distension, among others. In many of these cases, NSTic activation is abolished by the chemical or surgical lesioning of vagal afferents [114, 118].

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 NSTic with relative anatomical segregation [105, 106]. For instance, a high density of gastric vagal afferents is concentrated in the lateral portion of the dorsomedial NST in a cell cluster known as the gelatinous nucleus [105–107, 111, 119], whereas afferents from the duodenum and other segments of the small intestine are distributed in different areas of the dorsomedial nucleus, especially in more caudal and medial areas of the intermediate region [105, 106, 117].

Our group recently demonstrated that the gelatinous subnucleus (SolG) participates in the learning of concurrent taste preferences induced by intragastrically administered "cephalic" foods [88]. It therefore appears that the gelatinous nucleus (SolG), alongside capsaicin-sensitive vagal afferents, may participate in the neural pathway that rapidly processes rewarding nutritional information from the upper gastrointestinal tract. This subnucleus almost exclusively concentrates gastric vagal afferents [106, 113, 117, 119] and is a receptor of fine vagal afferents [120], that is, the type of fibers lesioned by capsaicin [108]. In addition, capsaicin-induced damage of small ganglion cells was found to produce axonal degeneration in the SolG, among other regions [121].

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.

The parabrachial complex is a grouping of subnuclei that surround the superior cerebellar peduncle along its course through the dorsolateral pons. In rats, the subnuclei localized dorsally to the peduncle constitute its lateral division (LPB) and those localized ventrally the medial division [122]. The external subnucleus (LPBe), localized at the most lateral border and throughout the rostrocaudal dimension of the LPB, concentrates information from both the stomach and duodenum, receiving a large number of the afferents projected from the dorsomedial NTS, including the SolG[107, 122, 123].

These anatomical connections allow modification of LPBe activity by electrical stimulation of the vagus nerve and by the intragastric administration of various nutrients [114, 124, 125]. Moreover, the intragastric application of nutrients induces c-fos expression in intermediate-caudal and dorsomedial NST subnuclei and in the LPBe, among other regions [114, 115]. 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) [126–131]. These effects of neuronal activation and/or intake can also be abolished or attenuated by truncal vagotomy or perivagal capsaicin treatment [114, 126, 130–134].

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 animals proved unable 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 [81].

We have also used other procedures to explore the involvement of the LPBe in rewarding processes, including the induction of taste and place preferences by electrical stimulation of this subnucleus [135]. In addition, large lesions of the LPB, including the external subnucleus, appear to reverse aversive effects of the intragastric administration of natural, nonpredigested nutrients, avoiding rejection of the associated taste stimulus and appearing to induce a flavor preference (*versus* water) in late trials of the task [85].

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 [81, 87, 88]. 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 [136] and SolG [137] or LPBe [138] 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 reingested 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 nonnutritional visceral information. We found that the vagus nerve [83] and NSTic [139] or LPBe [140] are necessary for concurrent taste aversion learning but not for sequential 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 unraveling these complex phenomena and for its potential 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 strategies that counteract its noxious effects.

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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