



Relevance of the nucleus of the solitary tract, gelatinous part, in learned preferences induced by intragastric nutrient administration



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ABSTRACT

Food preferences have been investigated in Wistar rats utilizing a learned concurrent flavor preference behavioral procedure. Previous studies have demonstrated that the perivagal administration of neurotoxin capsaicin disrupts the learning of preferences induced by intragastric administration of rewarding nutrients (pre-digested milk). The vagus nerve projects almost exclusively towards the nucleus of the solitary tract (NST), a brain medullary gateway for visceral signals. The objective of this study was to investigate the participation of the lateral portion of the dorsomedial region, the gelatinous subnucleus (SolG), in the learning of a concurrent preference task. Results show that unlike neurologically intact animals, which learn this task correctly, animals lesioned in the gelatinous part of NST manifest a disruption of discrimination learning. Thus, intakes of the flavored stimulus paired with predigested liquid diet and of the flavored stimulus paired with physiological saline were virtually identical. However, SolG- and sham-lesioned groups consumed similar total amounts of both flavors. These findings suggest that SolG, as a relay of the vagus nerve, along with its anatomical projection, the external lateral parabrachial subnucleus (LPBe), may constitute an anatomical axis that is important in the induction of concurrent flavor/side preferences. It also appears to be relevant in other behavioral processes that require rapid processing of information from the upper gastrointestinal tract.

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1. Introduction

The behavior of organisms in selecting food is largely directed by learning mechanisms. Thus, a nutrient initially preferred by a subject can be actively rejected if the consequences of its consumption prove negative (García, Hankins, & Rusiniak, 1974), even when this preference is innate (Sclafani & Ackroff, 2012).

Various behavioral procedures have been utilized to investigate food preferences in the laboratory (Zafra, Molina, & Puerto, 2007; Zafra, Simón, Molina, & Puerto, 2007), including “concurrent preference”. This involves the presentation of two non-nutritive flavor stimuli for a short time period, during which consumption of one of the stimuli is associated with the concurrent intragastric administration of a rewarding nutritive stimulus, while intake of the other stimulus is associated with the intragastric injection of a non-caloric and innocuous product, e.g., physiological saline (PS).

Accomplishment of this behavioral task theoretically requires rapid detection and transmission to the brain of the visceral stimulus to enable a correct association of the visceral stimulus with the corresponding flavor (Mediavilla, Molina, & Puerto, 2005; Zafra, Prados, Molina, & Puerto, 2006).

The neurobiological components of the rapid information transmission pathway required have been studied. Thus, it has been reported that the vagus nerve, a neuroanatomical structure capable of the sensory detection of visceral stimuli (Blackshaw, Grundy, & Scratcherd, 1987; Mei, 1985; Melone, 1986; Sengupta & Gebhart, 1994), is essential for the induction of learned concurrent preferences. This learning was found to be blocked by the perivagal application of capsaicin (Zafra, Molina et al., 2007), a neurotoxin that mainly destroys afferent fibers (Holzer, 1991; Jancsó, Király, Such, Joó, & Nagy, 1987).

The vagus nerve almost exclusively projects towards the medullary nucleus of the solitary tract (NST) (Altschuler, Bao, Bieger, Hopkins, & Miselis, 1989; Barraco, el-Ridi, Ergene, Parizon, & Bradley, 1992), a brain gateway for visceral signal processing (D'Agostino et al., 2016; Roman, Derkach, & Palmiter, 2016).

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Sensory information from abdominal viscera is topographically organized with relative anatomical segregation (Altschuler et al., 1989; Barraco et al., 1992). Specifically, vagal afferents from the stomach are densely concentrated in the lateral portion of the dorsomedial NST, the gelatinous nucleus (SolG) (Altschuler et al., 1989; Barraco et al., 1992; Herbert, Moga, & Saper, 1990; Rinaman & Schwartz, 2004; Rinaman, Card, Schwaber, & Miselis, 1989; Shapiro & Miselis, 1985; Young, Cooper, & Blackshaw, 2008), while afferents from the duodenum and other segments of the small intestine are distributed elsewhere, mainly in more caudal and medial areas of the intermediate region (Altschuler et al., 1989; Barraco et al., 1992; Zhang, Fogel, & Renehan, 1992; Zhang, Fogel, & Renehan, 1995).

Given the need for rapid information processing in the concurrent procedure, we hypothesized that the digestive segments most likely to be involved in this learning procedure, i.e., those responsible for initial detection of the visceral stimulus, would be proximal segments, preferentially the stomach and duodenum. The SolG, unlike other dorsomedial regions or even other NST regions (Altschuler et al., 1989; Barraco et al., 1992; Shapiro & Miselis, 1985), almost exclusively receive gastric vagal afferents (Barraco et al., 1992; Zhang et al., 1995, 1992; Zittel, De Giorgio, Sternini, & Raybould, 1994).

With this background, the objective of the present study was to determine the participation of the SolG subnucleus of the NST in concurrent flavor learning, investigating whether it forms part of a pathway for the rapid transmission of rewarding nutritional information to the brain.

In flavor discrimination learning tasks, the intragastric administration of a wide variety of foods that are rewarding when orally consumed can frequently cause the rejection of associated flavors in subsequent presentations (Deutsch, Molina, & Puerto, 1976; Zafra, Simón et al., 2007). This has been attributed to the fact that the nutrients lack the physiological secretions that characterize the cephalic stage of digestion and are present during the oral consumption of these substances (Puerto, Deutsch, Molina, & Roll, 1976; Zafra, Molina, & Puerto, 2006; Zafra, Simón et al., 2007; Zafra et al., 2009). Accordingly, the present study used cephalic rewarding nutrients, obtained from donor animals after their oral consumption and likely to contain the corresponding cephalic secretions (Zafra, Simón et al., 2007).

2. Materials and methods

2.1. Subjects

Thirty-two adult male Wistar rats (weighing 286–335 g at time of surgery) were used in this experiment, randomly assigning 10 to a SolG-lesioned group, 10 to a control sham-lesioned group, and 12 to a donor group. All rats were individually housed in 30 × 15 × 30 cm methacrylate cages with *ad libitum* access to water and pelleted stock diet (Panlab, S.L. Barcelona). The laboratory was maintained under a 12/12 h light-dark cycle (lights on 08:00 h) at 22 ± 1 °C. All experiments were conducted during light periods in accordance with the Animal Care and Use Guidelines established by European Community Council Directive (86/609/CEE) and Spanish legislation (Royal Law 1201/2005). Every effort was made to minimize animal suffering and the number of animals used.

2.2. Surgical procedure

2.2.1. SolG lesions

Surgery was performed under general anesthesia with sodium pentothal (50 mg/kg, ip; B Braun Medical S.a. Barcelona, Spain). Once anesthetized, the animals were placed in a stereotaxic unit

(Stoelting Co. Stereotaxic 51.600), and an incision of approximately 1.5 cm in length was made in the upper area of the cranium. Connective tissue was removed and two small trephine holes were drilled at the anteroposterior and lateral coordinates corresponding to the SolG. After sectioning the dura mater, a 00 monopolar stainless steel electrode with diameter of approximately 200 μm and insulated throughout its length (except at the tip) was introduced up to the dorsoventral coordinate. A cathodal electric current (0.3 mA) was bilaterally applied for 10 s using a DCML-5 lesion-maker (Grass Instruments Corp., Quincy, MA, USA). Anatomical coordinates for the SolG (interaural references), taken from the Paxinos and Watson (1996), were: anterior/posterior (AP) = −4.3 mm; lateral (L) = ±1.05 mm; and ventral (V) = +2.2 mm. All of the above steps were followed in the sham-lesion control group except that a vertical coordinate of +3.2 mm was used and no current was applied.

2.2.2. Intragastric catheters

After brain surgery (SolG-lesioned and sham-lesioned), two intragastric catheters were implanted following a previously reported procedure (Zafra, Molina, Puerto, 2016). After laparotomy of approximately 3 cm, the stomach was carefully pulled out from the abdominal cavity. An incision of approximately 2 cm was made in the cardia region at the greater curvature, and a silastic tube (ID = 1.0 mm; OD = 2.0 mm) with small silicone protuberance around the end (to prevent outward catheter displacement) was inserted. The incision was closed with a suture around the stomach tissue surrounding the catheter at its insertion site. In addition, the catheter was anchored to the stomach using the remaining suture thread to make a suture point on the surface of the gastric tissue. This procedure was then repeated for implantation of the second catheter. The exteriorized organs were continuously irrigated with isotonic physiological saline (Apirosesum. Lab. YBIS, Madrid). The stomach was then returned to the gastric cavity in its original position, and the catheters were routed through the abdominal muscle wall and subcutaneously tunneled, one on each side of the animal, to the dorsal surface of the neck. Wounds were stitched, the catheters were capped to avoid gastric content leaking, and silicone was applied around the tip of the catheters to prevent its displacement within the subcutaneous tunnel. As prophylactic measures against infection, povidone iodine (Betadine, Asta Medica, Madrid, Spain) was topically applied to the wounds, and 0.1 cc penicillin (10,000 U; Penilevel Retard. Lab., Level, S.A. Barcelona) was intramuscularly injected. The same surgical procedure was performed to implant two intragastric catheters in the donor animals.

2.3. Behavioral procedure

2.3.1. Donor rats

Donor rats were placed in a different room and habituated to consume a liquid diet (Ideal Evaporated whole milk, 50% diluted. Nestlé, Barcelona, Spain) over four days following one day of food and water deprivation; 100 mL of this liquid diet contained 5.75 g carbohydrates, 3.93 g fat, and 3.93 g protein (total energy: 74.37 Kcal). During this habituation period, the liquid diet was offered for 3 h (from 10:00 to 13:00) followed by 10 min of access to water; in the first two days of this period, they received 7.5 g of solid food after removal of the water.

This four-day period was followed by a two-day period with solid food (pelleted stock diet) and tap water *ad libitum* before surgery (implantation of two intragastric catheters), maintaining this diet on the day of surgery and for the next six days. Animals were then offered a liquid diet (re-adaptation period), following the same procedure as in the adaptation period (also offering 7.5 g of

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