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Rewarding effects of the electrical stimulation of the parabrachial complex: Taste or place preference?

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ABSTRACT

The lateral parabrachial complex has been related to various emotional-affective processes. It has been shown that electrical stimulation of the external Lateral Parabrachial (LPBe) nucleus can induce reinforcing effects in place preference and taste discrimination tasks but does not appear to support self-stimulation. This study examined the relative relevance of place and taste stimuli after electrical stimulation of the LPBe nucleus. A learning discrimination task was conducted that simultaneously included both sensory indexes (taste and place) in order to determine the preference of animals for one or the other. After a taste stimulus reversal task, the rewarding effect of stimulation was found to be preferentially associated with place. These results are discussed in the context of the rewarding action and biological constraints induced by different natural and artificial reinforcing agents.

1. Introduction

The Lateral Parabrachial (LPB) complex appears to participate in neurobiological systems related to the motivational or hedonic evaluation of rewarding natural products and other substances for which preference has been acquired by learning (Calingasan & Ritter, 1993; Edwards & Ritter, 1989; Yamamoto & Sawa, 2000a, 2000b; Yamamoto et al., 2009). Thus, it has been related to the aversive processing of lithium chloride (Sakai & Yamamoto, 1997; Yamamoto & Sawa, 2000a) and drugs of abuse, such as opiates (Bechara, Martin, Pridgar, & Van der Kooy, 1993; Nader, Bechara, & Van der Kooy, 1996), and in the processing of pain and its affective components (Bernard, Huang, & Besson, 1994; Bester, Menendez, Besson, & Bernard, 1995; Jasmin, Burkey, Card, & Basbaum, 1997).

The external Lateral Parabrachial (LPBe) nucleus is located in the ventral region of the lateral parabrachial complex (Fulwiler & Saper, 1984; Herbert & Bellintani-Guardia, 1995) and has been related to various homeostatic, sensory, and learning processes (De Lacalle & Saper, 2000; Edward & Ritter, 1989; Karimnamazi, Travers, & Travers, 2002; Mediavilla, Molina, & Puerto, 2000; Yamamoto, Shimura, Sakai, & Ozaki, 1994). More specifically, rewarding food (Zafra, Simon, Molina, & Puerto, 2002) and/or intake-related substances such as fenfluramine (Li & Rowland, 1995; Li, Spector, & Rowland, 1994; Simansky & Nicklous, 2002; Trifunovic & Reilly, 2001), amphetamines (Sakai & Yamamoto, 1997), and opiates (Chamberlin, Mansour, Watson, & Saper, 1999; Ding, Kaneko, Nomura, & Mizuno, 1996; Gutstein, Thome, Fine, Watson, & Akil, 1998) may be processed *via* the LPBe, among other brain nuclei.

It has been demonstrated that electrical stimulation of the LPBe nucleus can induce aversion or preference for associated stimuli in learning tasks of taste discrimination and conditioning place preference, although it does not appear to support self-stimulation, or at least not as readily as can be achieved by stimulation of the lateral hypothalamus, for example (Simon, García, & Puerto, 2011, 2013; Simon, García, Zafra, Molina, & Puerto, 2007; Simon, Zafra, Molina, & Puerto, 2008). These tasks have proven useful to analyze specific preferences (Spiteri, Le Pape, & Agmo, 2000) generated by natural (food or water intake) (Schroeder & Packard, 2000; Stefurak & Van der Kooy, 1992; Zafra et al., 2002) or artificial (electrical stimulation, drugs of abuse) (Jaeger & van der Kooy, 1996; McBride, Murphy, & Ikemoto, 1999; Schecter & Calcagnetti, 1998; Simon et al., 2007; Tzschentke, 2007) reinforcing treatments. In the case of electrical stimulation, animals learn the task by relating the rewarding (or aversive) stimulation to simultaneously available place, space, proprioceptive, or sensory (taste/flavor) stimuli (Simon et al., 2007, 2008). Some treatments frequently induce an associative bias (biological constraint) towards specific related stimuli (Garcia, Hankins, & Rusiniak, 1974; Garcia & Koelling, 1966; Lett, 1985). Thus, there is a tendency to associate taste stimuli with states of internal malaise or sickness and to associate place/exteroceptive cues with the aversive effects induced by noxious exteroceptive stimuli (Garcia & Koelling, 1966; Garcia et al., 1974; Lett, 1985). Moreover, morphine and amphetamines, among

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other drugs of abuse, induce preferences for associated environmental cues, whereas aversive components of these drugs are more readily evidenced in taste discrimination tasks (Bechara et al., 1993; Parker, 2003; White, Nessier, & Carr, 1987). LPBe nucleus reinforcing effects may initially be associated to both types of stimuli, taste and place (Simon et al., 2007, 2013; Yamamoto et al., 1994; Zafra et al., 2002). However, the nature of the reinforcement induced by the electrical stimulation of the LPBe nucleus is not known and it would be relevant to determine any biological constraint or associative preference (e.g., for taste or place) that may help to define this rewarding effect. With this background, the objectives of this study were to examine the relative importance of taste and place sensory indexes simultaneously presented in a discriminative learning task induced by electrical stimulation of the LPBe nucleus. The initial hypothesized preference for a taste stimulus located in a (right or left) place was re-examined in a second test in which taste and place were dissociated (by reversing the place of the taste), with the aim of establishing the priority ranking assigned by animals to one or other type of stimulus.

2. Materials and methods

2.1. Subjects and surgery

Forty male Wistar rats from the breeding colony at the University of Granada, weighing 270–360 g at the time of surgery, were randomly assigned to an experimental group ($n = 27$) for implantation with intracerebral electrodes in LPBe nucleus or to a control group ($n = 13$) with the reference electrode on the skull surface. Animals were housed in individual methacrylate cages ($30 \times 15 \times 30$ cm) that also served as training chambers during the experiments, in which they remained for at least one week of habituation before the surgery, with water and food *ad libitum* (Panlab Diets S.L., Barcelona, Spain).

The laboratory was maintained at 20–24 °C with a 12:12 h light/dark cycle. Experimental procedures were conducted during light periods with white noise. All behavioral procedures and surgical techniques complied with Spanish legislation (Royal Law 1201/2005) and the European Community Council Directive (86/609/EEC).

Animals were implanted with a stainless steel grounded monopolar electrode (00) (Hawkins, Roll, Puerto, & Yeomans, 1983; Simon et al., 2007) in the LPBe nucleus [Coordinates: AP = −0.16; $V = +3.0$; $L = +2.5$, according to the atlas by Paxinos and Watson (1998)] using a stereotaxic unit (Stoelting Co., Wood Dale, IL) under general anesthesia (Sodium Pentathol, 50 mg/kg, B Braun Medical S.A. Barcelona, Spain). As prophylactic measures, 0.1 cc penicillin (Penilevel, (Laboratorio Level, S.A., Barcelona, Spain) was intramuscularly injected, and povidone-iodine (Betadine, Asta Médica, Madrid, Spain) was applied around the implant.

After the surgery, animals were returned to their cages, in which they remained for a recovery period of $\geqslant 10$ days with water and food *ad libitum*.

2.2. Apparatus

2.2.1. Concurrent place preference task

An unbiased, counterbalanced concurrent place preference procedure was used for trials 1 and 2. Animals were concurrently stimulated in one of two distinct compartments of a rectangular maze ($50 \times 25 \times 30$ cm), which differed in color, texture, and wall pattern. These lateral compartments were separated by a narrow area in which animals were placed at the start of each test. The walls of the two lateral compartments were painted with black and white 1 cm wide stripes that were vertical in one compartment and horizontal in the other. In one compartment, the floor was synthetic cork painted with black and white stripes and in the other it was brown cork. The floor of the central area (8×25 cm^2) was white methacrylate, and the walls were a natural wood color (Simon et al., 2007).

2.2.2. Taste/place discrimination task

The taste/place discrimination test was conducted in the methacrylate home cages in which the animals were housed upon arrival at the laboratory (Mediavilla, Molina, & Puerto, 1998). The sides of the cages were black and opaque and the front and back panels 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. Through those orifices, the animal had access to spouts attached to cylindrical graduated burettes for the delivery of flavors and water (Mediavilla et al., 1998; Simon et al., 2007).

2.2.3. Electrical brain stimulation

For the electrical stimulation, a continuous current range of 60–170 μA with rectangular cathodic pulses at 66.6 Hz and 0.1 ms pulse duration was supplied by a CS-20 stimulator (Cibertec, Madrid, Spain) connected to an ISU 165 isolation unit (Cibertec, Madrid, Spain) and HM 404-2 oscilloscope (HAMEG Instrument GMBH, Frankfurt, Germany). The current intensity was established individually for each animal, avoiding current levels that could generate involuntary movements, escape responses, or pain (Simon, Molina, & Puerto, 2009; Simon et al., 2007, 2008; Tehovnik, 1996).

2.3. Behavioral procedures

2.3.1. Concurrent place preference

At 48 h after establishing the optimal current intensity, animals underwent a concurrent place preference task. For the 10-min session-test, one of the two lateral compartments was randomly selected as the area of intracranial electric stimulation, the animal was placed in the center of the maze, and the voluntary stay of the animal in one of the two areas was accompanied concurrently by intracranial electrical stimulation (half of the animals received stimulation in one lateral compartment of the maze and the other half received it in the other lateral compartment). The time the animal stayed in each compartment was recorded. Control group animals bore stimulation connectors connected to the reference electrode but received no electrical stimulation. This procedure was repeated in a second session after a 24-h interval. After each session, the animal was returned to its cage with water and food available *ad libitum*.

Following the behavioral criteria established in previous studies (Simon et al., 2007, 2009), animals staying in the "stimulated" compartment for >50% of the total time were classified as "positive", those staying for <30% of total time as "negative", and those staying for 30–50% of total time each session or showing alternating behavior between sessions, as "neutral".

2.3.2. Experiment A: learning of taste/place preference

2.3.2.1. Pre-training. At 48 h after the concurrent place preference phase, a two-day pre-training period was initiated, during which water was available to the animals for only 10 min on day 1 and 7 min on day 2 from a burette placed alternately in the left or right hole on the front panel of the cage. After removing the water, the animals were supplied with 14 g of food.

2.3.2.2. Taste/place preference. Table 1 exhibits the discriminative learning procedure: In each of the four experimental sessions, animals were offered one of two flavored solutions [0.5% Strawberry