Behavioural Brain Research 336 (2018) 15–21

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Tolerance to rewarding brain electrical stimulation: Differential effects of contingent and non-contingent activation of parabrachial complex and lateral hypothalamus

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ARTICLE INFO

Keywords:
Place preference
Rewarding brain electrical stimulation
Contingent and non-contingent stimulation
External lateral parabrachial subnucleus
Lateral hypothalamus
Tolerance

ABSTRACT

Electrical stimulation of the parabrachial complex and related insular cortex induces concurrent conditioned place preference (CPP) in a naloxone-dependent manner. Furthermore, repeated rewarding activation of these regions generates tolerance, *i.e.*, a reduction of the reinforcing effect. This study examined the effects of contingent and non-contingent stimulation in a CPP task. In the former modality, the animals can voluntarily select areas of the maze and thereby determine whether or not they receive stimulation. In the non-contingent procedure, the animals passively receive the administration of the rewarding electrical current while confined in the preferred place. Tolerance to the rewarding stimulation was observed in the non-contingent procedure, in which the external lateral parabrachial subnucleus (LPBe) was stimulated in a behaviorally passive task, but not in the contingent procedure. In contrast, no tolerance was observed in the group receiving rewarding stimulation of the lateral hypothalamus after either contingent or non-contingent brain activation. These findings are discussed in terms of the rewarding effects induced after contingent or non-contingent administration of electrical or chemical rewarding agents.

1. Introduction

The parabrachial (PB) complex has been related to the processing of both rewarding [1–3] and aversive substances [4,5,1,6], including the aversive properties of drugs of abuse such as morphine [7,5].

Specifically, lesions of the external lateral PB subnucleus (LPBe) interrupt concurrent taste aversion [8] and preference [3] induced after intragastric injections. Electrical stimulation of the LPBe and related insular cortex generates preference behaviors for associated stimuli in both taste preferences and in CPP tasks [9–11]. Naloxone administration impedes the acquisition of concurrent place preferences induced by electrical stimulation of the PB complex and insular cortex [12,10,13], which is consistent with the high density of opioid receptors in these regions [2,14]. However, this naloxone blockade is not observed when electrical stimulation is applied to the central nucleus of the amygdala [15] or lateral hypothalamus [13], indicating that the rewarding effects do not involve the opioid system in these cases [16].

Tolerance to rewarding stimulation was recently demonstrated; thus, animals subjected to daily activation sessions progressively reduced their stay in the stimulation-associated area after daily stimulation of the PB complex [9] or the related insular cortex (IC) [17], which is known to participate in various reward processes [18–22] and is compatible with reports on its involvement in processing drugs of abuse such as opiates [23,24] or stimulants [25–27].

The decay in rewarding effect found after daily electrical stimulation of the PB and insular cortex was not observed in animals receiving intermittent activation (day off/day on) [17,9]. In both intermittent and daily procedures, the animals were able to choose between stimulation-associated and non-stimulation-associated areas in half of the sessions, and both groups were confined within their preferred maze area (non-contingent task) in the other half of the sessions, in which the activation group but not the intermittent group (day off) received electrical brain stimulation. In other words, only the daily group received intracranial stimulation corresponding to both contingent and non-contingent modalities; hence, the application or not of stimulation in these animals did not always depend on their behavior.

Intracranial electrical stimulation is known to exert different neuroadaptative effects depending on its administration by the animal itself or by the experimenter [28,29], and dopamine release was found to differ between these situations [28,29]. However, the different behavioral consequences of self- *versus* experimenter-administered rewarding electrical stimulation have not yet been determined.

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http://dx.doi.org/10.1016/j.bbr.2017.08.030
Received 4 January 2017; Received in revised form 14 August 2017; Accepted 17 August 2017
Available online 24 August 2017
0166-4328/

The main objective of this study was to examine possible causes of the reward decay demonstrated in previous studies [17,9], specifically investigating the potential effects of both the duration and administration modality (contingent or non-contingent) of rewarding electrical stimulation of the LPBe. A secondary objective was to explore the possible anatomical specificity of this reward decay by studying repeated electrical stimulation of the lateral hypothalamus, which is highly related to brain reward processes.

2. Methods

This study comprises two experiments that follow the same procedure except for the localization of the electrode in the LPBe in the first experiment and the lateral hypothalamus in the second.

2.1. Subjects and surgical procedure

The first experiment used 40 male Wistar rats from the breeding colony at the University of Granada, which weighed 310–410 g at surgery and were randomly distributed into two groups: one implanted with intracranial electrodes in the LPBe nucleus (25 animals) and an intact control group (15 animals). The second experiment used 48 male Wistar rats from the breeding colony at the University of Granada, weighing 360–480 g at baseline, which were randomly distributed into one of two groups: neurologically intact control group (n = 16) or implanted group (n = 32).

Animals were housed in methacrylate cages with water and food *ad libitum* (A-04, Panlab Diets S.L., Barcelona, Spain). The laboratory was maintained at 20–24 °C with a 12:12 h light/dark cycle. All experimental procedures were conducted during light periods with white noise. The animals remained under these conditions for a pre-surgery adaptation period of at least 7 days. All behavioral procedures and surgical techniques complied with the relevant Spanish regulation (Royal Law 23/1988) and European Community Council Directive (86/609/EEC).

Animals were implanted with a stainless steel monopolar electrode (00), insulated except at the tip, in the LPBe nucleus [Coordinates: AP = − 0.16; V = 3.0; L = ± 2.5, according to the atlas by Paxinos and Watson [30]], using a stereotaxic apparatus (Stoelting Co. Stereotaxic 511.600) under general anesthesia (sodium thiopental, 50 mg/kg, B. Braun Medical S.A. Barcelona, Spain). As prophylactic measures, 0.1 cc penicillin (Penilevel, Level Laboratory, S.A., Barcelona, Spain) was intramuscularly injected and an antiseptic solution was applied around the implant (Betadine. Povidone-Iodine. Asta Médica, Madrid, Spain). There was a post-surgery recovery period of at least 7 days.

In the implanted group of the second experiment, the same procedure was followed as in the first experiment but using the following coordinates from the De Groot atlas [31] for the lateral hypothalamus: AP: +5.8, V: +2.8 and L: ± 1.8, which are widely used in our laboratory for this specific brain region [32,11,13,16]. One animal died during surgery and another was sacrificed after displaying turning behavior. The remaining 46 animals (30 implanted and 16 intact) underwent the first stage of the behavioral procedure (see below).

2.2. Equipment

For the monopolar electrical stimulation, cathodal constant-current rectangular pulses of 66.6 Hz with 0.1 ms pulse duration were 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).

A three-chamber rectangular maze was used [10] in all experimental stages (50 × 25 × 30 cm): it was oriented North-South, and 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) was white methacrylate, and the walls were a natural wood color.

2.3. Behavioral procedure

2.3.1. Stage 1: classification and distribution of animals into the different groups, according to the effects of electrical stimulation

As in previous experiments in our laboratory [12,33,34,9–11], this stage began by establishing the appropriate electrical stimulation parameters for each animal [35], increasing the current intensity in steps of 10 μA and observing the response of the animal. When some initial manifestation of negative behaviors was observed, the current was reduced to a level at which behavioral activation was produced but without any escape or pain responses. This level ranged between 70 and 320 μA in the animals in experiment 1 and between 100 and 370 μA in the animals in experiment 2.

Implanted animals underwent two contingent 10-min trials on two successive days. In each trial, animals were placed in the center of the maze and allowed to wander freely into any compartment, one of which was associated with electrical stimulation in a randomized and counterbalanced manner. Animals received intracranial electrical stimulation when inside the stimulation-associated compartment but not when inside the other compartment or central space. The length of stay in each compartment was recorded.

According to the criteria adopted in previous studies in our laboratory [12,33,10,11], only "positive" animals (spending > 50% of available time in stimulated compartment) were selected for these studies, excluding "aversive" (< 30% of time in stimulated compartment) and "neutral" (30–50% of time in stimulated compartment) animals. For the first experiment, a positive group was formed by the 14 animals showing consistent preference for the area associated with electrical LPBe stimulation, while a neurologically intact group (controls) comprised 15 non-implanted animals. The positive group was then randomly divided into two subgroups of 7 animals, the "Contingent Positive Group" and "Non-Contingent Positive Group" using the yoked procedure. For this purpose, animals were first paired according to their length of stay in the stimulated compartment during the second trial, and one member of each pair was then randomly assigned to the "Contingent Positive Group" and the other to the "Non-Contingent Positive Group". The neurologically intact group was also randomly divided into two groups in the same manner: Contingent Control Group (n = 8) and Non-Contingent Control Group (n = 7).

In the second experiment and based on the same behavioral criteria, 24 animals were initially considered "positive" for showing consistent preference for the place associated with electrical stimulation of the LH. Then, in order to match group numbers, the 16 most positive animals were selected for the Positive Group. The 16 intact controls (Intact Group) received no surgery or electrical stimulation. As in experiment 1, the positive group was randomly divided between the Contingent Positive Group" (n = 8) and "Non-Contingent Positive Group" (n = 8) following the yoked procedure (see above). The intact group was divided in the same manner between the Contingent Control Group (n = 8) and Non-Contingent Control Group (n = 8).

2.3.2. Stage 2: baseline

At two weeks after stage 1, all animals underwent a 15-min CPP trial to establish baseline values.

2.3.3. Stage 3: administration of contingent/non-contingent electrical stimulation

The Contingent Positive Group underwent three 15-min CPP trials on consecutive days, with stimulation of the LPBe in experiment 1 and the lateral hypothalamus in experiment 2, in which the electrical stimulation always depended on the voluntary stay of animals in the stimulation-associated maze compartment, as in stage 2. The same