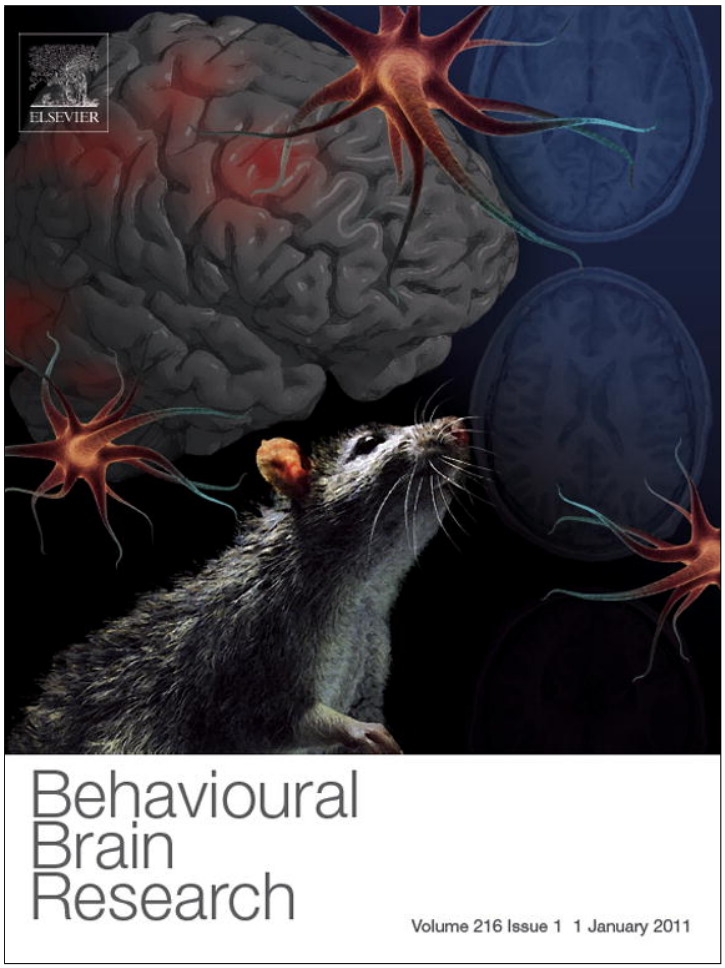

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Research report

Concurrent stimulation-induced place preference in lateral hypothalamus and parabrachial complex: Differential effects of naloxone

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ABSTRACT

Place preference induction by intracerebral electrical stimulation was initially shown by Olds and Milner. It has since proven possible to induce concurrent stimulation-induced place preference (cCPP) after electrical stimulation of the lateral hypothalamus (LH) and, more recently, of the external lateral parabrachial nucleus (LPBe). The objective of this experimental study was to examine whether the rewarding effects of electrical stimulation of the LH and LPBe involve the activation of similar opioid systems in an alternative cCPP task. Administration of the opioid antagonist naloxone (4 mg/kg) blocked the conditioned place preference effect induced after LPBe but not after LH stimulation (at 4 or 10 mg/kg). These results are interpreted in relation to the presence of multiple reward systems that might anatomically and neurochemically differ with respect to the involvement of the opioid system.

1. Introduction

Since the original study by Olds and Milner (1954) [1], intracerebral electrical stimulation has been a procedure of choice for the study of brain reward mechanisms [2–7]. Researchers have generally adopted an operant methodology, but reward can also be assessed in laboratory animals by tasks such as conditioned place preference (CPP) ([8–10], for a review). Thus, CPP tasks are frequently used to study the reinforcing effects of natural stimuli, including foods and drinks [11–14] and drugs of abuse [10,15–19].

Many of the anatomical regions identified by rewarding electrical stimulation may form part of a general reward system localized around the medial forebrain bundle (MFB), especially the lateral hypothalamus (LH) [2,4,6,20–24]. However, it was recently demonstrated that electrical stimulation of the external lateral parabrachial nucleus (LPBe) can also generate preferences for associated environmental stimuli in both gustatory and place discrimination tasks [25–27]. The LPBe has been related to the processing of natural rewarding substances and other substances for which preference has been acquired by learning [28–32]. This subnucleus also participates in the processing of substances, such as fenfluramine [33–36], amphetamines, cocaine [37], and opiates [38–40]. In this context, recent studies in our laboratory indicated the likely involvement of the endogenous opioid system in the reward induced by electrical stimulation of the LPBe [25].

Intracranial self-stimulation (ICSS) behavior induced in the MFB has been related to dopaminergic ([6], for a review [23,41–46]) and opioid systems [41,47]. With regard to the opioid system, controversial results have been obtained by studies using antagonists such as naloxone in operant tasks ([47], for a review [48–50]). Some authors found that naloxone does not alter the rate of lever-pressing in ICSS when electrodes are located in the MFB-LH area, except at very high doses ([51,52], cited by [47]), whereas others, using various opioid antagonists, reported that opioid systems can play a significant role in modulating ICSS behavior [53–57].

The objective of this study was to examine the effect of naloxone administration in an alternative, place discrimination test [8,9,18,58,59]. This concurrent stimulation-induced place preference task (cCPP) was induced by electrical stimulation of the LH and LPBe, two brain regions with opioid neurotransmitters [38–41,47,60,61]. Similar to standard CPP, this procedure is also a rate-free learning procedure, but it is more potent in producing place conditioning effects [18,58,59]. The primary reinforcement measure is the *time spent in the positive chamber*, preventing any influence on behavior from variables other than reward [8,9,58]. However, unlike the standard CPP procedure, the concurrent task appears to be initially based more on motivation than on learning.

We carried out a cCPP test using rectangular mazes formed by two lateral compartments communicated by a small central space; the animals received concurrent electrical stimulation whenever

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they voluntarily entered one of the two main compartments, previously selected at random by the experimenter. Under these conditions, animals were subjected to two behavioral tests, receiving i.p. administration of distilled water in the first and 4 mg/kg naloxone in the second. When this dose did not block preference behavior, a dose of 10 mg/kg naloxone was injected in a subsequent test.

2. Materials and methods

2.1. Subjects and surgery

Sixty male Wistar rats (weight 295–425 g at beginning of experiment) were used in this study. They were individually housed in cages with free access to water and food (Panlab, Barcelona, Spain) for one week before the surgery. The room was maintained on a 12-h light/12-h dark cycle at 23 ± 2 °C. All behavioral and surgical procedures and pharmacological techniques complied with the animal care guidelines established by Spanish Royal Law (1201/2005) and European Community Council Directive (86/609/EEC).

Chronic implant surgery was performed under general anesthesia (sodium pentothal, 50 mg/kg, B. Braun Medical S.A. Barcelona, Spain) using a stereotaxic instrument (Model 51.600, Stoelting Co., USA), as previously described [25].

For the lateral hypothalamus electrical stimulation group (LH-S), 23 animals were implanted with a monopolar 00 stainless steel electrode insulated except at the tip (Coordinates: AP = +5.8; V = +2.8 and L = ±1.8 according to the atlas of De Groot [62]) to obtain self-stimulating animals [27,63], while 7 animals were implanted only with the reference electrode and served as a neurologically intact control group (LH-C).

For the external lateral parabrachial stimulation group (LPBe-S), 23 animals were implanted with a monopolar electrode in the LPBe (Coordinates: AP = −0.16; V = 3.0 and L = ±2.5 according to the atlas of Paxinos and Watson [64], and 7 animals served as an unimplanted neurologically intact control group (LPBe-C).

There were two types of control group for each brain area (LH and LPBe): (a) a neurologically intact control group of animals with no implantation of intracerebral electrode (LH-C and LPBe-C); and (b) a control group of implanted animals for each brain area, in which animals only received electric stimulation during the initial shaping phase and showed no reward behaviors (LH-I and LPBe-I). From this moment onwards, none of these animals received intracerebral electric stimulation during the cCPP trial. Because no significant differences were found between the two types of control groups (a and b), their results were pooled.

2.2. Apparatus

Electrical stimulation was delivered by a CS-20 stimulator connected to an ISU-165 isolation unit (both from Cibertec, Madrid, Spain), monitoring the current on an oscilloscope (Model HM 507, Hameg Instruments, Frankfurt, Germany). Aversive electrical stimulation was avoided by establishing an optimal current intensity for each animal in each group before the experimental test and maintaining this value throughout the experiment. Determination of the current intensity was based on behavioral criteria. Thus, the optimal intensity was ascertained by increasing the current until a behaviorally observable level of response was achieved without producing escape behaviors, jumping, or vocal reactions. We applied a current range of 70–115 μA in the LPBe-S group (mean of 86.05 μA) and 320–470 μA in the LH-S group (mean of 412 μA) with rectangular cathodic pulses at 66.6 Hz and 0.1 ms pulse duration.

The self-stimulation procedure to test the rewarding effect of electrical stimulation in the LH and LPBe was conducted in a 50 cm × 55 cm × 60 cm Plexiglas chamber with a lever mounted on the front wall and connected to a stimulator, oscilloscope, and lever-press counter [25–27,63]. For ICSS shaping, the mean current intensity in LH animals was 550 μA, with rectangular cathodic pulses of 0.1 ms duration. Train duration was 0.25 s for each lever press. An ICSS curve was obtained for each animal by modifying the frequency, as can be observed in Fig. 5.

The cCPP test was conducted in two different rectangular mazes. Maze 1 consisted of a 50 cm × 25 cm × 30 cm rectangular maze in which 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. The floor was synthetic cork painted with black and white stripes in one compartment and brown cork in the other. The floor of the central area (8 × 25 cm^2) was white methacrylate, and the walls were a natural-wood color. Maze 2 consisted of a 70 cm × 15 cm × 15 cm rectangular maze with black methacrylate walls, with a round hole in one end-wall and a square hole in the other. The floor was made of cork with transversal or longitudinal incisions, respectively. The central area (10 × 15 cm^2) had a metal grille floor and the walls were white.

2.3. Behavioral procedures

2.3.1. Intracranial self-stimulation (ICSS) behavior

A standard operant procedure [25,27,63] was used to screen the rewarding effect of electrical stimulation of the LH in a Skinner box (see above). After a shaping phase, and as a screening test, a rate–frequency curve was obtained for each LH-S animal, as previously reported [27]. As in previous studies, LPBe-S animals failed to learn a lever press task to induce electrical self-stimulation (see Section 4). A larger number of trials or different stimulation parameters from those habitually used in this type of test may perhaps be needed for this response to be observed.

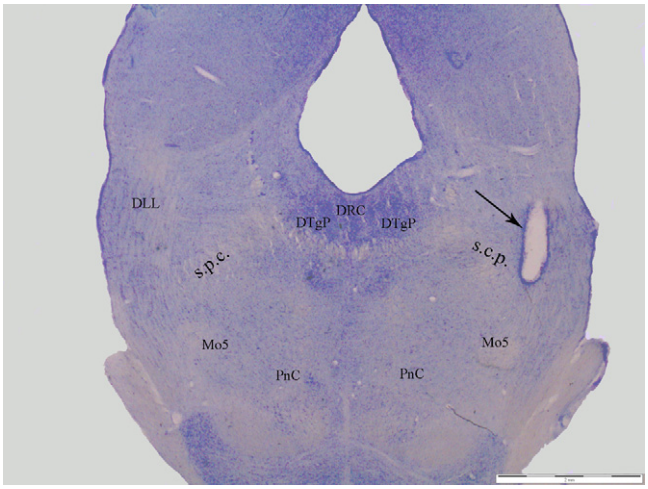

Fig. 1. Representative image of the localization of the electrode tip in LPBe stimulated and LPBe control implanted animals (LPBe-S and LPBe-I).

2.3.2. Concurrent stimulation-induced place preference (cCPP) in the two mazes: effect of naloxone administration

2.3.2.1. First test: cCPP in maze 1. Twenty minutes before each session, the animals received an s.c. injection of distilled water (vehicle for naloxone) and underwent two 10-min sessions of cCPP in maze 1′ separated by an interval of 24 h. During each session, the LH or LPBe was electrically stimulated concurrently with the voluntary stay of the animal in one of the two lateral compartments of the maze, which was previously selected at random and maintained for both sessions. The total time that each animal remained in the stimulated compartment was recorded. Animals were classified according to the results of their second cCPP trial into one of the three subgroups (positive, negative or neutral) as described above [25–27].

All electrically stimulated (LH-S, LPBe-S) and control (LH-C, LPBE-C) animals underwent a concurrent CPP task and were then classified into three subgroups (positive, negative and neutral) according to behavioral criteria used in previous studies, assigning animals remaining in stimulated compartment for >50% of the session time to a 'positive' group, those remaining for <30% of the time to a 'negative' group', and those remaining for 30–50% of session time (i.e., showing no preference) to a 'neutral group' [25–27].

2.3.2.2. Second test: naloxone injection and cCPP in maze 2. On the next day, all animals received an s.c. injection (4 mg/ml/kg) of naloxone (Naloxone Hydrochloride, Lab Sigma, St. Louis, USA) at 20 min before a 10-min cCPP session in maze 2. Maze 2 contained different internal sensory cues, and the orientation was changed from the previous N–S to E–W.

When the dose of 4 mg/kg naloxone did not interrupt the preference conditioning in a stimulated group, a third cCPP session was conducted 24 h later, after the s.c. injection of 10 mg/kg naloxone.

The behavioral procedures and substance administration were identical for animals in the control groups, except that they received no brain stimulation.

2.4. Histology

After concluding the behavioral experiments, all animals were deeply anesthetized and intracardially perfused with isotonic saline and 4% formaldehyde solution. Placement of the electrical stimulation electrode was verified after an electrolytic lesion (0.5 mA of cathodic current for 10 s.). Brains were removed, stored in paraformaldehyde, and sectioned. Sections were then mounted, stained with Cresyl violet, and verified under light microscope (see Figs. 1 and 2).

2.5. Statistical analysis

Statistica 5.0 (Statsoft. Inc., OK) and SPSS 15 software were used for the statistical analysis. The behavior of animals in cCPP trials and the effect of naloxone administration were analyzed by means of a mixed two-factor ANOVA (Group × Drug). Analyses included the LH- and LPBe-stimulated groups, their respective implanted control groups, and two intact groups (one with implantation of the reference electrode), using direct data on the length of stay in the stimulated compartment.

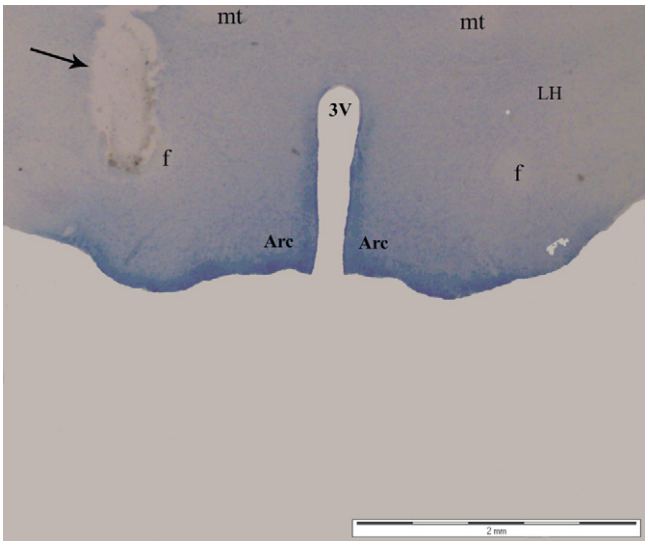

Fig. 2. Representative image of the localization of the electrode tip in lateral hypothalamus of stimulated and control implanted animals (LH-S and LH-I).

Because the 4 mg/kg naloxone dose failed to block place conditioning in the LH-S group, these animals and their respective controls received a dose of 10 mg/kg in a second experiment, and another ANOVA (Group × Drug) was performed to analyze this effect.

3. Results

Six of the twenty-three animals implanted with an electrode in the lateral hypothalamus were excluded during the experimental phase because the implant became detached. After the shaping process, 10 animals of this group developed ICSS (LH-S group) and the other 7 were used as implanted control group (LH-I Group). We also used a neurologically intact group with 7 control animals with a reference electrode alone (LH-C Group), although 1 of these was excluded because the implant became detached.

One animal in the lateral parabrachial external stimulated group (LPBe-S) did not survive the surgery. The remaining animals were classified according to the above-reported behavioral criteria [25–27], assigning 12 to the positive group (LPBe-$S_{(+)}$), 6 to the negative group (LPBe-$S_{(-)}$), and 4 to the neutral group (used as implanted control group [LPBe-I]). Another intact control group was formed by 7 animals (LPBe-C).

The results of the first ANOVA (which included all groups and the dose of 4 mg/kg naloxone) showed significant effects of Group [6,46) = 6.125, $p < 0.001^{**}$], DRUG [$F(1,46) = 4.090$, $p < 0.049^{*}$], and Group × Drug interaction [$F(6,46) = 7.674$, $p < 0.001^{**}$] (Fig. 3).

In the planned comparisons of results after vehicle administration, no differences were found among the control groups (LH-I, LPBe-I, LH-C, and LPBe-C) [$F(1,46) = 759$, $p < 0.7840$] or between the LH-S and LPBe-$S_{(+)}$ groups [$F(1,46) = 1.2342$, $p < 0.2723$]. Significant differences were observed between the LPBe-$S_{(+)}$ and LPBe-$S_{(-)}$ groups [$F(1,46) = 50.1267$, $p < 0.001^{**}$], between pooled data for the LH-S and LPBe-$S_{(+)}$ groups and for the four control groups [$F(1,46) = 20.1221$, $p < 0.001^{**}$], and between the LPBe-$S_{(-)}$ group and the control groups [$F(1,46) = 11.2442$, $p < 0.001^{**}$].

In comparisons between the effects of *naloxone and vehicle*, significant differences were observed in the LPBe-$S_{(+)}$ group [$F(1,46) = 48.4830$, $p < 0.001^{**}$] and LPBe-$S_{(-)}$ group [($F(1,46) = 5.1946$, $p < 0.027^{*}$] but not in the LH-S group [$F(1,46) = 0.1094$, $p < 0.7422$] or in the pooled control group [$F(1,46) = 0.7529$, $p < 0.3900$].

In the comparison of the behavior of groups after the administration of 4 mg/kg *naloxone*, no differences were found among

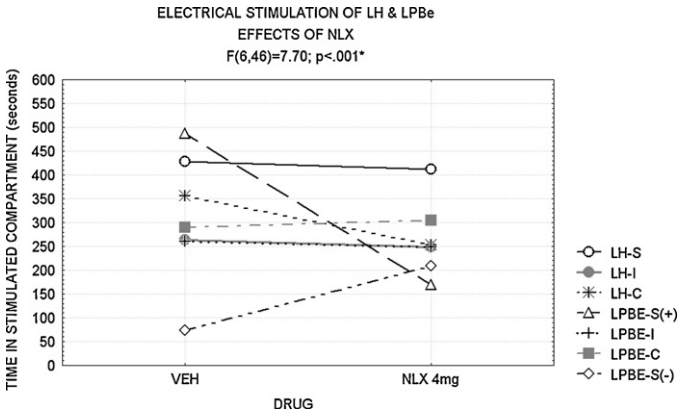

Fig. 3. Rewarding effects of the electrical stimulation of the animals with an electrode implanted in the lateral hypothalamus and their controls (LH-S, LH-I and LH-C) and of the animals with an electrode implanted in the LPBe and their controls (LPBe-$S_{(+)}$, LPBe-$S_{(-)}$, LPBe-I and LPBe-C) in a concurrent CPP task. Effects of administration of the opiate antagonist naloxone.

the four control groups [$F(1,46) = 0.2212$, $p < 0.6403$], between the LPBe-$S_{(+)}$ group and pooled control group [$F(1,46) = 3.7915$, $p < 0.0576$], or between the LPBe-$S_{(-)}$ group and pooled control group [$F(1,46) = 1.1454$, $p < 0.2900$]. No difference was now found between the LPBe-$S_{(+)}$ and LPBe-$S_{(-)}$ groups [$F(1,46) = 0.4091$, $p < 0.5255$], but the difference between the LH-S group and pooled control group persisted [$F(1,46) = 149.8915$, $p < 0.001^{**}$].

The second ANOVA on the effect of the naloxone dose (4 mg/kg *versus* 10 mg/kg) in the LH-S and corresponding control animals [LH-I and LH-C] showed that it did not differ from the effect of the vehicle administration in the three groups considered in combination (LH-S, LH-I, LH-C) [$F(1,20) = 0.3997$, $p < 0.5353$] or separately [LH-S group: $F(1,20) = 0.0314$, $p < 0.8609$; LH-I group: $F(1,20) = 0.0663$, $p < 0.7993$; LH-C group: $F(1,20) = 0.8787$, $p < 0.3594$] (see Fig. 4).

4. Discussion

This study confirms that electrical stimulation of the LPBe can induce preferences (or aversions) in a cCPP task, finding a consistent result between trials and across different tasks, as previously shown [25–27]. LH-stimulated animals, unlike parabrachial-stimulated animals, have a great facility to learn operant self-stimulation behaviors [27] and show clear behavioral preferences in a similar cCPP test [18,27,65]. However, in contrast to our observations

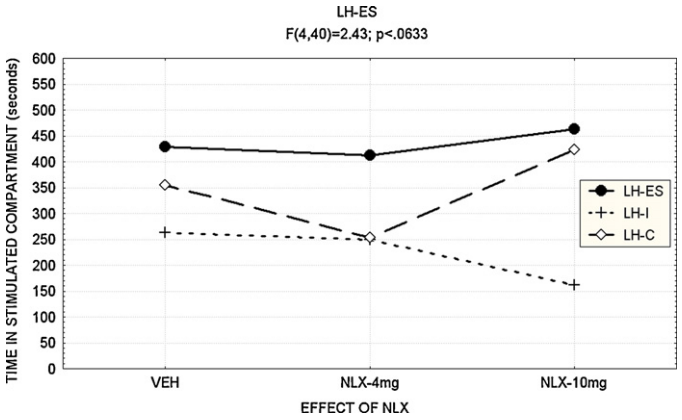

Fig. 4. Electrical stimulation of the lateral hypothalamus in a concurrent CPP task and effect of the administration of 4.0 and 10.0 mg/kg of the opiate antagonist naloxone.

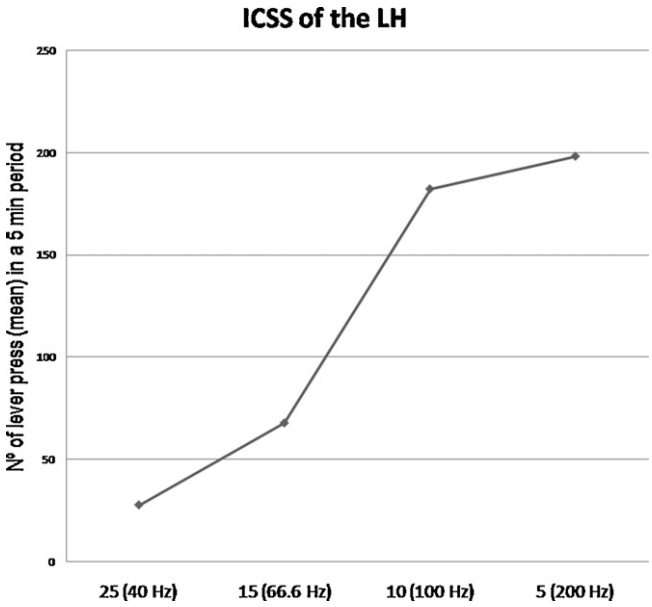

Fig. 5. Rate–frequency curve for LH-S animals ($n = 10$). The *X* axis shows the current interpulse interval followed by the frequency in parentheses. The *Y* axis shows the mean lever press rate for each frequency during a 5-min recording period.

in the LPBe-stimulated group, the administration of 4 mg/kg naloxone to LH-stimulated animals did not block stimulation-associated place preferences.

The contrast between the rewarding effects of LPBe electrical stimulation in a rate-free cCPP paradigm and their apparent absence in operant ICSS tasks [27] (and present results) may constitute a similar effect to that observed in other studies. Thus, Cazala et al. [66] observed higher ICSS rates in LH-stimulated than in septum medial- or septum lateral-stimulated animals, which was explained in terms of a dissociation between 'reward' and 'learning' processes. Moreover, the activation of distinct thalamic regions allows 'rewarding' and 'facilitating' aspects of learning to be differentiated [67,68].

It has also been observed that the presence of the opioid system can promote ICSS behavior in some brain regions [41,47] but not in others, including the lateral part of the parabrachial complex [27,69,70], where moderate amounts of mu and kappa receptors have been detected [38–40,60,61,71].

The LPBe region has been related to the processing of natural rewarding substances and others that acquired rewarding value after a learning process [29–31]. It also participates in the processing of visceral and gustative information that is qualitatively and evolutionarily characterized by the induction of a 'positive marker', such as food intake [72–77]. In addition, this pontine region has been implicated in the processing of drugs of abuse, such as amphetamines, cocaine, or opiates [37,78], whose capacity to induce positive affective states may explain the facility with which the animals establish associative learning [6,18].

Schneider et al. [79] recently demonstrated that naloxone can block the rewarding effect of appetitive nutrients in a dose-dependent manner in tasks involving the hedonic and motivational aspects of behavior but not in tasks requiring a progressive increase in the number of responses to obtain reward (progressive ratio paradigm). Although we cannot provide supporting data, our results may point to a similar phenomenon, i.e., two brain regions with distinct hedonic impacts, in which the rewarding effect of electrical stimulation can be blocked by naloxone in the LPBe but not in the LH, an essential region for the induction of operant ICSS behaviors.

The above data may also be compatible with the finding that naloxone blocks 'reward' but not 'motivation' in an operant runway model of heroin-seeking behavior [80]. This opiate antagonist may also be more specifically related to 'hedonic impact' or 'positive affective states' rather than to 'incentive salience' or 'seeking' effects [6,80], with the former being considered more characteristic of reward "liking" than reward "wanting" [81].

In the same line, Wassum et al. [82] administered naloxone in different brain regions and were able to dissociate opioid mechanisms responsible for processing the reward value of nutritive stimuli (palatability) in nucleus accumbens shell and ventral pallidum from incentive mechanisms that could be blocked by administering the antagonist in the basolateral amygdala [82].

In our study, blocking by naloxone of the opioid system in the LH did not interrupt the place preference induced by electrical stimulation of this area, although the rewarding power of LPBe and LH stimulation appears to be similar (Fig. 1). It could be hypothesized that the naloxone dose applied was too low to have the desired effect in the LH-stimulated group, but this is ruled out by our finding that a higher dose (10 mg/kg) also failed to reverse the preference effect in the LH animals, especially given that the lower dose (4 mg/kg) was adequate to block place preference in the LPBe-stimulated animals. In general, the doses used in this experiment are within the range considered by other authors. Using operant tasks, Cazala and David [54], observed that the s.c. injection of 10 mg/kg naloxone significantly increased the approximation latency to initiate a continuous electrical stimulation in the lateral hypothalamus in a shuttle box, while Bielajew et al. [53] administered doses of 10 and 20 mg/kg naloxone and reported a dose-dependent shift in rate–frequency curves to the right, for reward, in ventral tegmental area self-stimulation, although this behavior was not completely blocked.

Easterling and Holtzman [55] demonstrated that the administration of morphine raises the titration point for operant behavior in ICSS, although this effect progressively decreases over time. Naltrexone administration initially reduces the titration point, but this effect is also less effective with the passage of time [55–57]. Accordingly, it is possible that the opioid system, acting through forebrain regions, may in some way modulate the processing of the 'hedonic' component, although opioid antagonists did not completely block this operant behavior. However, the results of our experiment are closer to reports that the administration of morphine or mu receptor-specific agonists in the LH does not appear to have a major effect on CPP tasks [83,84].

In conclusion, the results of our study suggest that electrical stimulation of the lateral hypothalamus and external lateral parabrachial nucleus may have activated different components of the rewarding system, which can be differentiated at behavioral, anatomical, and neurochemical levels. Hence, some authors have proposed that ICSS of the LH can simultaneously activate ascendant and descendent pathways of the 'brain reward system', whereas natural reward can only recruit some branches originating in posterior regions [3,85]. Further investigation is required to establish whether LPBe stimulation can be included in the latter category.

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