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Tiapride prevents the aversive but not the rewarding effect induced by parabrachial electrical stimulation in a place preference task

María M. Hurtado*, Raquel García, and Amadeo Puerto

Department of Psychobiology & Mind, Brain and Behavior Research Center (CIMCYC), University of Granada, Spain,
** Email: mariena@ugr.es*

The parabrachial complex has been related to the processing of both rewarding and aversive signals. This pontine area is activated after the gastrointestinal administration of rewarding nutrients, in taste aversion learning, and in response to the reinforcing and aversive effects of some drugs of abuse. Electrical stimulation of this region can induce, in different animals, preference or aversion behaviors towards a place in a rectangular three-chamber maze task. This study examined the effect of tiapride, a D2/D3 receptor antagonist, on the aversive or rewarding effects induced by electrical stimulation of the external lateral parabrachial subnucleus (NLPBe). As previously observed, administration of tiapride interrupted the aversive effect induced by NLPBe electrical stimulation. However, in contrast to the effects of dopamine antagonists on other rewarding systems, tiapride did not impair the place preference induced by NLPBe stimulation, an activation effect that is subject to tolerance. Tiapride administration also appeared to have no effect on the horizontal motor activity (crossings) of the electrically stimulated animals. We discuss the specific relevance of parabrachial reward with respect to other reinforcing brain components or systems, especially in relation to the preference effect of drugs of abuse, such as opiates, after dopamine antagonist administration.

Key words: parabrachial complex, brain electrical stimulation, tiapride, place aversions, place preferences

INTRODUCTION

The parabrachial complex has been related to both rewarding and aversive behavioral processes. Its involvement has been reported in taste aversion learning (Mediavilla et al. 2005, Carter et al. 2015), the processing of affective and autonomic dimensions of pain (Gauriau and Bernard 2002), the aversive effects of some drugs of abuse (Nader et al. 1996), and in the effects induced by administration of various rewarding nutrients (Yamamoto and Sawa 2000a, b).

More specifically, the PBLe subnucleus appears to contain intermingled cell populations that process rewarding and aversive information, as also observed in other brain areas (Hawkins et al. 1983, O`Doherty et al. 2001). Thus, electrical stimulation of the PBLe induces consistent aversion or preference behavior towards associated stimuli in different animals (Simón et al. 2007, 2008), and its effect on preference behavior is subject to tolerance after repeated activation (Hurtado and Puerto 2016).

For its part, the dopaminergic system has been found to increase its activity in the processing of various aversive stimuli (Salamone 1994, Fenu et al. 2001). Conversely, administration of dopamine synthesis inhibitors or dopaminergic antagonists impairs the acquisition of different aversive behaviors (Fenu et al. 2001).

However, the function most commonly attributed to the dopamine system is related to the processing of natural rewards (e.g., food intake) or artificial rewards (e.g., drugs of abuse or mesolimbic electrical stimulation), which all commonly produce an increase in brain dopamine levels (Roitman et al. 2004, Aragona et al. 2008, Ma et al. 2009, Hernández and Shizgal 2009). The administration of dopamine antagonists usually increases the response latency or slows the response in tasks related to goal-directed behavior or after stimulation of the mesolimbic system (Kirkpatrick and Fowler 1989, Benaliouad et al. 2007).

However, some authors have associated the release of dopamine in the nucleus accumbens with the action of pressing the lever and the facilitation of instrumental behaviors rather than with the subsequent rewarding consumption (Roitman et al. 2004, 2005). Likewise, studies on the effects of electrical brain self-stimulation in the same system found that the increase in dopamine may be more closely correlated with the learning than with the hedonic value (Owesson-White et al. 2008). Moreover, mice lacking

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Correspondence should be addressed to MM. Hurtado
Email: mariena@ugr.es

dopamine (DD mice) maintain the capacity to detect the positive hedonic value of rewarding foods (Cannon and Palmiter 2003, Cannon and Bseiki 2004).

Hence, the objective of the present study was to examine the role of dopamine in place preferences induced by electrical stimulation of the NPBe subnucleus, a rewarding naloxone-dependent non-mesolimbic region (Simón et al. 2007). Tiapride, a D2/D3 receptor antagonist prescribed in patients undergoing alcohol detoxification (among others), interrupts ongoing place aversions induced by electrical stimulation of the NPBLe (Hurtado et al. 2014).

In the present experiment, freely-moving rewarding and aversive groups of NLPBe-stimulated animals were both subjected to a concurrent place preference (cPP) task after tiapride administration. The potential motor side effects of this dopaminergic antagonist were examined during the task by recording the crossings of the animals as horizontal motor activity index.

METHOD

Subject and surgical procedure

Fifty male Wistar rats from the breeding colony at the University of Granada, weighing 280-350 g at baseline, were used in this study. The animals were first randomly assigned to two surgical groups, which were later subdivided (after Phase 1) according to their responses to the electrical stimulation. One of these surgical groups was implanted with intracranial electrodes in the NLPBe (n=34) and the other was a neurologically intact control group (n=16). 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 light/dark cycle. All experimental procedures were conducted during light periods with white noise.

The animals remained under these conditions for an adaptation period of at least 7 days before surgery. All behavioral procedures and surgical techniques complied with Spanish legislation (Royal Law 23/1988) and the European Community Council Directive (86/609/EEC).

Animals were implanted with a stainless steel monopolar electrode (00) in the NLPBe [Coordinates: AP=-0.16, V=3.0, L=+ 2.5, according to the atlas by Paxinos and Watson (1998)] using a stereotaxic apparatus (Stoelting Co. Stereotaxic 511.600, USA) 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.

Equipment

For the monopolar electrical stimulation, cathodal constant-current rectangular pulses of 66.6 Hz and a current range of 95 and 200 μA 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). As in previous studies in our laboratory (Hurtado et al. 2014, 2016), the appropriate current intensity was individually established for each animal by applying progressive increments of 10 mA and observing in detail the behavior of the animal after each increase, selecting for subsequent experimental phases the intensity level immediately below that at which behavioral signs of nervousness were observed, e.g., unmotivated motor activity or vocalizations (Tehovnik 1996).

The following three-chamber mazes were used (Simón et al. 2007):

Model 1: Rectangular maze (50×25×30 cm) oriented East-West, 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. 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.

Model 2: Rectangular maze (70×15×15 cm.) oriented North-South, in which the walls of the two lateral compartments were made of black methacrylate, with a round hole in one end-wall and a square hole in the other. The floor was made of brown cork with transverse or longitudinal incisions, respectively. The central area (10×15 cm) had a metal grill floor and the walls were white.

Behavioral procedure

Phase 1: Baseline classification of animals (Model 1 maze)

The cPP task in model 1 maze commenced at 48 h after establishing the optimal individual electrical current. At 30 min before each test, animals received an injection of distilled water as vehicle. After placing each animal in the center of the maze, the voluntary stay of the animal in one of the two compartments was accompanied by the corresponding intracranial electrical stimulation (half of the animals received stimulation in one side of the maze and the rest in the other), and the stay time in each area was recorded. The place in which the animals received stimulation was distributed at random. Each

session lasted for 10 min. The 16 neurologically intact animals underwent the same procedure without stimulation. This procedure was repeated in two sessions on consecutive days.

As commonly observed in studies using NLPBe electrical stimulation (Simón et al. 2007, 2008, 2009, García et al. 2014, Hurtado et al. 2014), three groups of animals could be distinguished by their behavior: a) "positive" animals, which preferred the stimulated maze compartment during the second learning session and stayed for >50% of the time in this area (showing no negative behavior during sessions) (n=8), b) "negative" animals, which avoided the stimulated compartment, staying in it for <30% of the time (showing no positive behavior during sessions) (n=6), and c) "neutral" animals that evidenced no consistent preference or aversive behavior, staying for 30-50% of the time in the stimulated compartment during the second session, or showing alternating negative and positive behavior between sessions (n=20). In subsequent experiments, seven "neutral" animals from the third group were randomly selected to serve as an implanted control group, while the remaining "neutral" animals were excluded from the study.

We also included two groups of neurologically intact animals, randomly distributed between a vehicle group, which received i.p. distilled water in both phases of the study (n=8), and an intact group, which received the same treatment as the NBLe-stimulated groups but with no surgery or NLPBe electrical stimulation (n=8).

In phase 1 of the study, we quantified the stay of each group in the stimulated area during two baseline sessions.

Phase 2: Effect of 30mg/kg tiapride administration (Model 2 maze)

At 48 h after ending phase 1, we conducted another cPP task in the model 2 maze (to avoid learning transferences) and recorded not only the time of stay in the stimulated compartment but also the number of crossings made by animals, considered as a horizontal motor activity index. The same procedure as in Phase 1 was followed, except that all groups save the vehicle group received an i.p. injection of 30 mg/kg tiapride (*Tiaprizal, Sanofi-Synthelabo S.A., Barcelona, Spain*) at 30 min before being placed in the maze. The "positive" and "negative" groups received electrical brain stimulation, but not the implanted control group or the two intact groups (vehicle and tiapride). The implanted control group was included to control for any possible effects of the surgery and electrode placement.

With regard to the intact animals, the tiapride control group (n=8) received the same tiapride dose as the surgical groups, while the vehicle control group (n=8) received a second dose of vehicle during the second phase. A summary of the experimental groups and treatments is given in Table I.

Phase 3: Effect of 40mg/kg tiapride administration (Model 2 maze)

At 48 h after ending this test, we conducted another cPP task in the same maze but now using an i.p. injection of 40 mg/kg tiapride.

Histology

After the behavioral tests, the animals were anesthetized and a small electrolytic lesion (0.3 mA/5 s) was performed, followed by the intra-cardiac perfusion of isotonic saline and 10% formaldehyde. Brains were extracted and kept in 10% paraformaldehyde until sectioned in 60-micron coronal sections. These were stained with Cresyl Violet, examined under a stereoscopic magnifying glass (VMZ-4F), and photographed with a PM-6 camera (Olympus, Tokyo, Japan) (see Fig. 1). In this manner, it was tested whether the lesions were confined to the NLPBe subnucleus in all of the animals, although the size of the lesion generated by the electrical current is much greater than the radius of action expected to be generated by the electrical stimulation applied in the present study (Yoemans 1990).

Table I. Summary of the behavioral procedure

	PHASE 1	PHASE 2	PHASE 3	n
Positive Group	St + Vehicle	St + Tiap 30	St + Tiap 40	8
Negative Group	St + Vehicle	St + Tiap 30	St + Tiap 40	6
Implanted Control Group	St + Vehicle	No St + Tiap 30	No St + Tiap 40	7
Tiapride Control Group	No St + Vehicle	No St + Tiap 30	No St + Tiap 40	8
Vehicle Control Group	No St + Vehicle	No St + Vehicle	No St + Vehicle	8

St: Electrical stimulation of the PBLe, Tiap 30: Tiapride 30mg/kg, Tiap 40: Tiapride 40 mg/kg

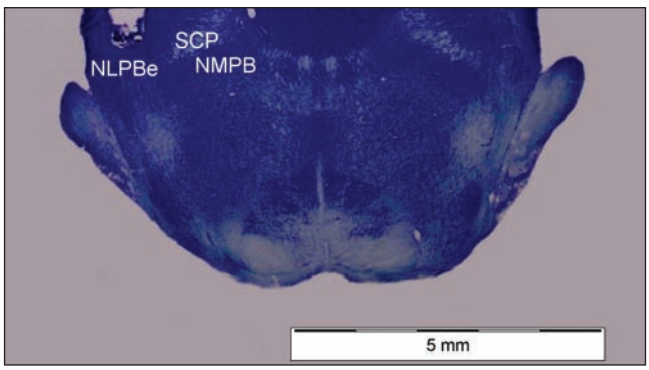

Fig. 1. Localization of the electrode in the external lateral parabrachial nucleus (NLPBe) of an animal in the Negative Stimulated Group. NMPB: medial parabrachial nucleus, SCP: superior cerebellar peduncle.

Statistical analysis

Statistical 6.0 (Statsoft Inc., Tulsa, OK) was used for the statistical analysis, which included a two-way ANOVA followed by application of the Tukey-Kramer test for post-hoc comparisons. Given that no significant differences were observed among the different control groups, the factors for the two-way ANOVA were Group (3 groups) and Phase (2 Phases). Results for the stimulated animals (positive and negative groups) were also analyzed using a repeated-measures ANOVA, adding the increased tiapride dose (baseline, 30, and 40mg/kg). The Student's t-test was used to compare the number of crossings (horizontal activity) between the vehicle group and the groups administered with the drug, and a two-way ANOVA was carried out to compare the number of crossings among the five original study groups, with Group (5 groups) and Phase (2 phases) as factors. P<0.05 was considered significant in all tests.

RESULTS

No differences were found among the control groups ($F_{4,40}$=1.35, *P*<0.2685), therefore, all three were included in a single control group for the main analysis.

The Group X Phase interaction was statistically significant ($F_{4,68}$=3.81, *P*<0.0075). The main group effect was also significant ($F_{2,34}$=7.2116, *P*<0.0025), (see Fig. 2).

Post-hoc comparisons showed significant differences in the negative group as a function of tiapride administration (Phase 1 *vs.* Phase 2, *P*=0.0253), although no such differences were observed in the other groups (*P*>0.05).

Results of the repeated-measures ANOVA for the two stimulated groups (positive and negative) showed a significant interaction ($F_{1,12}$=210.905, *P*<0.001) and a significant main effect of Group ($F_{1,12}$=8.596, *P*<0.013).

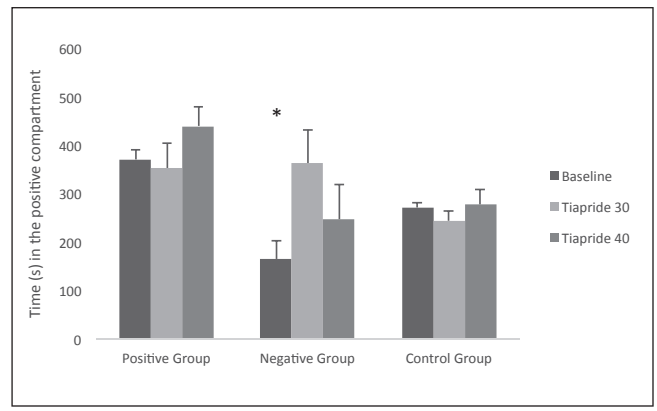

Fig. 2. Effects of tiapride on Conditioned Place Aversion (CPA) and Conditioned Place Preference (CPP) of positive and negative and control groups. *: p<0.05. SD values are shown in error bars. This figure shows that, unlike in the positive and control groups, the administration of 30 mg but not 40 mg of tiapride increases preference for the place associated with the originally aversive electrical stimulation.

With respect to the crossings of the animals, the repeated-measures ANOVA for two groups (vehicle *versus* tiapride-treated) showed no significant results for the interaction ($F_{1,35}$=0.0603, *P*<0.8074) or for the main effect of Group ($F_{1,35}$=0.0011, *P*<0.9740).

No significant differences in crossings were found between the vehicle group and the intact control group ($F_{1,32}$=0.1346, *P*<0.7161), positive group ($F_{1,32}$=0.0045, *P*<0.9472), or negative group ($F_{1,32}$=2.0179, *P*<0.1651) (see Fig. 3). However, significant differences were observed between the vehicle group and the implanted control group ($F_{1,32}$=4.4454, *P*<0.04292). Furthermore, significant differences were also observed between the implanted control group and the negative group ($F_{1,32}$=10.5203, *P*<0.0008) as well as between the implanted control group and the positive group ($F_{1,32}$=4.844, *P*<0.046).

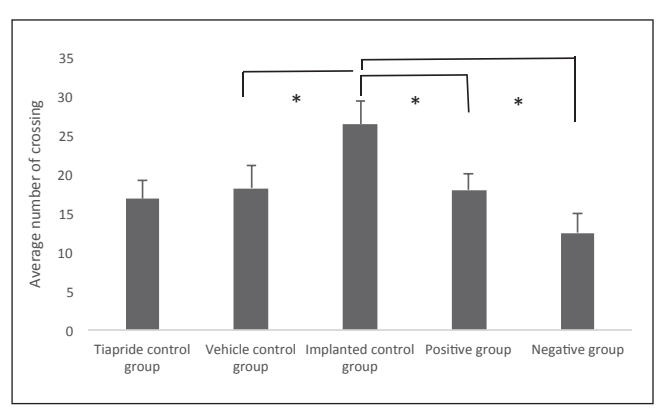

Fig. 3. Mean number of crossings by the different groups during the second experimental phase. *: p<0.05. SD values are shown in error bars. This figure shows that, with the exception of the implanted control group (in which the number of crossings is increased), administration of tiapride does not generate differential effects in the other groups with respect to the vehicle control group.

DISCUSSION

This study confirms that the administration of tiapride, an D2/D3 antagonist, impairs ongoing place aversion induced by activation of the LPBe subnucleus. However, in contrast to the relevance of dopamine (e.g., Simón et al. 2016) and dopamine antagonists (Ettenberg and White 1981, Fenton and Liebman 1982, Benaliouad et al. 2007) in other rewarding systems or components, tiapride did not impair conditioned place preferences generated by reinforcing electrical activation of the PBLe subnucleus.

The present results confirm that electrical stimulation of the NLPBe consistently generates differentiated animal groups according to their preference or aversion for a place in a rectangular maze task (Simón et al. 2007, 2008, 2009, 2011, García et al. 2014). These effects appeared to be specific to the electrical stimulation of this region, because none of the neurologically intact animals (vehicle control group or intact control group) sustained a stable behavior towards a given area of model 1 maze during the baseline phase.

In relation to the CPA, these results are compatible with previous reports that the parabrachial complex as a whole is related to aversive processes (Bernard et al. 1994, Nader et al. 1996, Mediavilla et al. 2000). More specifically, it has been suggested that the NLPBe may play a major role in processing the affective and emotional components of nociception (Gariau and Bernard 2001) or taste (Hajnal and Norgren 2004) and even in generating human feelings of wellbeing or malaise (Balaban and Thayer 2001, Schachter 2004).

The present findings also confirm that tiapride administration impairs the place aversion induced by NLPBe electrical stimulation (Hurtado et al. 2014), while the utilization of a higher tiapride dose (40 mg/kg) allowed a dose-response curve to be constructed, suggesting a DA-receptor drug window for the aversive behavior rather than adverse associated heterogeneous actions, which would also have been observed in the positive group, which was not the case. These data are consistent with previous observations by our group that the NLPBe forms part of a brain pathway underlying concurrent taste learning (Mediavilla et al. 2000, 2005). Thus, specific lesions of this subnucleus were found to impair the acquisition of concurrent taste aversions (Mediavilla et al. 2000, 2011), an implicit learning modality that is also interrupted by tiapride administration (Mediavilla et al. 2012).

Hence, electrical stimulation of the NLPBe in the "negative" animals may have activated a specific brainstem component of the neurobiological system used under natural conditions for vagally-transmitted negative visceral information (Mediavilla et al. 2000), for taste information (Yamamoto et al. 1994), and even for some drugs of abuse such as morphine (Bechara et al. 1993, Mansour et al. 1995, Nader et al. 1996). In this context, some authors have related the lateral parabrachial area to the processing of the aversive properties of morphine (Bechara et al. 1993, Nader et al. 1996) in interaction with the dopaminergic system (Zito et al. 1988). In the clinical setting, tiapride became used in the treatment of aversive processes, including the withdrawal syndrome and craving in patients with alcoholism (Soyka et al. 2002, Bender et al. 2007).

With respect to the CPP data, the present results suggest that tiapride (at a dose of either 30 or 40 mg/kg) does not interfere with the development of ongoing place preferences induced by concurrent electrical stimulation of the non-mesolimbic NLPBe, in contrast to the decisive role of dopamine proposed by some authors in other rewarding learning components. However, our data are compatible with findings that some dopamine systems critically participate in goal-directed behavior, in the attribution of incentive salience, and in behavioral reactivity (Salamone 1994, Peciña et al. 1997, Garris et al. 1999, Cannon and Palmiter 2003, Phillips et al. 2003, Cannon and Bseikri 2004, Roitman et al. 2004, 2005, Robinson et al. 2005, Flagel et al. 2011). In fact, it has been proposed that interference with the dopaminergic system has a greater effect on the performance of learned instrumental behaviors (Smith et al. 2002, Robinson et al. 2005) than on the affective value of appetizing stimuli. Thus, dopamine knock-out animals show appropriate preference reactions to rewarding stimuli, e.g., sucrose (Cannon and Palmiter 2003, Cannon and Bseikri 2004), as long as the task does not involve major efforts.

In contrast to the results obtained with tiapride in the present study, administration of the opiate antagonist naloxone was reported to block ongoing place preferences induced by electrical brain stimulation of the NLPBe (Simón et al. 2007), a tolerance-dependent brainstem subnucleus connected to the insular cortex (Fulwiler and Saper 1984, Bernard et al. 1991, Dobolyi et al. 2005), in which induction of a reward-decay effect with repeated stimulation was also recently demonstrated (Hurtado et al. 2016, Hurtado and Puerto 2016). The present study dissociates the role of DA, initially with respect to the parabrachial aversion system but also in relation to the rewarding mesolimbic component. These data are compatible with the proposal of multiple reward components (Schultz 2000) that might anatomically and neurochemically differ with respect to the involvement of the opioid and dopaminergic systems. Thus, it has been suggested that the neural mechanisms responsible for the affective effects of substance abuse may differ from those underlying seeking behavior for these substances (Berridge and Robinson 1998, McFarland and Ettenberg 1999). Hence, whereas naloxone blocks affective effects, it does not affect seeking/goal behavior motivation (McFarland and Ettenberg 1999, Simón et al. 2007, 2009),

including the rewarding effects of electrical stimulation of the lateral hypothalamus (Simón et al. 2011).

There appears to be a well-established relationship between the rewarding effects of drugs of abuse and dopaminergic mechanisms in limbic structures, e.g., the central amygdala, dorsal hippocampus, or striate nucleus (Deslandes et al. 2002, Rezayof et al. 2002, 2003, Vorel et al. 2002). In this way, it has been demonstrated that dopaminergic antagonists usually reduce the rewarding effects induced in CPP tasks by different drugs of abuse, such as cocaine (See et al. 2001, Vorel et al. 2002), amphetamines (Mackey and Van der Kooy 1985), nicotine (Le Foll et al. 2005), and, in certain narcotic states, opiates (Nader et al. 1994).

With respect to opiates, however, no relationship has been observed between the rewarding capacity of heroin (measured by self-administration tasks) and dopaminergic activity in the accumbens nucleus (Caillé and Parsons 2003, Koob and LeMoal 2006). Moreover, neuroleptics do not always interrupt the preferences induced by morphine or heroin (MacKey and Van der Kooy 1985, Nader et al. 1994, McFarland and Ettenberg 1999, Laviolette et al. 2002). Therefore, it appears likely that rewards related to opiates may not necessarily involve the mesolimbic dopaminergic system, unlike those related to other addictive drugs (Koob 1992, Olmstead and Franklin 1996, Nader and Van der Kooy 1997, Hnasko et al. 2005). In other words, the rewarding action of opiates may be both DA-dependent and DA-independent, explaining some recent reports that dopamine is only essential in the motivation of seeking/goal-directed behaviors (Salamone 1994, Peciña et al. 1997, Garris et al. 1999, Cannon and Palmiter 2003, Phillips et al. 2003, Cannon and Bseikri 2004, Roitman et al. 2004, 2005, Robinson et al. 2005, Flagel et al. 2011).

In our study of the potential motor side-effects of tiapride administration, no significant differences were found in the number of crossings (in phase 2 experiment) between the animals receiving tiapride and those receiving vehicle or between the vehicle group and any other group with the exception of the intact control group. The meaning of this last difference has yet to be determined, although there may have been a similar sensitization effect to that observed by our group after applying stimulation to the anatomically related insular cortex (García et al., 2014). Thus, the higher number of crossings observed in the implanted control group might have been because, unlike the positive and negative groups, these animals did not receive the electrical stimulation that they had received in previous phases of the experiment, suggesting an increase in exploratory and seeking behaviors. At any rate, these results indicate that the motor side-effects produced by tiapride administration would be, in the worst of cases, of little importance.

CONCLUSIONS

In summary, these results suggest that administration of tiapride, an D2/D3 antagonist, impairs ongoing place aversion induced by electrical stimulation of the NLPBe subnucleus but does not interfere (at a dose of either 30 or 40 mg/kg) with the ongoing place preferences induced in this manner. The present study dissociates the role of dopamine in CPP and aversion induced by parabrachial activation and also contrasts with the decisive role of DA in other rewarding learning components. Similar results have been obtained by authors who administered dopaminergic antagonists to animals in preference tasks induced by drugs of abuse such as opiates (MacKey and Van der Kooy 1985, Zito et al. 1988, Nader et al. 1994, McFarland and Ettenberg 1999, Laviolette et al. 2002) and nicotine (Laviolette and Van der Kooy 2003).

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This study was approved by the ethics committee of the University of Granada. The authors declare no conflict of interest.

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