IBRO Neuroscience Reports 14 (2023) 195–201

Contents lists available at ScienceDirect

IBRO Neuroscience Reports

journal homepage: www.sciencedirect.com/journal/IBRO-Neuroscience-Reports

The central blockade of the dopamine DR4 receptor decreases sucrose consumption by modifying the microstructure of drinking behavior in male rats

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ARTICLE INFO

Keywords:
Sucrose intake
D4R receptor
Drinking microstructure
Locomotor activity

ABSTRACT

Sugar solutions promote hedonic feeding and increase the risk of obesity and binge-type behavior. In rodents, ingestion of sugar solutions enhances dopamine release to mesolimbic regions, suggesting changes in hedonic intake and brain reward processes. Moreover, dopaminergic D2R/D3R receptors contribute to the hedonic intake of palatable solutions. Although the experimental evidence indicate that the dopaminergic D4 receptor (D4R) modulates feeding at homeostatic levels, it is currently unknown whether D4R also regulate the hedonic intake of sugar solutions. In this study, we evaluated the effect of the central blockade of D4R on the consumption of a 20% sucrose solution, the drinking microstructure parameters, and levels of locomotor activity in sated rats. In the first experiment, male Wistar rats were daily exposed to a 20% sugar solution in the first hour of the light phase of the light:dark cycle. On day 10, rats received i.c.v injections of the D4R antagonist, L-745870 (0, 1 or 2 μg/5 μl) and sucrose consumption and drinking microstructure parameters (latency to start drinking, bouts, drinking duration, bout size, inter-bout interval, time in activity and time in resting) were evaluated. In the second experiment, rats were trained to receive the 20% sucrose solution as described in experiment 1. On day 10, after the 1 h of sucrose access, the rats were placed in the open field for 5-min (habituation phase). Then, rats received i.c.v injections of L-745870 (0, 1 or 2 μg/ 5 μl), and were placed again in the open-field test for 10-min (pharmacological phase). The number or crosses trough squares and number of rears were scored for both the habituation and pharmacological phase. Here we found that administration of L-745870 decreased the consumption of sucrose in a dose-depended manner. Moreover, L-745870-treated rats displayed microstructural changes, including greater number of bouts and reduced drinking duration, bout size and inter-bout intervals. Furthermore, the number of crosses and number of rears in the open field test remained unchanged for habituation and pharmacological phase. Finally, present findings suggest that D4R modulates the consumption of sugar solutions by alteration of hedonic responses, but the contribution of homeostatic systems is discussed. These results open perspectives for the potential use of the D4R antagonists for treating obesity or binge-eating behavior.

1. Introduction

Obesity is one of the most alarming health problems worldwide, and according to the World Health Organization (World Health Organization, 2022), more than 1.9 billion adults and 38 million children are overweight or obese. Among the multiple causes leading to obesity, the consumption of sugary beverages (e.g., juices and soft drinks) is a main factor that disrupts metabolism and the balanced food intake (Bray and Popkin, 2014). Experimental and clinical evidence indicates that sugar beverages stimulate further sugar intake in the future (Liu and Bohórquez, 2022), progressively escalate the intake and favor binge eating (Avena et al., 2005; Eikelboom and Hewitt, 2016), which in the short

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https://doi.org/10.1016/j.ibneur.2023.02.001
Received 30 September 2022; Received in revised form 30 January 2023; Accepted 4 February 2023
Available online 8 February 2023

term leads to increased adiposity and obesity (Avena et al., 2005; Boggiano et al., 2007).

Ingestion of sugar favor the activation of gut receptor, that via vagus nerve, lead to stimulation of homeostatic feeding circuits in the hypothalamus and dopaminergic reward circuits that stimulate current and future sugar consumption in sated rodents (de Araujo et al., 2020; Liu and Bohórquez, 2022). Specifically, sugar and palatable food stimulate the release of mesolimbic dopamine to the nucleus accumbens like drugs of abuse (Rada et al., 2005). Therefore, dopamine release is associated with hedonic eating, brain reward, drug addiction and compulsive-like behavior (Rada et al., 2005). In rats trained to ingest daily a sugar solution the binding of the dopamine receptor 1 (D1R) and the optic density of D1R in the nucleus accumbens was increased (Colantuoni et al., 2001; Osnaya-Ramírez et al., 2020) suggesting a main role in the anticipation and the reward response to sucrose. On the other hand, pharmacological studies have revealed that the systemic administration of D2R/D3R agonist exerts inhibitory effects on food intake (Billes et al., 2012; Cooper and Al-Naser, 2006; Rusk and Cooper, 1989). Moreover, D2R signaling into nucleus accumbens is required for the hedonic and rewarding intake of palatable solutions (Baldo et al., 2002; Suárez-Ortíz et al., 2018). However, the knowledge about the functional contribution of D4R to the control of hedonic eating is limited.

Different brain regions involved in the homeostatic or hedonic function for food ingestion, such as the amygdala, the central cortex, hypothalamus, and the striatum, express the D4R (Ariano et al., 1997; Gan et al., 2004; Huang et al., 2005). Although the evidence for the role of DR4 in the homeostatic control of feeding is limited. In food-deprived rats the administration of PD-168,077 (selective D4R agonist) within the paraventricular hypothalamus (PVN) increased food intake and these effects were reversed by the selective D4R antagonist L-745870 (Tejas-Juárez et al., 2014), suggesting an orexigenic function of the DR4 in the PVN. Similarly, diet-induced obese rodents expressed higher levels of D4R rRNA in the ventromedial hypothalamus, suggesting the suppression of the satiety response and an enhanced motivation for palatable diets (Huang et al., 2005). Consistently, clinical studies reported that polymorphisms in the human *d4r* gene (7-repeat allele) is associated with food craving, drug addiction, and obesity (Le Foll et al., 2009; Pelufo et al., 2014; Silveira et al., 2014). Together, clinical, and experimental studies suggest that D4R drive the intake of palatable foods and opens a potential therapeutic pathway for pharmacological treatment of obesity and binge-eating disorder (Giorgioni et al., 2021).

Nocturnal rodents consume more water and sugar solutions during the night than during the day, due to the circadian function (Bainier et al., 2017; Osnaya-Ramírez et al., 2020). The synthesis and release of dopamine is also under circadian regulation (Golombek et al., 2014; Parekh et al., 2015), which imposes a temporal stamp to hedonic behavior (Abarca et al., 2002; Hampp et al., 2008; McClung et al., 2005). In order to better dissect the daily homeostatic drive of thirst from a reward-driven sugar consumption, rats are exposed to sugar under a sated phase, that includes the first hours of the light phase, when normally rats should be sleeping (Osnaya-Ramírez et al., 2020). After 5–6 days of restricted access in the light phase, rodents anticipate and consume large amounts of sugar solution or palatable food in their rest phase, which shifts circadian rhythms in brain regions involved in hedonic and reward responses (Angeles-Castellanos et al., 2008; Blancas et al., 2014; Osnaya-Ramírez et al., 2020)

Therefore, the current study examined the contribution of D4R signaling on the sucrose hedonic intake rats. Experiment 1 explored the effects of i.c.v injections of the D4R antagonist, L-745870 on sated rats trained to drink a 20% sugar solution for 1 h in the light phase. The effects of L-745870 on the consumption of the sucrose solution and the drinking microstructure (latency, bout frequency, drinking duration, bout duration, interbout interval time and bout size) were assessed. In experiment 2, rats received i.c.v injections of the L-745870, and spontaneous locomotor activity was measured in the open field test.

2. Materials and methods

2.1. Animals and general conditions

Male Wistar rats weighing of 200–230 g at the beginning of the experiment, were individually housed in acrylic home-cages (27×36×15 cm) in a room maintained under a 12/12-h light-dark cycle (lights on 10:00 am) and controlled temperature (22 ± 1 °C). Each cage was equipped with the BioDAQ 2.2 system (Research Diets Inc.), which automatically monitors food or water intake. All experiments comply with the Official Mexican Norm for Animal Care (NOM-062-ZOO-1999), and the FES-Iztacala Ethics Committee approved the experimental protocol (CE/FESI/102020/1365).

2.2. Diet

Animals had free access to tap water and standard chow pellets (28% protein, 13% fat, and 58% carbohydrates, 3.4 kcal/g; LabDiet 5010, USA). The 20% sucrose solution (0.8 kcal/ml) was available daily for 1 h at the moment of lights on (10:00 am). The sucrose solution was prepared daily, 20 min before the access.

2.3. Stereotaxic surgery

Animals were deeply anesthetized with ketamine/xylazine 112.5/22.5 mg/kg (Laboratorios Aranda/PiSA Agropecuaria; Mexico). A sterile 23 G stainless-steel cannula was placed unilaterally in the right lateral ventricle (posterior to bregma 0.4 mm, lateral to the median line 1.5 mm and dorsoventral −3.0 mm; (Paxinos and Watson, 2013). The cannula was fixed to the skull with dental cement and stainless-steel screws. Immediately after the surgery and 48 h post-surgery, animals were treated with the antibiotic enrofloxacine (25 mg/kg) to prevent bacterial infections. Animals had a recovery period of 7 days and then the experimental procedure started.

2.4. Drug and pharmacological administration

The L-745870 (D4R selective antagonist; Tocris Bioscience, UK) was used. The drug was initially prepared in a stock solution dissolved in 5% dimethyl sulfoxide (DMSO), and then dissolved in aliquots with sterile saline solution (0.9%). In a previous study performed in our laboratory, the intra-PVN administration of 0.1 μg of L-745870 prevented the PD-168,077-induced hyperfagia (Tejas-Juárez et al., 2014). Based on this evidence, we increased this dose 10-fold and 20-fold more to evaluate the intraventricular effect of the L-745870. The final concentrations infused in each experiment were 1-μg and 2-μg in a volume of 5 μl at a speed of 1 μl/min in the right lateral ventricle, using a high-precision digital syringe (Hamilton Co., Reno, NV). After administration, the microinjector remained 1-minute in the site to avoid backflow. Control animals received a volume of 5 μl of sterile saline 0.9% + 0.05% DMSO.

2.5. Liquid intake monitoring

The BioDAQ food and liquid-intake monitoring system (Research Diets Inc) provides accurate and continuous collection of fluid and food intake data with minimal intervention of the experimenter (Boyle et al., (2012)). The BioDAQ system weights the hopper with the plastic liquid bottle (± 0.01 g) second by second. Stable weight indicates that animal is “not drinking” while unstable weight indicates “drinking.” Variations in the weight of the liquid hopper are recorded as bout vectors with a startup time, duration and amount consumed (minimum 0.02 g). Bouts end if the hopper weight remains stable for more than 5 s. Each bout is separated by an inter-bout interval (IBI) of 5 s. Based on these definitions, the following drinking parameters were evaluated: latency to start drinking (sec), bout frequency (number of bouts/60 min), total time drinking (min), average of bout duration (min/ bouts), inter-bout

interval (IBI, min) and drinking rate (g/min). Additionally, rats were videotaped with a digital video camera positioned 90 cm in front the cage to score activity duration (min) (rearing, sniffing, locomotion, grooming) and resting duration (min). All microstructure parameters were calculated using the integrate software BioDAQ Monitoring 2.2.

2.6. Open field test

The open-field test is commonly used to examine general locomotion in rodents (Rinaldi et al., 2007). The open-field test was made of white acrylic square (50 cm × 50 m) surrounded by white acrylic walls (40 cm in height) and 25 squares (10×10cm) outlined on the floor, with a digital video camera collocated 90 cm over the open field. Rats were individually located in the open field and locomotor activity was recorded. After each trial, the box was cleaned with 70% alcohol to remove urine and fecal residues. The number of crossings through the squares and number of rearing events were scored.

2.7. Experiment 1

Before evaluating the role of D4R signaling on sucrose consumption, the preference for a specific sucrose concentration was determined in an independent group of rats (see Supplementary Method). After simultaneous exposure to 3 different concentrations (5%, 10% and 20%), the rats displayed a preference for the 20% sucrose solution. This was the concentration chosen for further experiments.

For 7 days, animals had access to standard diet and tap water for 23 h, measuring the food and water consumption (g) each day. Daily, at the onset of the light phase (10:00 am), the food and water bottle were removed, and a bottle containing the 20% sucrose solution was placed in the cage. Rats had access to the sugar solution for 1 h. The bottle was weighed daily before and after the restricted access. After the 1 h of access, the sucrose bottle was removed and food and tap water were placed back for the following 23 h. On days 8 and 9, 30-min before the sucrose access, mock intra-ventricular injections were performed to minimize the stress caused by the experimental manipulation. On day 10, 30-min before sucrose access, animals were randomly assigned to receive the pharmacological treatments as follow: vehicle (saline+ DMSO, n = 7), L-745870 at 1 μg, n = 7) or L-745870 at 2 μg, n = 7). After completing the intraventricular injections, animals received access to the sucrose solution, monitoring sucrose consumption and drinking microstructure for 60-min.

2.7.1. Experiment 2

For experiment 2, rats were maintained under the same dietary conditions described in experiment 1. In brief, for 7 days rats had access to a standard diet and tap water consumption for 23 h. Daily, at the onset of the light phase (10:00 am), the food and water bottle were removed and a bottle containing the 20% sucrose solution was placed in the cage for 1-h. On days 8 and 9, mock intraventricular injections were performed in order to habituate the animal with the experimental manipulation and minimize the stress. On day 10, animals received access to the sucrose solution for 1-h. After that, the sucrose bottle was removed from the cage and then the open-field test was conducted following the protocol described by Rinaldi et al. (2007). The animals were individually placed in the bottom right corner of the open-field for 5-min in order to become familiar with the apparatus (habituation phase). After that, rats were placed back to their home-cages for the intraventricular injections. Rats were randomly assigned to receive the respective pharmacological treatment as follow: vehicle (saline + DMSO, n = 6), L-745870 at 1 μg (n = 5) or L-745870 at 2 μg, (n = 5). Five min after the injection, the rats were placed again in the open field for 10-min (pharmacological phase). The number of crossings through squares and the number of rearing events were scored for the habituation and the pharmacological phase.

2.8. Histology of the brain

To verify the correct position of the cannula, the animals received 5 μl of 1% blue methylene in the cannula and were then euthanized with ketamine/xylazine (112.5/22.5 mg/kg). The brains were removed and placed in 10% formaldehyde solution. Coronal sections of 300 μm were cut with a vibratome (Electron microscopy science, USA). Brain slices were macroscopically inspected for visualization of the location of the canula into the lateral ventricle and dispersion of the blue methylene following the method described by Santos et al. (2022) (see Fig. 1). Data from animals with incorrect implantation of the cannula were excluded from the statistical analysis.

2.9. Data analysis

Data presented in this study are expressed as mean ± S.E.M. Since the data complied with the assumptions of normality and homoscedasticity, parametric statistical tests were performed. A total of 5 rats that had incorrect positioning of the cannula were excluded. For the experiment 1, effects of the L-74570 (0, 1 and 2 μg) were tested on the sucrose intake (g) and drinking microstructure parameters and analyzed with a one-way ANOVA test. In experiment 2, effects of L-74570 (0, 1 and 2 μg) were tested on the number of crosses and number of rears for both habituation phase and pharmacological administration and analyzed with a one-way ANOVA test. A significant ANOVA test was followed by a post hoc Tukey's test. Significance was defined as $p < 0.05$. Data were analyzed using the software GraphPad Prism Version 8.01 (San Diego, USA).

3. Results

3.1. Central blockade of D4R decreased sucrose consumption and altered the drinking microstructure

In a preliminary experiment, we found that rats markedly preferred the 20% sucrose solution compared to 5% and 10% concentrations (see Fig. S1). Based on this finding, we evaluated the pharmacological effect of L-745870 on the consumption of the 20% sucrose solution.

Sucrose consumption during the first 9 days of training did not show significant differences among the groups (Fig. 2). On experimental day, the intraventricular injection of L-745870 decreased the consumption of the 20% sucrose solution [$F_{(2.18)=}$ 15.69, $p < 0.0001$]. This decrease was dose-dependent, showing that at the 1-μg dose reduced the sucrose ingestion by 32.53%, while the 2-μg dose reduced the ingestion by 46.16% as compared with the vehicle group (Fig. 3).

The drinking microstructure was affected differentially by L-745870 in a dose-dependent manner. No significant differences were found in the latency to start the first drinking episode (Fig. 4A). L-745870 at 1 and 2 μg increased the bout frequency (bouts/ 60 min) compared with the vehicle group [$F_{(2,18)=}$ 9.99, $p < 0.0012$] (Fig. 4B). L-745870 decreased the drinking duration [$F_{(2,18)=}$ 10.89, $p < 0.0008$] (Fig. 3C) and bout duration [$F_{(2,\ 18)}$ = 10.89, $p = 0.0008$] in a dose dependent manner (Fig. 4D). Analysis of bout size (g/bout frequency) revealed a significant decrease by effect of 1 and 2 μg of L-745870 as compared with the vehicle-treated rats [$F_{(2,15)=}$ 25.85, $p < 0.0001$] (Fig. 4E). Finally, L-745870 at 1 and 2-μg decreased the inter-bout intervals as compared with the vehicle group [$F_{(2,18)=}$ 8.37, $p < 0.0027$] (Fig. 4F). No significant differences were observed for the drinking rate (g/min), the time dedicated to activity or time spent resting among the groups (see Table 1, upper panel). Together, the drinking microstructure analysis suggests that L-745870-induced sucrose decreased consumption resulted from reduction in bout duration and bout size (g/bout) as well as a reduction in the drinking duration.

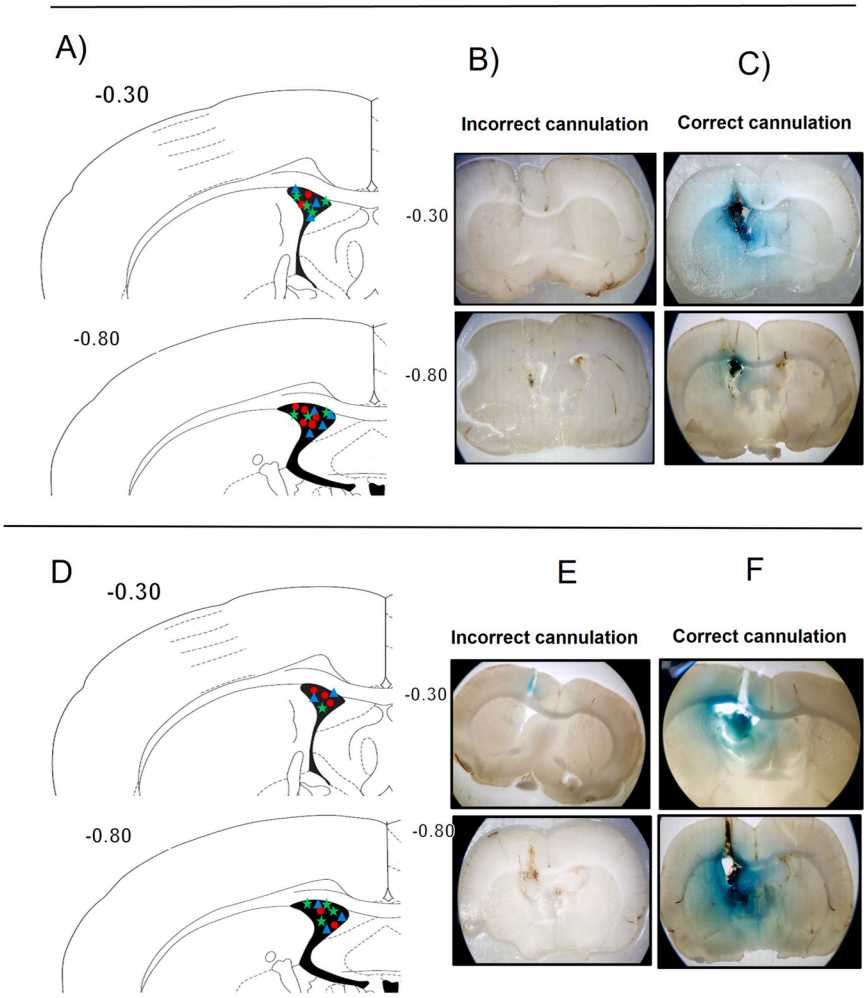

Fig. 1. Schematic illustration of coronal sections of the rat brain (−0.30, −0.80 from bregma, according to the stereotaxic atlas from Paxinos and Watson) for experiment 1 (A) and experiment 2 (D), indicating the location of the tip of the cannulas in the sample of animals of each group (Vehicle group, L-745870 1 μg and L-745870 2 μg) for both experiments. Representative brain slices representing animals with incorrect location of the tip of the cannula into the lateral ventricle and no dispersion of the 1% methylene blue for experiment 1 (B, upper and lower panel) and experiment 2 (upper and lower panel). Representative brain slices representing animals with correct location of the tip into the lateral ventricle and dispersion of 1% methylene blue experiment 1 (C, upper and lower panel) and experiment 2 (F, upper and lower panel).

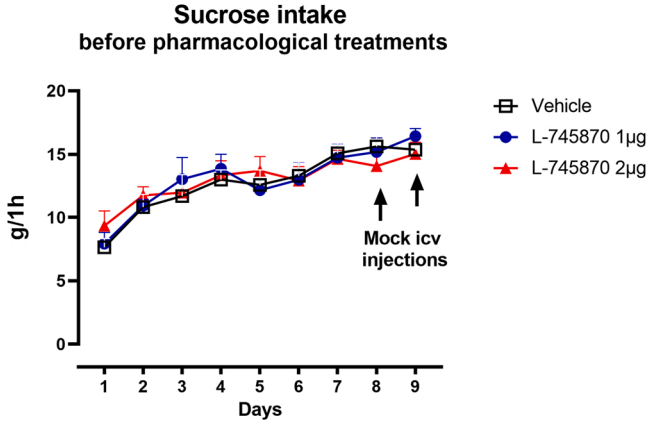

Fig. 2. Daily sucrose consumption in the three groups before to the administration of pharmacological treatments. Statistically Significant Differences Were Not observed between the groups.

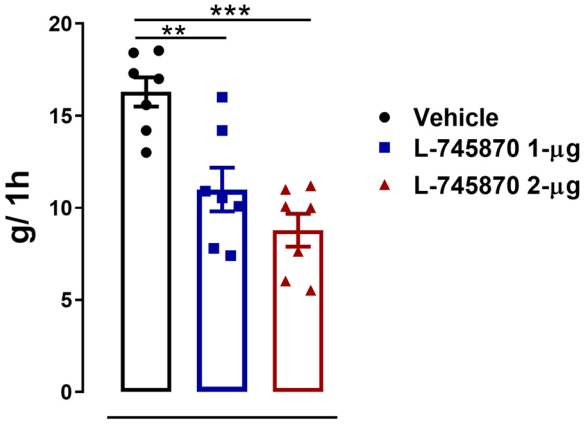

Fig. 3. Effect of the central infusion of L-745870 (1 and 2 μg) on the consumption of a 20% sucrose solution. Posthoc test: vehicle vs L-74587 1 μg: $p < 0.0032$; vehicle vs L-74587 2 μg: $p < 0.001$; Data show the mean ± SE.M. of 7 rats *per* group. **$p < 0.01$, ***$p < 0.001$.

3.2. *Central blockade of D4R did not alter the locomotor activity*

The open-field test was used to evaluate the effect of L-745870 on locomotor activity. Table 1 (lower panel) shows that levels of locomotor activity during the 5-min habituation phase (before the drug administration) were similar among groups since no significant differences were observed for the number of crosses [$F_{(2, 12)} = 0.11$, $p = 0.89$] or number of rears [$F_{(2, 12)} = 0.053$, $p = 0.94$]. Similarly, after administration of L-745870 or vehicle (pharmacological phase), no significant differences were observed for the number of crosses [$F_{(2, 12)} = 0.37$, $p = 0.69$] or number of rears [$F_{(2, 12)} = 0.19$, $p = 0.82$] (Fig. 5). These data indicated that the central blockade of D4R did not alter the locomotor activity of the rats.

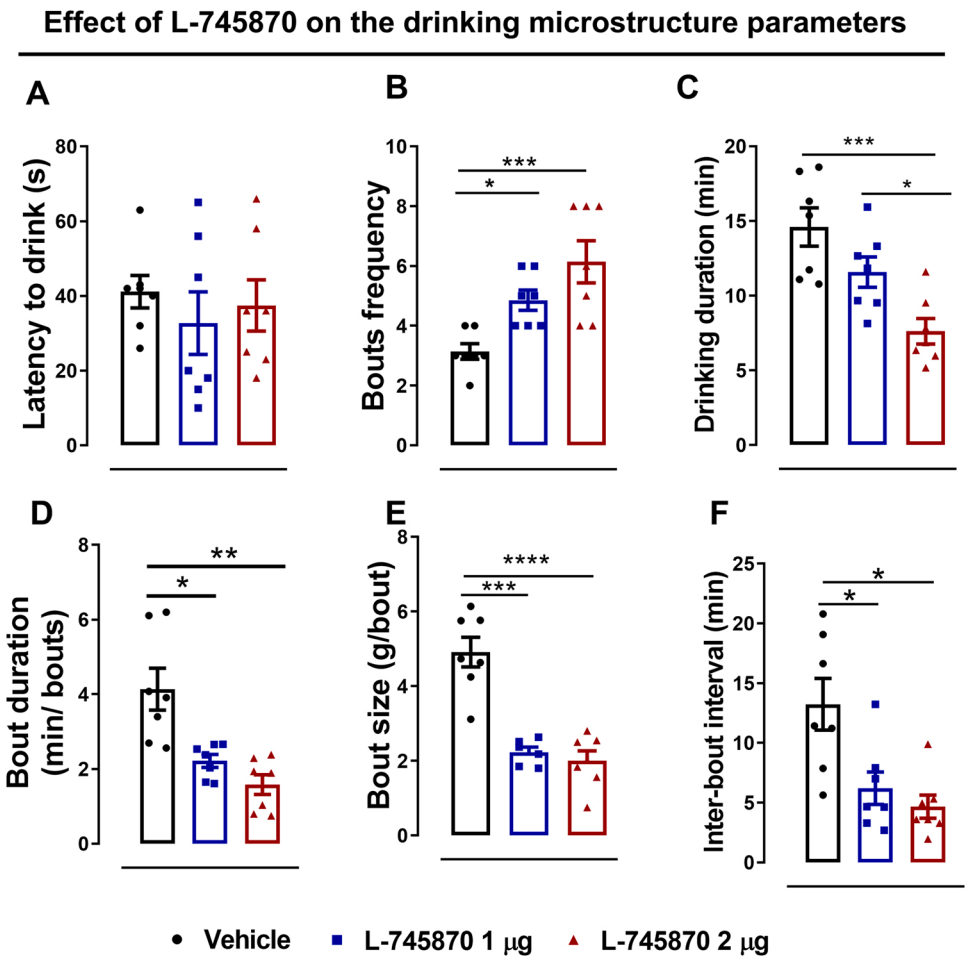

Fig. 4. Effect of the central infusion of L-745870 (1 and 2 µg) on the parameters of the drinking microstructure for A) latency to drink; Posthoc test: vehicle vs L-74587 1 µg: $p < 0.65$, vehicle vs L-74587 1 µg: $p < 0.92$, B) bouts frequency; Posthoc test: vehicle vs L-74587 2 µg: $p < 0.009$, C) drinking duration; Posthoc test: vehicle vs L-74587 1 µg: $p < 0.0006$; L-74587 2 µg vs 1 µg: $p < 0.041$, D) average of bout duration; Posthoc test: vehicle vs L-74587 1 µg: $p < 0.0051$, vehicle vs L-74587 2 µg: $p < 0.009$, E) bout size (g/bouts); Posthoc test: vehicle vs L-74587 1 µg: $p < 0.0001$,: vehicle vs L-74587 2 µg: $p < 0.0001$ and F) inter-bout interval; Posthoc test: vehicle vs L-74587 1 µg: $p < 0.014$, vehicle vs L-74587 2 µg: $p < 0.0033$. Data show the mean± SE.M. of 7 rats *per* group. *$p < 0.05$, * *$p < 0.01$, * **$p < 0.001$.

Table 1
Effects of L-745870 on the parameters of the drinking microstructure for experiment 1 (drinking rate, time spent resting and time spent in activity) and for the parameters of the open field test during habituation phase for experiment 2 (number of crosses and number of rears).

Experiment 1. Microstructure of drinking behavior			
Drinking rate (g/min)	1.217 ± 0.1376	1.048 ± 0.1044	1.187 ± 0.1361
Resting (min)	36.15 ± 2.445	35.02 ± 2.107	38.09 ± 2.426
Activity (min)	10.33 ± 1.152	12.60 ± 1.360	14.66 ± 1.654
Experiment 2. Open-field test (habituation)			
Number of crosses	61.60 ± 9.20	67.20 ± 8.77	68.00 ± 12.44
Number of rears	21.00 ± 3.13	19.60 ± 3.17	20.60 ± 3.07

4. Discussion

Present data show that central administration of the D4R selective antagonist L-745870 (1 and 2-µg) decreased the ingestion of a palatable 20% sucrose solution. Blockade of D4R altered the drinking microstructure by decreasing the drinking duration and bout size (g/bout), and the inter-bout interval. Importantly, the second experiment confirmed that central infusion of L-745870 did not alter levels of general locomotion in the open field test. Together, our findings indicated that D4R signaling participates in the regulation of consumption of sucrose in sated rats and this effect was not attributable to locomotor alterations.

In rodents, the main feeding episodes occur during the active phase (dark), while it is assumed that during the inactive phase (day), nocturnal rodents are sated (Bainier et al., 2017; Okauchi et al., 2019).

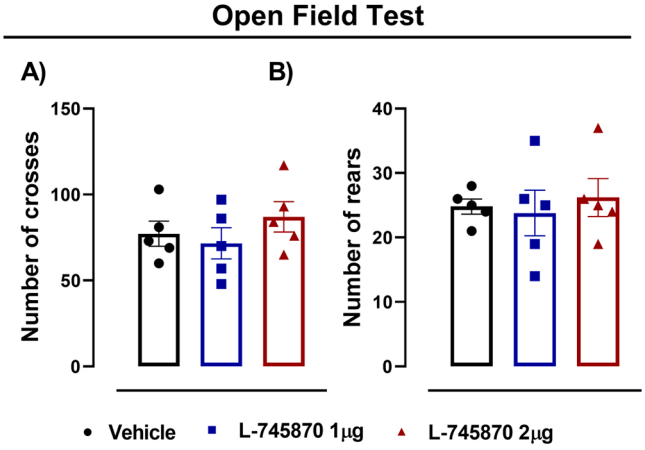

Fig. 5. Effect of the central infusion of L-745870 (1 and 2 µg) on the spontaneous locomotor activity for A) number of crosses; Posthoc test: vehicle vs L-74587 1 µg: $p < 0.88$, vehicle vs L-74587 2 µg: $p < 0.69$ B) number of rears; Posthoc test: vehicle vs L-74587 1 µg: $p < 0.96$, vehicle vs L-74587 1 µg: $p < 0.93$. Data show the mean± SE.M of 5 rats *per* group.

In the present study, to discriminate the hedonic intake of the sweet solution with the regular drive of hunger, the access to the 20% sugar solution was restricted to the start of the light phase. Thus, our results suggest the L-745870-induced sucrose consumption decrease can be explained by a decrease in the hedonic regulation (de Araujo et al., 2020).

Considering that the rats drank the sweet solution for its intrinsic value instead of hunger signals, our findings open the possibility that L-745870-induced sucrose intake decrease could be modulated by D4R located in brain areas that drive motivation, and reward for palatable solutions, such as the nucleus accumbens (NAcc) (Floresco, 2015). Whitin the NAcc, the D4R is presynaptically expressed in glutamatergic terminals that contact with NAcc-GABAergic neurons (Svingos et al., 2000). Moreover, the NAcc-GABAergic neurotransmission is involved in reward, hedonic intake, and drug addiction (Salamone et al., 2005), and its dysfunction is related to anhedonia and depressive-like behavior (Francis and Lobo, 2017; Zhu et al., 2017). Thus, antagonizing NAcc-Glutamatergic-D4R terminals may increase the GABAergic neurotransmission and thus inhibit hedonic intake. Moreover, the behavioral drinking pattern showed that intraventricular injection of L-745870 decreased bout duration and bout size, indicating that blockade of D4R may decrease the hedonic value of the solution. In agreement with this rationale, previous studies indicate that animals that drink sweet solutions display large lick clusters size, and this response is considered a hedonic reaction to the solution, but the opposite effect is observed when animals drink unpalatable or aversive solutions (e.g., quinine) (Dwyer, 2012; Dwyer, 2009). However, our findings also showed that L-745870-treated rats displayed a greater number of bouts and low inter-bout intervals, suggesting that hedonic reactions for the sugar solution are partially preserved and consummatory drinking behavior could be disrupted by the enhancement of homeostatic satiation signals. These discrepant results could be explained due D4R is expressed in hypothalamic regions modulating satiation-satiety responses (Huang et al., 2005; Tejas-Juárez et al., 2014).

In this study, the intraventricular infusions may have reached multiple brain areas, including corticostriatal regions controlling locomotor activity (Bonaventura et al., 2017; Erlij et al., 2012). Therefore, here we used the open-field test, to assess the general locomotion vehicle and L-745870-treated rats. Present results agree with previous findings indicating that blockade of D4R does not produce locomotor alterations in rats (Erlij et al., 2012; Zhang et al., 2002). Early preclinical studies demonstrated that D4R signaling contributes to the control of locomotion. In animal models of the attention deficit hyperactivity disorder (ADHD) (Zhang et al., 2001; Zhang et al., 2002), The administration of L-745870 reversed the hyper-locomotor effects displayed in adolescents' rats that were lesioned with 6-hydroxydopamine (which destroys dopaminergic projections to the forebrain) during the neonatal period. Moreover, levels of motor activity in Sham-control rats treated with CP-293,019 (DR4 antagonist) or L-745870 were unaffected. Similarly, clinical studies demonstrated that administration of L-745870 did not produce extrapyramidal or sedative side effects in patients with schizophrenia (Bristow et al., 1997; Kramer et al., 1997).

5. Conclusion

This study provides evidence that central infusion of the selective D4R antagonist, L-745870, decreases the intake of a sugar solution by modifying the drinking microstructure. This was observed in the decrease of the time drinking sucrose and the size of the drinking episodes. Moreover, the alterations of number of bouts and inter-bout interval suggest that blockade of D4R partially attenuates the hedonic reactions elicited by the sugar solution. The present findings highlight that D4R signaling participates in the neural pathway driving the hedonic-homeostatic consumption in sated rats and opens a potential therapeutic line of research for pharmacological treatment of obesity and binge-eating disorder.

Further studies are needed to explore the brain areas and molecular circuits responding to the D4R that modulate the hedonic consumption of sugar solutions.

CRediT authorship contribution statement

Verónica E. López-Alonso Conceptualization, Supervision, Funding acquisition Writing – original draft, Writing – review & editing. **Samantha Hernandez-Correa**: Methodology, Investigation, Formal analysis. **Carolina Escobar**: Formal Analysis, Writing – review & editing, Visualization. **Juan M. Mancilla-Díaz**: Formal analysis, Writing – review & editing. **Rodrigo E. Escartín-Pérez**: Formal analysis, Investigation. **Daniel Díaz-Urbina**: Conceptualization, Designed of the experiments, Investigation, Formal analysis, Data curation, Supervision, Writing – original draft, Writing – review & editing, Visualization.

Declaration of Competing Interest

The authors declare that there are no potential conflicts of interest.

Acknowledgments

The experiments described in this study were supported by UNAM-DGAPA grants IN 307720, IN 232120 and IN 217117. The authors want to thank Fernando Barrón M. and Tomas Villamar D. for their assistance with the care of the animals used in this study. The authors also want to thank Luisa M. Monreal-Gonzalez for her thechnical assistance.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ibneur.2023.02.001.

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