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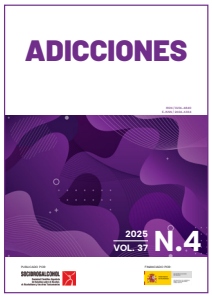

ORIGINAL

Blocking the increased reinforcing effects of cocaine induced by social defeat: Effects of palatable food

Bloqueo del incremento en los efectos reforzantes de la cocaína inducidos por la derrota social: Efecto de la comida palatable

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Abstract

Preclinical studies suggest that stimulation of the brain's reward system by high-fat diets (HFD) could act as an alternative reinforcer. The main aim of the present study was to evaluate the effect of a limited and intermittent exposure to an HFD administered during and after exposure to Social Defeat (SD) on a non-effective dose of cocaine-induced Conditioned Place Preference (CPP). Experiment 1 consisted of modulating SD episodes with three different patterns of HFD access: 1h access before each session of SD; 2h access three days a week during the two weeks of SD exposure; and 2h access 4h after each SD. Experiment 2 consisted of modulating the effects of stress on CPP acquisition with three patterns of HFD access: 1h access before each conditioning session; 2h access three days a week throughout the two-week period of the CPP; and 2h access three days a week from the last SD episode to the end of CPP. HFD administered during the period of SD episodes counteracted the increased sensitivity that SD produces on the reinforcing effects of cocaine. Access to HFD before the conditioning session or three days a week (CPP-SD-MWF) during the acquisition of CPP blocked this increased sensitivity. In the striatum, SD induced a decrease in the cannabinoid 1 receptor (*Cb1r*) gene expression, not affected by HFD, and increased corticotrophin releasing hormone receptor 1 (*Crhr1*) gene expression, except for those mice fed on HFD after SD encounters. Our findings indicate that a small intake of HFD may attenuate the social stress–induced increase in the rewarding properties of cocaine.

Key words: social defeat, male mice, cocaine, high-fat diet

Resumen

Los estudios preclínicos sugieren que la estimulación del sistema de recompensa cerebral mediante dietas ricas en grasa (DRG) podría actuar como un reforzador alternativo. El objetivo principal del presente estudio fue evaluar el efecto de una exposición limitada e intermitente a una DRG, administrada durante y después de la exposición a Derrota Social (DS), sobre una dosis no efectiva de la Preferencia de Lugar Condicionado (PLC) inducida por cocaína. El Experimento 1 consistió en modular los episodios de DS con tres patrones diferentes de acceso a la DRG: acceso de 1 hora antes de cada sesión de DS; acceso de 2 horas tres días a la semana durante las dos semanas de exposición a DS; y acceso de 2 horas, 4 horas después de cada DS. El Experimento 2 consistió en modular los efectos del estrés sobre la adquisición de la PLC con tres patrones de acceso a la DRG: acceso de 1 hora antes de cada sesión de condicionamiento; acceso de 2 horas tres días a la semana durante el período de dos semanas de la PLC; y acceso de 2 horas tres días a la semana desde el último episodio de DS hasta el final de la PLC. La DRG administrada durante el período de episodios de DS contrarrestó el aumento de la sensibilidad que la DS produce sobre los efectos reforzadores de la cocaína. El acceso a la DRG antes de la sesión de condicionamiento o tres días a la semana (PLC-DS-LXV) durante la adquisición del PLC bloqueó este aumento de sensibilidad. En el estriado, la DS indujo una disminución en la expresión génica del receptor cannabinoide tipo 1 (*Cb1r*), no afectada por la DRG, y un aumento en la expresión del gen del receptor 1 de la hormona liberadora de corticotropina (*Crhr1*), excepto en los ratones alimentados con DRG después de los encuentros de DS. Nuestros hallazgos indican que una pequeña ingesta de DRG puede atenuar el aumento inducido por el estrés social en las propiedades reforzantes de la cocaína.

Palabras clave: derrota social, ratones machos, cocaína, dieta rica en grasa

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Stress is widely recognized as a central factor in the onset, progression, and persistence of addictive behaviors (Buchanan & Lovallo, 2019; Burke & Miczek, 2015; Volkow & Blanco, 2023), playing a crucial role in the negative emotional state caused by dependence, leading to both substance withdrawal (Koob, 2009) and relapse episodes (Koob, 2010; Koob & Volkow, 2010). Social stress stands out as a particularly significant stressor in humans, arising from interpersonal relationships and the contextual environment in which individuals develop (Carnevali et al., 2020; Dickerson & Kemeny, 2004). Given the profound physical and psychological impact of social stress in humans, animal models such as the social defeat (SD) paradigm have been established to investigate its neurobiological consequences (Miczek et al., 2008; Shimamoto, 2018). Preclinical studies using the SD model have revealed that exposure to social stress produces lasting effects (Wang et al., 2021), including reduced exploratory behavior and social interaction (Burke et al., 2011; Shimizu et al., 2020), increased anxiety (Weathington & Cooke, 2012), enhanced ethanol consumption (Arenas et al., 2025; Reguilón et al., 2020; Reguilón et al., 2021), and increased sensitivity to the conditioned rewarding properties of psychostimulants like cocaine, in both adolescent (Burke et al., 2016; Burke & Miczek, 2015; Rodríguez-Arias et al., 2018) and adult rodents (Ballestín et al., 2021; Ferrer-Pérez et al., 2018; Giménez-Gómez et al., 2021; Montagud-Romero et al., 2015; Montagud-Romero et al., 2016; Rodríguez-Arias et al., 2017).

Stress also influences nutritional habits. Clinical studies indicate that individuals exposed to stress are more likely to increase their consumption of highly palatable foods (Kim et al., 2013; Konttinen, 2020; Linders et al., 2022), due to their comfort-inducing properties, which help mitigate psychological distress (Dallman et al., 2003; Gemesi et al., 2022). In fact, consumption of such foods in humans reduces plasma cortisol levels and perception of stress (Herhaus et al., 2020; Leigh Gibson, 2006). Parallel findings in animal models show that rodents under chronic stress prefer high-fat diets (HFD) over standard chow (STD) (Packard et al., 2014; Pecoraro et al., 2004), thus attenuating physiological responses to acute stress such as hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis (Kalyani et al., 2016; Linders et al., 2022; Ulrich-Lai et al., 2011;). Notably, a previous study from our group demonstrated that adolescent-isolated mice that were intermittently exposed to HFD exhibited significantly lower corticosterone levels compared to isolated controls receiving only standard diet (Blanco-Gandía et al., 2018), suggesting a stress-buffering effect of palatable food.

Therefore, social stress increases the reinforcing properties of both psychostimulants (Montagud-Romero et al., 2015; Peleg-Raibstein et al., 2016) and palatable diets (Kim et al., 2013), potentially through shared neurobiological mechanisms. Similar to addictive substances, hypercaloric foods rich in fat and/or sugar increase dopamine levels in the nucleus accumbens (NAcc) (DiLeone et al., 2012; Pitman & Borgland, 2015), with the activation of several key structures of the reward system, such as the ventral tegmental area (VTA), the prefrontal cortex, and the amygdala (de Macedo et al., 2016; Volkow et al., 2013). Growing evidence suggests that dietary interventions can influence responses to drugs and addiction vulnerability. For instance, HFD exposure modulates sensitivity to alcohol and cocaine, either enhancing reward responsiveness (Avena et al., 2008; Blanco-Gandía et al., 2017a; Blanco-Gandía et al., 2017b; Puhl et al., 2011) or serving as an alternative reinforcement under drug withdrawal-induced negative emotional states (Blanco-Gandía et al., 2017c). Indeed, both continuous (Blanco-Gandía et al., 2017c) and intermittent (Ródenas-González et al., 2021) HFD administration during cocaine withdrawal facilitates the extinction learning and inhibits reinstatement of cocaine-seeking behaviors, in addition to reducing behavioral withdrawal symptoms (Loebens & Barros, 2003). We have previously observed that EtOH-induced impairment on spatial memory retrieval is absent in mice exposed to continuous or intermittent access to HFD, although the aversive memory deficits persist (Del Olmo et al., 2019). Regarding alcohol use disorders, the pattern of HFD exposure and the stress condition seem to be critical. Prolonged binge-eating or continuous access to HFD during adolescence increases the reinforcing effects of EtOH (Blanco-Gandia et al., 2017b). However, a recent study suggests that intermittent HFD access effectively prevents stress-induced increases in ethanol consumption (Arenas et al., 2025). These results highlight the close relationship between HFD, stress and addiction, which interact not only within the dopaminergic circuitry and the HPA axis, but also with the cannabinoid and the opioid systems (Cristino et al., 2014; Parylak et al., 2012; Sakamoto et al., 2015).

The convergence of these three factors (stress, drugs of abuse intake and nutritional habits) is particularly critical during adolescence, a period when structural changes in many limbic and cortical regions can be disrupted by these factors (Baladi et al., 2012; Daws et al., 2011; Spear, 2000). During this period, individuals display enhanced reward sensitivity, rendering them more vulnerable to the reinforcing effects of drugs (Steinberg, 2010). However, the influence of palatable food consumption on the increased cocaine-reinforcing effects induced by social stress in adolescent animals remains unexplored.

Considering the overlapping neurobiological pathways stimulated by HFD and drugs of abuse, and their modulation by stress-related systems, we hypothesize that the intake of HFD may influence the development of cocaine-induced CPP in adolescent mice, particularly when subthreshold doses of cocaine are used. To test this hypothesis, our study was designed to explore two different approaches. In the

first experiment, we modulated the SD episodes with HFD administration; in the second experiment, after the animals had been exposed to stress, cocaine CPP acquisition was modulated by HFD administration. Mu-opioid receptors are modulated by HFD, contributing to the rewarding effects and hedonic value of palatable food (Mahdavi et al., 2023). Prior findings indicate reduced mu opioid receptor gene expression in the NAcc following binge-like HFD administration (Blanco-Gandia et al., 2017a; Blanco-Gandia et al., 2017b; Martire et al., 2014; Ong et al., 2013), whereas continuous exposure appears to increase its expression (Blanco-Gandia et al., 2017c; Smith et al., 2002). On the other hand, CB1 receptors are also implicated in the rewarding properties of palatable food, particularly HFD (Friuli et al., 2025). Our research group reported reduced CB1r gene expression in the NAcc following exposure to HFD (Blanco-Gandia et al., 2017a; Blanco-Gandia et al., 2017c). Collectively, these findings suggest that food intake can modulate not only dopaminergic but also non-dopaminergic systems, including the cannabinoid and opioid systems. Given the involvement of the opioid and cannabinoid systems, as well as the HPA axis, in stress, addiction, and palatable food reward, we also assessed gene expression of the mu opioid receptor (*Oprm*), cannabinoid receptor 1 (*Cb1r*), and corticotropin-releasing hormone receptor 1 (*Crhr1*) in the striatum at the end of the experiments.

Material and methods

Subjects

A total of 180 male mice of the OF1 outbred strain on PND 42 were acquired commercially from Charles River (France). Of these, 30 animals were housed under standard isolated conditions and were used as aggressive residents during the Social Defeat (SD) procedure. The remaining 150 experimental mice arrived at the laboratory on PND 21 and were housed under standard conditions in groups of four (cage size 28 × 28 × 14.5 cm), at a constant temperature (21 ± 2 °C), with a reversed light schedule (white lights on 19:30–7:30) and food and water available ad libitum (except during behavioral tests). All procedures involving mice and their care complied with national, regional and local laws and regulations, which are in accordance with Directive 2010/63/EU of the European Parliament and the Council of September 22, 2010 on the protection of animals used for scientific purposes. The Animal Use and Care Committee of the University of Valencia approved the present study (2017/VSC/PEA/00224).

Drugs

For CPP, animals were injected i.p. with 1 mg/kg of cocaine hydrochloride (Laboratorios Alcaliber S. A. Madrid, Spain) diluted in physiological saline. The 1 mg/kg dose of cocaine used to induce CPP was based on previous studies (Maldonado et al., 2006; Vidal-Infer et al., 2012), where it was shown to be a subthreshold dose that is not effective in standard animals.

Experimental design

After 5 days of adaptation in the vivarium, at PND 26, mice were exposed to SD, except for the exploration groups (EXP). Following the last SD/EXP session, animals were kept in the vivarium for three weeks, housed in their respective home cages, and then they performed 1 mg/kg cocaine-induced CPP (PND 55). After completing the entire experimental procedure, the animals were euthanized to enable the collection of biological samples.

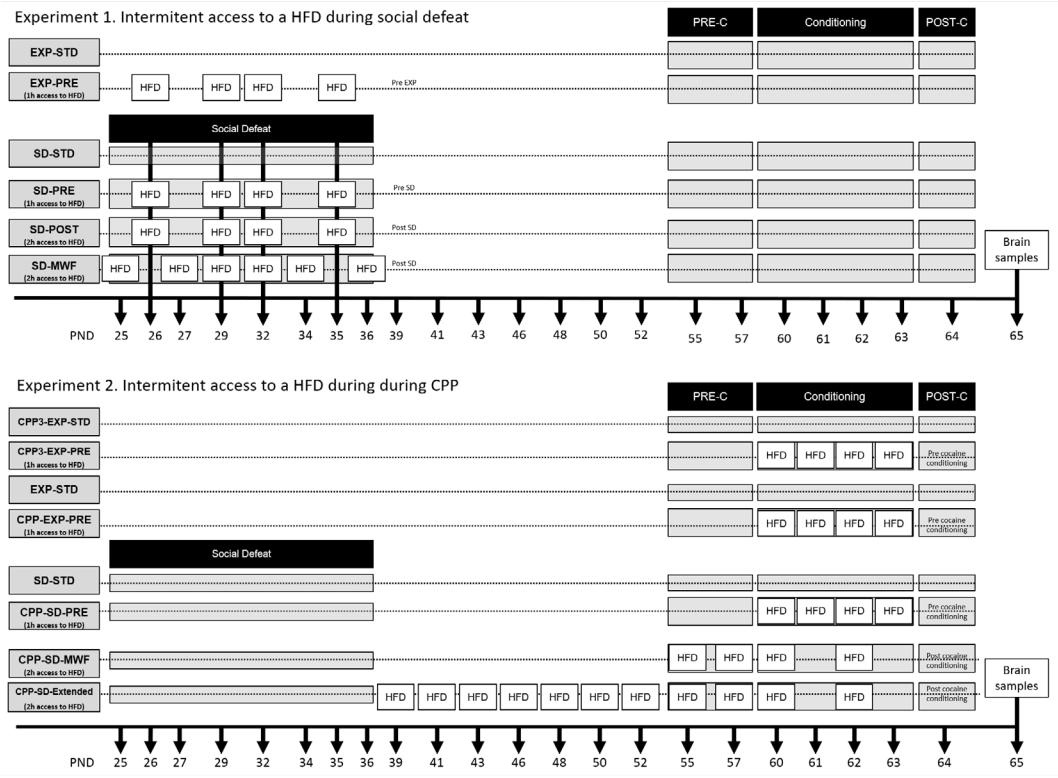
In this study, two different experiments were performed: Experiment 1 consisted of modulating SD episodes with different patterns of HFD access and Experiment 2 tested how different patterns of HFD access modulated the effects of stress on CPP acquisition. An overall and more detailed description of the sets of animals and experimental procedure of each experiment is provided in *Figure 1*.

In Experiment 1, experimental animals (n = 76) were exposed to four episodes of EXP/SD with different HFD administrations during the two weeks of stress exposure. Mice were randomly divided into six groups with similar average body weights (25–26 g) and assigned to the following groups: EXP-STD (non-stressed mice on a standard diet, n = 12), EXP-PRE (non-stressed mice with 1 h access to HFD before each exploration session, n = 12), SD-STD (defeated mice on a standard diet, n = 15), SD-PRE (defeated mice with 1 h access to HFD before each SD, n = 14), SD-MWF (defeated mice with 2 h access to HFD on Monday, Wednesday and Friday during the two weeks of SD, accessing the HFD after SD sessions on overlapping days, n = 13) and SD-POST (defeated mice with 2 h access to the HFD after 4 h of an SD episode, n = 10). Three weeks after the last SD, all groups performed the cocaine-induced CPP.

In Experiment 2 (n = 80), mice were randomly divided into six groups with similar average body weights (25–26 g) and assigned to the following groups: EXP-STD (non-stressed mice on a standard diet, n = 12), CPP-EXP-PRE (non-stressed mice with 1 h access to the HFD before each conditioning session, n = 12), SD-STD (defeated mice on a standard diet, n = 15), CPP-SD-PRE (defeated mice with 1 h access to the HFD before each conditioning session, n = 15), CPP-SD-MWF (defeated mice with 2 h access to the HFD on Monday, Wednesday and Friday during the two weeks of CPP, n = 15) and CPP-SD-Extended (2 h access to the HFD on Monday, Wednesday and Friday, starting from the last SD episode until the end of CPP, n = 11). To minimize the unnecessary use of mice, the groups designated as EXP-STD and SD-STD in Experiment 1 consisted of the same mice in Experiment 2.

Figure 1

Experimental design



Note. In Experiment 1, mice were divided into six groups: EXP-STD (non-stressed mice on a standard diet), EXP-PRE (non-stressed mice with 1 h access to HFD before each exploration session), SD-STD (defeated mice on a standard diet), SD-PRE (defeated mice with 1 h access to HFD before each SD), SD-MWF (defeated mice with 2 h access to HFD on Monday, Wednesday and Friday during the two weeks of SD, accessing the HFD after SD sessions on overlapping days) and SD-POST (defeated mice with 2 h access to the HFD after 4 h of an SD episode). In Experiment 2, mice were divided into eight groups: EXP-STD (non-stressed mice on a standard diet), CPP-EXP-PRE (non-stressed mice with 1 h access to the HFD before each conditioning session), SD-STD (defeated mice on a standard diet), CPP-SD-PRE (defeated mice with 1 h access to the HFD before each conditioning session), CPP-SD-MWF (defeated mice with 2 h access to the HFD on Monday, Wednesday and Friday during the two weeks of CPP) and CPP-SD-Extended (2 h access to the HFD on Monday, Wednesday and Friday, starting from the last SD episode until the end of CPP), CPP3-EXP-STD (non-stressed mice on a standard diet conditioned with 3 mg/kg cocaine) and CPP3-EXP-PRE (non-stressed mice with 1 h access to the HFD before each conditioning session with 3 mg/kg cocaine).

Two more groups of mice (n = 21) were employed to evaluate the effect of HFD on 3 mg/kg cocaine-induced CPP, named as CPP-C3 (non-stressed mice on a standard diet, n = 11) and CPP-C3-PRE (non-stressed mice with 1 h access to the HFD before each conditioning session, n = 10).

Feeding conditions

Two different types of diet were administered in the study. A standard diet (Teklad Global Diet 2014, 13 Kcal % fat, 67 Kcal % carbohydrates and 20 Kcal % protein; 2,9 kcal/g; no sugars added) was given to the control groups, and a high-fat diet (TD.06415, 45 Kcal % fat, 36 Kcal % carbohydrates and 19 Kcal % protein; 4.6 Kcal/g; 20% of carbohydrates are sucrose) was administered in a limited way to the high-fat diet groups. Both diets were supplied by Harlan Laboratories Models, S. L. (Barcelona, Spain) and will be referred to from now on as the standard diet, while the sporadic limited access to the high-fat food will be referred to as the HFD. Ad libitum standard diet and water were always freely available in their home cages. Animals were weighed every week throughout the study, and their daily intake of standard diet in their home cage was also measured.

Repeated social defeat encounters

Animals in the corresponding group were exposed to four episodes of SD, each lasting 25 min. Each episode consisted of three phases, which began by placing the experimental animal or intruder in the home cage of the aggressive opponent or resident for 10 min. During this initial phase, the intruder was protected from attack by a wire mesh wall that permitted social interaction and species-typical threats from the male-aggressive resident (Covington & Miczek, 2001). In the second phase, the wire mesh was removed from the cage and a 5 min confrontation period began. In the third phase, the wire mesh was put back for 10 min to allow social threats from the resident. Mice were exposed to SD on postnatal days (PNDs) 26, 29, 32, and 35. The exploration group (EXP) underwent the same protocol, but without the presence of a Resident mouse in the cage. Following this last phase, animals were kept in the vivarium for three weeks, housed in their respective groups.

Conditioning Place Preference

For place conditioning, we employed 16 identical Plexiglas boxes with two equally sized compartments (30.7 cm length x 31.5 cm width x 34.5 cm height) separated by a gray central area (13.8 cm length x 31.5 cm width x 34.5 cm height). The compartments have different colored walls (black vs white) and distinct floor textures (fine grid in the black compartment and wide grid in the white one). Four infrared light beams in each compartment of the box and six in the central area allowed the recording of the animal's position and crossings between compartments. The equipment was controlled by two IBM PC computers using MONPRE 2Z software (CIBERTEC S.A., Spain).

Acquisition of CPP

The place conditioning procedure, unbiased in terms of initial spontaneous preference, was performed as previously described (Maldonado et al., 2006) and consisted of three phases. Briefly, in the first phase, known as Pre-Conditioning (Pre-C), mice at PND 55 were allowed access to both compartments of the apparatus for 15 min (900 s) per day on 3 days. On day 3, the time spent in each compartment over a 900 s period was recorded, and animals showing a strong unconditioned aversion (less than 33% of the session time) or preference (more than 67%) for any compartment were excluded from the rest of the experiment. Two defeated animals on the standard diet met these criteria and were excluded from SD-STD (n = 13) and SD-STD (n = 13) groups from Experiment 1 and Experiment 2, respectively. Half of the animals in each group received the drug or vehicle in one compartment, and the other half in the other compartment. After assigning the compartments, no significant differences were detected in the time spent in the drug-paired and vehicle-paired compartments during the preconditioning phase. In the second phase (conditioning), which lasted 4 days, animals received an injection of physiological saline immediately before being confined to the vehicle-paired compartment for 30 min. After a 4 h interval, they received an injection of cocaine immediately before being confined to the drug-paired compartment for 30 min. Confinement was carried out in both cases by closing the guillotine door that separated the two compartments, making the central area inaccessible. In the third phase, known as post-conditioning (Post-C), the guillotine door separating the two compartments was removed (day 8) and the time spent by the untreated mice in each compartment was recorded over a 900 s observation period. The difference in seconds between the time spent in the drug-paired compartment during the Post-C test and the Pre-C phase is a measure of the degree of conditioning induced by the drug. If this difference is positive, then the drug has induced a preference for the drug-paired compartment, whereas the opposite indicates that an aversion has developed.

Gene expression analyses: RNA isolation and quantitative RT-PCR

At the end of the experiments, animals were euthanized by cervical dislocation and the brains were immediately removed from the skull and placed on a cold plate. The striatum was dissected, and brain tissue samples were immediately stored at -80ºC until the rt-PCR assay was performed (n = 8/condition).

Total RNA from the striatum was isolated using the Tri Reagent Method (Sigma-Aldrich, St. Louis, MO, USA), as described in the manufacturer's protocol. Reverse transcription of 1 mg of total RNA was performed using the Transcriptor First Strand cDNA synthesis kit (Thermo Fisher Scientific, Madrid, Spain). Amplification of the target and housekeeping (b-glucuronidase) genes was performed using the Taqman Gene Expression Master Mix (Thermo Fisher Scientific, Madrid, Spain) in a LightCycler 480 System (Roche Diagnostics) following the manufacturer's instructions. The assay codes of the primers used were Mm01212171, Mm01188089 and Mm00432670 for cannabinoid receptor 1 (*Cb1r*), opioid receptor μ (*Oprm*) and *Crhr1*, respectively. Data were analyzed using the LightCycler 480 relative quantification software and were normalized to the amplification product of b-glucuronidase or Gusb (Mm00446953).

Statistical analyses

Data related to the percentage of body weight increase were analyzed by a mixed ANOVA, with a between variable -Diet-, with 6 levels (EXP-STD, EXP-PRE, SD-STD, SD-PRE, SD-MWF, SD-POST) for Experiment 1 and 6 levels (CPP-EXP, CPP-EXP-PRE, CPP-SD, CPP-SD-PRE, CPP- SD-MWF, CPP-SD-Extended) for Experiment 2 and a within variable -Week-, with 5 levels. Data for the mean of total Kcal intake were analyzed by a one-way ANOVA with the between variable -Diet- (EXP-PRE, SD-PRE, SD-MWF, SD-POST for Experiment 1 and CPP-EXP-PRE, CPP- SD-PRE, CPP- SD-MWF, CPP-SD-Extended for Experiment 2).

For the CPP procedure, the time spent in the drug-paired compartment was analyzed by two repeated measures ANOVA, with a between variable -Diet-, with 6 levels (EXP-STD, EXP-PRE, SD-STD, SD-PRE, SD-MWF, SD-POST for Experiment 1 and CPP-EXP, CPP-EXP-PRE, CPP-SD, CPP-SD-PRE, CPP- SD-MWF, CPP-SD-Extended for Experiment 2), and a within variable –Days–, with two levels (Pre-C and Post-C).

A one-way ANOVA was conducted to assess the conditioning score (defined as the time spent in the drug-paired side minus the time spent in the saline-paired side) and the gene expression data, with a between variable -Group- (EXP-STD, SD-STD, SD-PRE, SD-MWF, SD-POST for Experiment 1 and CPP-EXP, CPP-SD, CPP-SD-PRE, CPP- SD-MWF, CPP-SD-Extended for Experiment 2). Post-

hoc comparisons were performed by means of Bonferroni tests. All data are presented as mean ± standard error of mean (SEM). A p-value < 0.05 was considered statistically significant. Analyses were performed using SPSS v26.

Results

1. Experiment 1. Modulating SD episodes with palatable food

1.1. Body weight and mean of total Kcal intake in HFD sessions.

The ANOVA for the percentage of weight gain (*Figure 2a*) revealed an effect of the variable *Week* ($F(5, 350) = 847.85$, $p < .001$). Body weight increased from the first week onwards ($p < .001$ in all cases).

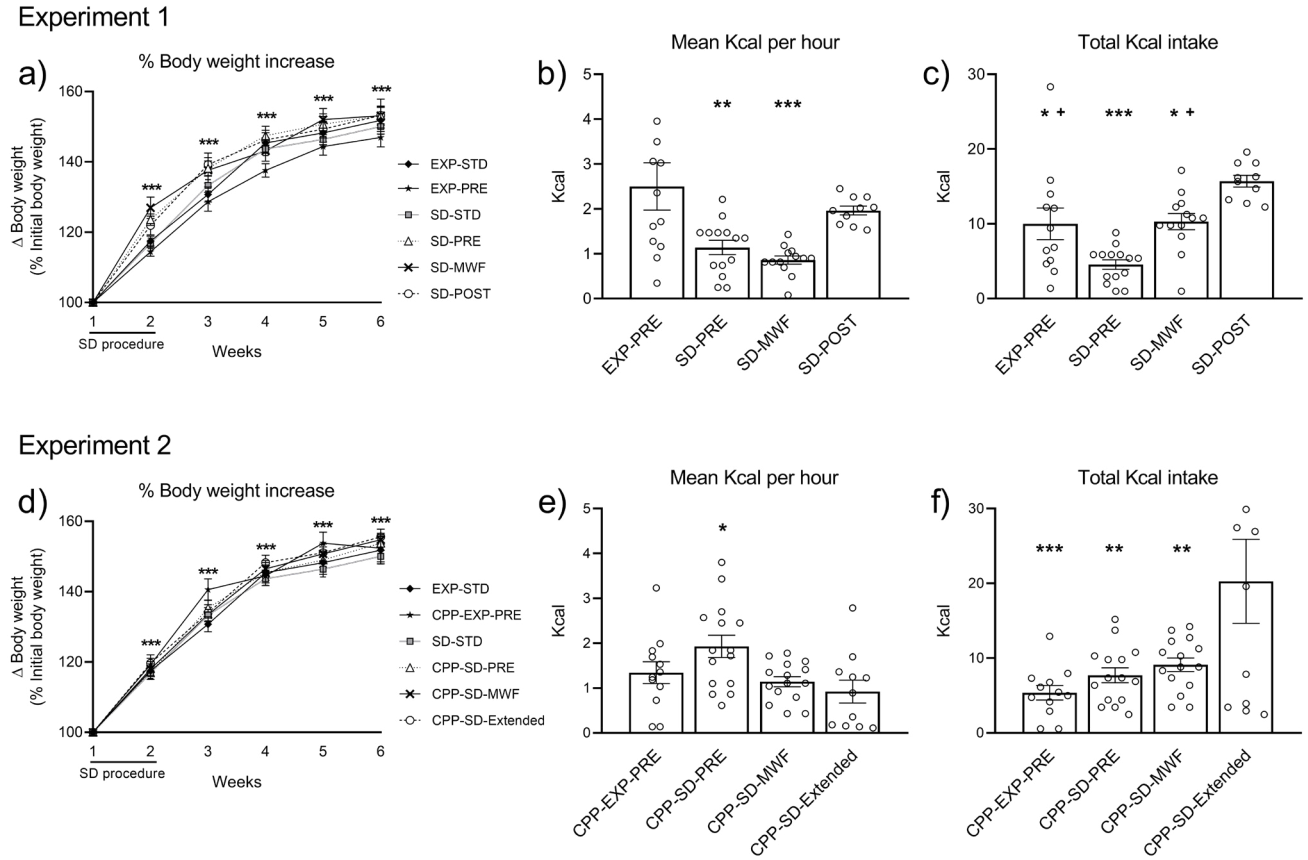
The ANOVA of the mean Kcal intake per hour (*Figure 2b*) revealed significant differences on the variable Diet ($F(3, 45) = 7.50$, $p < .001$). Mice in the SD-PRE and SD-MWF groups consumed less Kcal per HFD session/hour than the EXP-PRE group ($p < .01$ and $p < .001$, respectively). With respect the total kcal intake (*Figure 2c*), the ANOVA also revealed an effect of the variable Diet ($F(3, 45) = 12.28$, $p < .001$). Mice in the SD-POST group consumed more Kcal than the other groups ($p < .05$ for EXP-PRE and SD-MWF and $p < .001$ for SD-PRE). In addition, mice in the SD-PRE group ingested less Kcal than those in the EXP-PRE and SD-MWF groups ($p < .05$).

1.2. Cocaine induced CPP

The results of the 1 mg/kg cocaine-induced CPP in Experiment 1 are presented in *Figure 3*. The ANOVA for the time spent in the drug-paired compartment revealed an effect in the interaction Days × Diet ($F(3, 68) = 3.39$, $p < .023$), Days × Stress ($F(1, 68) = 10.92$, $p < .002$), and Days × Diet × Stress ($F(1, 68) = 4.14$, $p < .05$). Only animals exposed to SD and fed with the standard diet (SD-STD) spent more time in the drug-paired compartment during POST-C compared to PRE-C ($p < .001$). The time spent in the drug-paired compartment during POST-C by the SD-

Figure 2

Body weight and caloric intake changes in mice during Experiments 1 and 2



Note. (a) % Body weight increase of mice over the 6 weeks in Experiment 1. Data are represented as the mean (± SEM) % increase of body weight referred to the initial body weight (week 1). ***p < .001 significant differences within each group between weeks. (b) Kcal per hour Experiment 1. Data are represented as the mean Kcal intake per hour (± SEM) during HFD sessions ***p < .001; ** p < .01 significant difference with respect to the EXP-PRE group (c) Total Kcal intake Experiment 1. Data are represented as the mean total Kcal intake (± SEM) during Experiment 1. *p < .05; **p < .01; ***p < .001 with respect to the SD-POST group; +p < .05 with respect to SD-PRE. (d) % Body weight increase of mice over the procedure Experiment 2. ***p < .001 significant differences within each group between weeks. (e) Kcal per hour Experiment 2. *p < .05 significant difference with respect to the CPP-SD-MWF and CPP-SD-EXTENDED groups; (f) Total Kcal intake Experiment 2. **p < .01; ***p < .001 with respect to CPP-SD-EXTENDED

STD group was significantly higher than that of the rest of the groups ($p < .01$ in all cases).

The ANOVA for the conditioning score revealed an effect of the interaction Diet × Stress ($F(1, 68) = 4.14$, $p < .05$). Among SD mice, those fed with the standard diet (SD-STD) presented a significantly higher conditioning score than those defeated but exposed to HFD on MWF ($p < .01$) or before the PRE-C test ($p < .05$). The SD-STD group also showed higher conditioning score than the EXP-STD group ($p < .001$).

1.3. Gene expression analyses

For the *Cb1r* gene expression (*Figure 4a*), the ANOVA revealed a significant effect of the variable Group ($F(4, 32) = 9.74$, $p < .001$). All mice exposed to SD, regardless of diet, exhibited a significant decrease in *Cb1r* gene expression in comparison with the EXP-STD group ($p < .001$). Regarding the expression of the *Crhr1* (*Figure 4b*) the ANOVA also revealed a significant effect of the variable Group ($F(4, 33) = 10.08$, $p < .001$). Mice in the SD-STD, SD-PRE and SD-MWF groups exhibited a significant increase in *Crhr1* gene expression in comparison with the EXP-STD and SD-POST groups ($p < .01$ in both cases). No significant differences were obtained in the gene expression of the opioid receptor mu (*Figure 4c*).

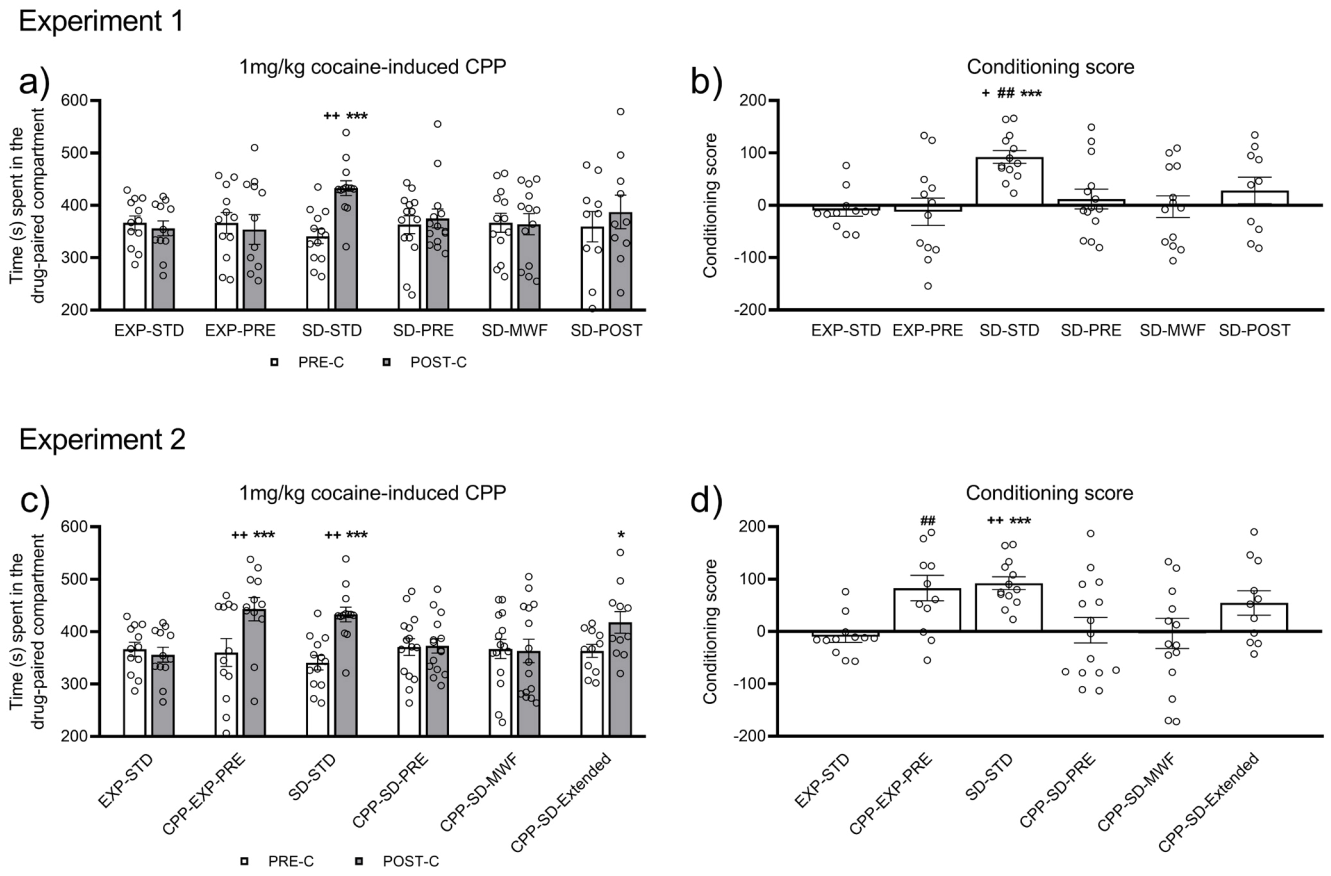
2. Experiment 2. Modulating the increase of cocaine-induced CPP with palatable food

2.1. Body weight and mean of total Kcal intake in HFD sessions.

As in the first experiment, body weight increased from PND 26 (1st week) onwards (*Figure 2d*). The ANOVA for the percentage of weight gain revealed an effect of the variable

Figure 3

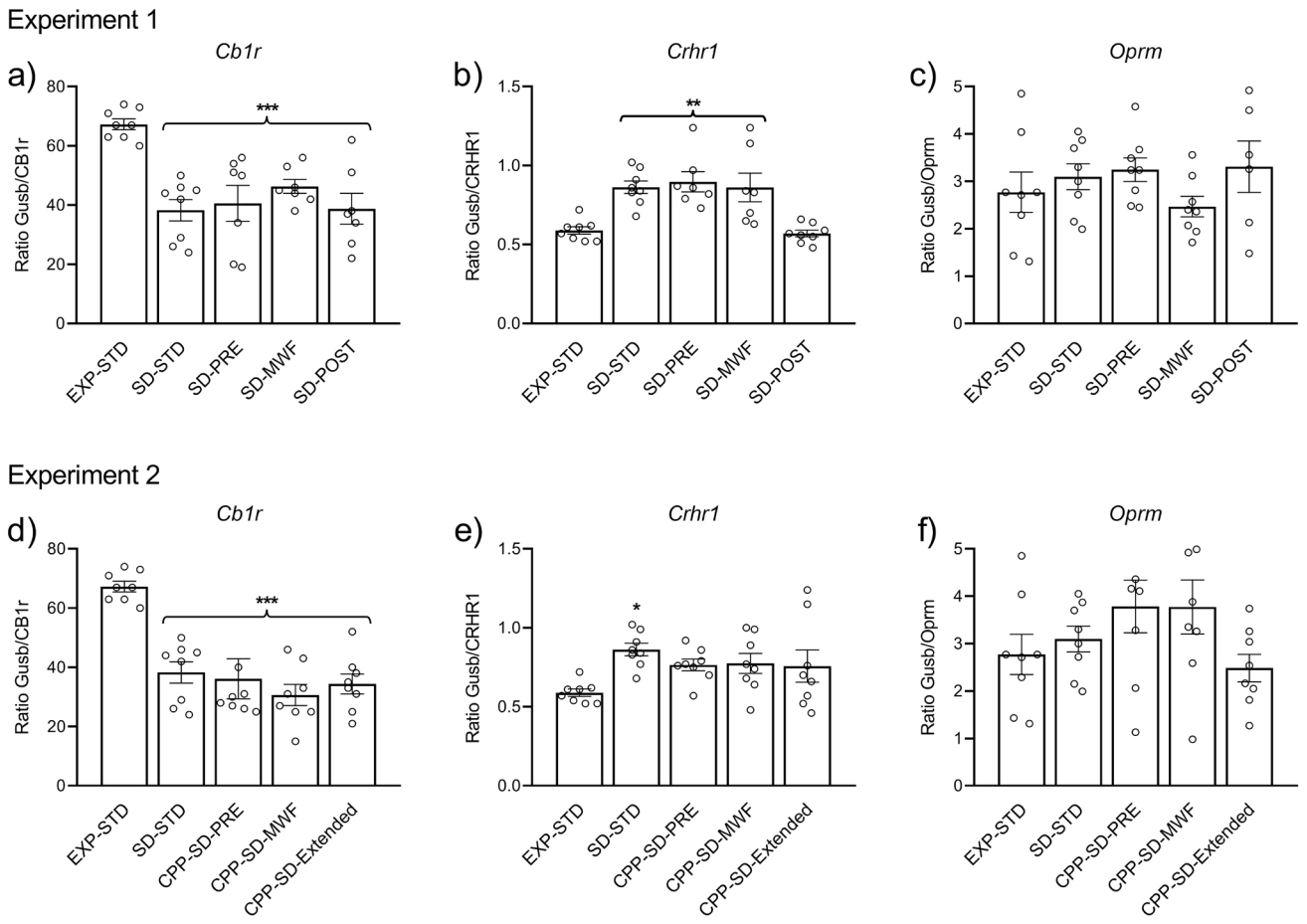
Effects of exposure to palatable food on cocaine-induced CPP in Experiment 1 and 2



Note. (a) Effects of modulating SD episodes with palatable food on cocaine-induced CPP, Experiment 1. Bars represent the mean (± SEM) time in seconds spent in the drug-paired compartment during pre-conditioning (PRE-C, white) and post-conditioning (POST-C, grey). ++p < .01 significant difference with respect to POST-C in the rest of the cases; ***p < .001 significant difference with respect to PRE-C in the SD-STD group. (b) Conditioning score, Experiment 1. Differences in the time spent in the drug-paired compartment versus the saline-paired compartment. Bars represent the mean (± SEM) time in seconds. +p < .05 significant differences with respect to SD-PRE; ##p < .01 significant differences with respect to SD-MWF; and ***p < .001 significant differences with respect to EXP-STD. (c) Effects of exposure to an HFD during CPP on cocaine-induced CPP, Experiment 2. Bars represent the mean (± SEM) time in seconds spent in the drug-paired compartment during pre-conditioning (PRE-C, white) and post-conditioning (POST-C, grey). *p < .05; ***p < .001 significant difference with respect to the corresponding PRE-C test. ++p < .01 significant difference with respect to the Post-C test of the CPP-EXP-STD and CPP-SD-PRE groups. (d) Conditioning score, Experiment 2. Differences between time spent in the drug-paired compartment versus the saline-paired compartment. Bars represent the mean (± SEM) time in seconds. ##p < .01 significant difference with respect to CPP-EXP-STD and CPP-SD-PRE; ++p < .01 significant difference with respect to CPP-SD-PRE and CPP-SD-MWF; ***p < .001 significant difference with respect to CPP-EXP-STD.

Figure 4

Real-time PCR Gene expression in the striatum



Note. (n = 8/condition). (a) Cannabinoid receptor 1 - ***Cb1r***, Experiment 1: ***p < .001 significant differences with respect to the EXP-STD group. (b) Corticotropin-releasing hormone receptor 1 - ***Crhr1***, Experiment 1: **p < .01 significant differences with respect to the EXP-STD and SD-POST groups. (c) Opioid receptor μ - ***Oprm*** Experiment 1: The columns represent means and the vertical lines ± SEM of gene expression in the striatum of OF1 mice. (d) Cannabinoid receptor 1 - ***Cb1r***, Experiment 2: ***p < .001 significant differences with respect to the CPP-EXP-STD group. (e) Corticotropin-releasing hormone receptor 1 - ***Crhr1***, Experiment 2: *p < .05 significant difference with respect to the CPP-EXP-STD group. (f) Opioid receptor μ - ***Oprm***, Experiment 2: The columns represent means and the vertical lines ± SEM of gene expression in the striatum of OF1 mice.

Week ($F(5, 370) = 1123.69$, $p < .001$). Body weight increased from the first week onwards ($p < .001$ in all cases).

The ANOVA of the mean Kcal intake per hour (*Figure 2e*) revealed significant differences on the variable Diet ($F(3, 49) = 4.11$, $p < .01$). Mice in the CPP-SD-PRE group consumed more Kcal per hour of HFD session than the CPP-SD-MWF and CPP-SD-EXTENDED groups ($p < .05$). The ANOVA also revealed an effect of the variable Diet ($F(3, 49) = 6.18$, $p < .001$) with respect the total kcal intake (*Figure 2f*). Mice on the CPP-SD-EXTENDED group consumed more Kcal than the other groups ($p < .001$ for CPP-EXP-PRE and $p < .01$ for CPP-SD-PRE and CPP-SD-MWF).

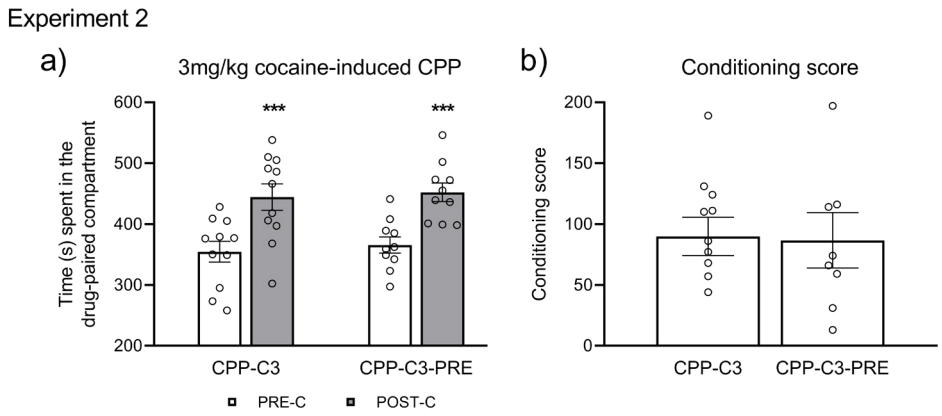
2.2. Cocaine induced CPP

The results of the 1 mg/kg cocaine-induced CPP from Experiment 2 are presented in *Figure 3c*. The ANOVA for the time spent in the drug-paired compartment revealed a significant effect of the variable Days ($F(1, 72) = 11.60$, $p < .001$), and the interaction Days × Diet × Stress ($F(1, 72) = 16.34$, $p < .001$). Preference for 1 mg/kg of cocaine was observed in the CPP-SD-STD ($p < .001$), CPP-SD-Extended ($p < .05$), and in non-stressed mice fed on HFD before conditioning (CPP-EXP-PRE) ($p < .001$). In addition, the SD-STD and CPP-EXP-PRE groups spent more time in the drug-paired compartment during POST-C than the CPP-EXP-STD and CPP-SD-PRE groups ($p < .01$ in all cases).

The ANOVA for the conditioning score revealed an effect of the interaction Diet × Stress ($F(1, 72) = 16.34$, $p < .001$] (*Figure 3d*). Among SD mice, those fed with the standard diet (CPP-SD-STD) presented a significantly higher conditioning score than non-stressed mice (CPP-EXP-STD) and defeated groups exposed to the HFD prior to conditioning (CPP-SD-PRE) and during 3 days a week (CPP-SD-MWF) ($p < .001$ for control and $p < .01$ for the rest of the cases). The non-stressed group fed with the HFD before conditioning (CPP-EXP-PRE) also presented

Figure 5

Effects of exposure to an HFD during CPP on 3 mg/kg cocaine-induced CPP



Note. (a) Effects of exposure to an HFD during CPP on cocaine-induced CPP. Bars represent the mean (± SEM) time in seconds spent in the drug-paired compartment during pre-conditioning (PRE-C, white) and post-conditioning (POST-C, grey). ***p < .001 significant difference with respect to PRE-C. (b) Conditioning score. Differences between time spent in the drug-paired compartment versus the saline-paired compartment. Bars represent the mean (± SEM) time in seconds.

a higher conditioning score than those of the CPP-EXP-STD and CPP-SD-PRE groups (p < .01 in both cases).

To further evaluate the effect of exposure to an HFD before cocaine-induced CPP, we evaluated the development of CPP induced by an effective dose of cocaine (3 mg/kg) (*Figure 5*). The ANOVA revealed an effect of the variable Days ($F(1, 19) = 41.88$, p < .001). As expected, 3 mg/kg of cocaine induced a clear preference (p < .001), which is not affected by HFD administration. The ANOVA of the conditioning score did not reveal differences between either of the groups ($F(1, 19) = 0.01$, p < .907).

2.3. Gene expression analyses

For the *Cb1r* gene expression (*Figure 4d*), the ANOVA revealed a significant effect of the Group variable ($F(4, 35) = 12.65$, p < .001). All groups exposed to an SD, regardless of diet, exhibited a significant decrease in *Cb1r* gene expression in comparison with the CPP-EXP-STD group (p < .001). The ANOVA for the expression of the *Crhr1* (*Figure 4e*) also revealed a significant effect ($F(4, 35) = 2.77$, p < .05). Mice in the SD-STD group exhibited a significant increase in *Crhr1* gene expression in comparison with the CPP-EXP-STD group (p < .05). No significant differences were obtained in the gene expression of the opioid receptor mu (*Figure 4f*).

Discussion

The present work evaluates the modulating effects of HFD on the increase in the conditioned rewarding effects of cocaine induced by social stress at two critical moments: a) during exposure to SD stress and b) long-term after SD during the procedure of cocaine-induced CPP. The present study demonstrated for the first time that intermittent intake of an HFD blocked the long-term increase in the conditioned rewarding effects of cocaine. Access to an HFD during the SD episodes (Experiment 1) efficiently counteracted the development of CPP with a subthreshold dose of cocaine (1 mg/kg). Similarly, we observed that access to an HFD prior to conditioning (CPP-Pre) or three days a week (CPP-MWF) during the acquisition of CPP (Experiment 2) blocked the increased sensitivity to the conditioned reinforcing effects of cocaine induced by SD. However, a longer exposure to HFD (CPP-SD-Extended) did not yield this effect. Despite this consistent result, none of the HFD schedules were able to counteract the decreased expression of the *Cb1r* gene. However, the SD-induced increase in *Crhr1* gene expression was lowered by HFD administration during the CPP or after each SD encounter.

Effects of HFD on body weight and Kcal intake.

A key observation in this research is that HFD consumption did not result in increased body weight. It is well known that prolonged HFD intake is linked to obesity, metabolic issues, and neuroinflammation (Blanco-Gandía et al., 2017c; Li et al., 2022; Tsai et al., 2022). Preclinical studies have observed that *ad libitum* access to an HFD leads to metabolic syndrome, increasing adiposity and leptin levels, and interfering with ghrelin and insulin signaling (Blanco-Gandía et al., 2017c; Davis et al., 2008; Morales et al., 2012). Nevertheless, the specific HFD regimens used in both experiments did not produce any significant alteration in body weight, which is in line with results obtained in previous studies using this administration pattern (Blanco-Gandía et al., 2017b; Hudson et al., 2007; Ródenas-González et al., 2021). We know that after 40 days of intermittent HFD exposure on MWF, leptin levels were not affected, although ghrelin

was significantly reduced (Blanco-Gandía et al., 2017a,b; Blanco-Gandía et al., 2019). In this line, intermittent access to HFD did not modify glucose nor insulin plasmatic levels (Del Olmo et al., 2019). Therefore, our current and previous results allow us to suggest that intermittent and limited exposure to HFD did not induce a deep affectation of 2017a,b2general metabolism.

Regarding HFD kcal intake, it is important to note that, although access to HFD was 1 h in some groups and 2 h in others, the amount of kcal intake remained similar except for the group with access after SD. In Experiment 1, the SD-POST group showed a significant increase in Kcal ingested compared to the rest of the HFD treatment groups. This group had access to HFD after each episode of stress, suggesting that this increased intake may be due to a compensatory response to stress, acting as comfort food. Several studies have reported the same phenomenon, where mice exposed to social stress subsequently increase their intake of HFD (Coccurello et al., 2018; Hassan et al., 2019; Sinha & Jastreboff, 2013). Confirming this effect, only defeated mice of the SD-POST group showed normalized *Crhr1* gene expression. Therefore, the capacity of HFD to block increased cocaine-induced CPP is not related to the amount ingested, highlighting that even a minimal amount of HFD can exert a potent, long-lasting effect.

Palatable food modulates the increase in cocaine-conditioned reward induced by social stress

As expected, and in line with previous studies, defeated mice fed with the standard diet exhibited increased sensitivity to a subthreshold dose of cocaine, developing CPP for the cocaine-paired compartment. This result has been reported in numerous studies, in which socially stressed animals show increased vulnerability to the rewarding effects of cocaine evaluated using the intravenous cocaine self-administration or the cocaine-induced CPP paradigms (Han et al., 2017; Neisewander et al., 2012; Reguilón et al., 2017; Shimamoto, 2018). Similar to the present results, we have also shown that defeated mice developed CPP using a subthreshold dose of cocaine (Ferrer-Pérez et al., 2019; Giménez-Gómez et al., 2021; Montagud-Romero et al., 2021).

In Experiment 1, we observed that the socially defeated groups that were exposed to the different patterns of HFD administration during the two weeks of social encounters did not develop CPP for cocaine. This result suggests that palatable food consumption might be acting as a buffer for stress effects (comfort food), as previous studies corroborate. For example, administering an HFD in socially stressed animals due to isolation decreases cocaine effects, with an attenuated response of cocaine-induced motor hyperactivity (Erhardt et al., 2006), a decrease in the corticosterone response, and a blockade of the acquisition of cocaine-induced CPP (Blanco-Gandía et al., 2018). HFD could reduce HPA activity (Auvinen et al., 2012; Pecoraro et al., 2004), which leads to a long-term reduction in the reinforcing effects of cocaine caused by that stress, especially in adolescence, when sensitivity to reward is enhanced (Blanco-Gandía et al., 2018; Steinberg, 2010).

The results obtained in Experiment 2, in which animals were exposed to different administration patterns of HFD during the CPP procedure, showed that all SD groups exposed to HFD during CPP acquisition did not develop cocaine preference, except for the Extended-CPP group. This group initiated exposure to HFD just after finishing the last episode of SD and continued until the end of the CPP. Despite this long exposure, this group showed increased sensitivity to the rewarding effects of the subthreshold dose of cocaine, similar to the SD animals fed with the standard diet. This suggests that when HFD exposure is prolonged over time and is not contingent with either the stress exposure or the acquisition of cocaine-induced CPP, the protective effect of palatable food is absent. Probably, long exposure to intermittent HFD can even sensitize the reward system, as previous studies suggest (Blanco-Gandía et al., 2017a, 2017b; Puhl et al., 2011). Supporting this hypothesis, we know that six weeks of intermittent HFD administration increases the sensitivity of adolescent mice to a subthreshold dose of cocaine, with the mice also needing more time to extinguish the preference (Blanco-Gandía et al., 2017b). However, we have previously reported that limited and intermittent exposure to HFD after cocaine preference acquisition blocks reinstatement and accelerates extinction in non-stressed mice (Ródenas-González et al., 2021), thus indicating that the timing of HFD exposure is critical in the modulation of the reward system. In line with this, the present results indicate that when intermittent administration of HFD is contingent and limited to the CPP session days, the reinforcing effects of cocaine increased by social stress are blocked, possibly due to a reward competition. These findings are in line with our recent report suggesting that the protective effect of intermittent HFD exposure may extend to various drugs of abuse, such as ethanol, potentially preventing stress-induced susceptibility to different addictive substances (Arenas et al., 2025).

An interesting effect was also observed in this experiment, since non-stressed mice exposed to HFD before CPP acquisition developed cocaine preference. The ability of HFD to induce conditioned preference has been described previously (Jarosz et al., 2007; Mizoguchi et al., 2021). Differently from these studies, our conditioning procedure only required four conditioning sessions and caloric intake was not restricted. In fact, our results did not prove that HFD per se induced conditioned preference, but that, in combination with a non-effective dose of cocaine, it was capable of developing preference. This additive effect has

also been described by Iqbal et al. (2023), who observed that the opiate oxycodone only developed preference in the HFD-associated compartment.

Changes in striatal gene expression after HFD administration of socially defeated mice

Considering the relevance of the cannabinoid and opioid systems in addiction and HFD effects (Barson et al., 2012; Kawahara et al., 2013), and the critical importance of corticotropin-releasing factor in stress (Puhl et al., 2011), we also explored changes in *Cb1r, Crhr1* and *Oprm* gene expression in the striatum at the end of the experimental procedure. Under the standard diet, SD induces a reduction in *Cb1r* and an increase in *Crhr1* gene expression, with no changes in *Oprm* gene expression. The aim of this study was to test the changes in gene expression in stressed mice exposed to intermittent HFD. The effects of HFD administered in non-stressed mice have been previously studied (Blanco-Gandia et al., 2017a,b).

The increase in *Crhr1* gene expression confirms what other studies have reported, namely that *Crhr1* gene expression is usually increased as a response to stress (Logrip et al., 2012). An increase in *Crhr1* gene expression can lead to higher vulnerability to the rewarding effects of cocaine, since some studies have demonstrated that CRHR1 antagonists can block this effect using both the CPP and SA procedures (Boyson et al., 2014; Ferrer-Pérez et al., 2018).

Only when administered after an episode of SD (SD-Post), HFD efficiently decreased *Crhr1* gene expression to levels similar to those observed in the exploration group. SD-Post was the group with the highest Kcal intake per session, suggesting that the rise in fat Kcal intake may play a role in this effect. As previously mentioned, there is a tendency to increase palatable food consumption in rodents exposed to stress (Coccurello et al., 2018; Pecoraro et al., 2004; Zellner et al., 2006). We can suggest that HFD induced a similar effect to CRHR1 antagonists, reducing *Crhr1* expression and consequently HPA activity (Foster et al., 2009; la Fleur et al., 2005; Pecoraro et al., 2004; Ulrich-Lai et al., 2011). Moreover, other studies have demonstrated that an HFD can reduce corticosterone levels in isolated mice (Blanco-Gandía et al., 2018) or in those exposed to restraint stress (Zeeni et al., 2013). HFD also reduced other consequences of social stress, such as social avoidance, anxiety and depression behavior (MacKay et al., 2017; Maniam & Morris, 2010; Otsuka et al., 2019).

On the other hand, HFD interventions during the acquisition of CPP in Experiment 2 only slightly decreased *Crhr1* gene expression. Therefore, although a decrease in the conditioned rewarding effects of cocaine was observed after all HFD administrations during SD, *Crhr1* gene expression was only blocked when access was granted after each stress episode. In Experiment 2, when HFD was administered long-term after stress exposure, although no significant increase in *Crhr1* gene expression was observed after any of the HFD administrations, the expression level of this gene was elevated in all defeated groups, indicating no valuable effect of HFD outside the stress period.

Opioid signaling is closely associated with the rewarding properties of food and plays a key role in regulating palatability (Esch & Stefano, 2024), while the endocannabinoid system is involved in the homeostatic control of intake and provides positive feedback specifically for the intake of fatty foods (Koch, 2001). According to the data available to date, intermittent fat intake could alter reward pathways through the interaction of the opioid and cannabinoid systems.

Regardless of diet, all groups exposed to SD presented a decrease in *Cb1r* gene expression, confirming that SD may have long-term effects on the cannabinoid system. Previous studies have shown that CB1 signaling modulates the stress response (Valverde & Torrens, 2012). For example, chronic stress is associated with a reduction in the *Cb1r* gene expression in the hippocampus (Hill et al., 2005; Hu et al., 2011; Reich et al., 2009), and in the striatum (Rossi et al., 2008; Wang et al., 2010). Furthermore, stimulation of CB1 receptors reduces stress-induced effects such as anhedonia (Rademacher & Hillard, 2007), depressive behaviors (Gobbi et al., 2005) and passive stress-coping behavior (Steiner et al., 2008).

Our results showed that the marked reduction in *Cb1r* gene expression observed in defeated animals was not reversed by any of the HFD administration patterns in either experiment. Consistent whit this, previous studies have also suggested that an HFD decreases *Cb1r* gene expression in the N Acc of adults (Bello et al., 2012; Martire et al., 2014) and adolescent rodents (Blanco-Gandía et al., 2017b). The similar effect of stress and HFD on *Cb1r* gene expression could explain the absence of an observable reversal in our study.

Finally, the results from both Experiment 1 and Experiment 2 suggest that neither social stress nor intermittent HFD administration causes alterations in *Oprm* gene expression. Although the involvement of the endogenous opioid system in stress responses (Komatsu et al., 2011) and fat consumption has been documented (Sakamoto et al., 2015), existing literature shows conflicting results regarding *Oprm* expression, suggesting a complex regulation of the endogenous opioid system. Increases in *Oprm* gene expression have been associated with continuous intake of palatable foods and some sugary or sweetened beverages (Blanco-Gandía et al., 2017a,b; Soto et al., 2015), but a downregulation has also been reported after chronic HFD intake in obese mice models (Vucetic et al., 2011). Moreover, prolonged but limited and intermittent intake of high-fat food seems to reduce *Oprm* expression in the NAcc (Blanco-Gandía et al., 2017a,b). Consequently,

our results could be due to the limited exposure to HFD compared to other studies, indicating that the kcal ingested by mice in our study was not enough to induce any change. These findings are further supported by our previous investigations with non-stressed mice exposed to limited and intermittent HFD after acquiring cocaine preference, which did not present changes in *Oprm* gene expression in the striatum (Ródenas-González et al., 2021).

Conclusion

The results obtained in this study confirmed that palatable food could be a good alternative reinforcer that reduced the acquisition of cocaine-conditioned preference in stressed animals. The specific period of HFD administration appears to be an important factor to be considered, while the duration of exposure was not critical. In fact, our results suggest that long exposure to the HFD may not be effective. Brief administration of a fatty diet after SD or during the acquisition of the preference for cocaine can reduce its conditioned rewarding effects. This effect could be mediated by a reduction in the increased *Crhr1* gene expression. Future studies should address other systems related to stress and reward to provide a broader explanation of the positive effect of HFD on the consequences of social stress.

Based on our previous and present results, we hypothesize that controlled administration of HFD might be a useful strategy to mitigate the effects of social stress on the reinforcing effects of cocaine, especially when this administration occurs during stress or cocaine exposure. Considering the influence of this diet on reward circuits and its effects when administered for a prolonged period of time, the present results highlight the potent effect of minimal exposure to fat. The lack of a suitable and validated model to study social defeat in female mice until recent years has delayed the implementation of this study in females. Additionally, the study of other brain structures, such as the hypothalamus, could shed more light on the mechanisms involved.

From a translational perspective, our results should not encourage prolonged HFD consumption. The value of our findings lies in the potential utility of consuming small amounts of high-fat food during stress experiences or cocaine exposure. It is essential to emphasize that fat intake should be predominantly derived from sources rich in monounsaturated and polyunsaturated fatty acids. It is well established that the consumption of fat-rich foods, such as highly processed and palatable products, stimulates the reward system and increases the risk of developing food addiction (Ulug et al., 2025). Therefore, special caution should be exercised when recommending this type of intake in patients who already present a cocaine use disorder. The consumption of such diets should be carefully controlled, and access to a healthy HFD should be ensured.

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Conflicts of interest

The authors of this article declare no conflict of interests.

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