Psychopharmacology (2021) 238:2091–2103
https://doi.org/10.1007/s00213-021-05834-7

ORIGINAL INVESTIGATION

A limited and intermittent access to a high-fat diet modulates the effects of cocaine-induced reinstatement in the conditioned place preference in male and female mice

Francisco Ródenas-González[1] · María del Carmen Blanco-Gandía[2] · María Pascual[1,3,4,5] · Irene Molari[1] · Consuelo Guerri[3,5] · José Miñarro López[1,5] · Marta Rodríguez-Arias[1,5]

Received: 18 June 2020 / Accepted: 22 March 2021 / Published online: 31 March 2021

Abstract

Rationale Palatable food and drugs of abuse activate common neurobiological pathways and numerous studies suggest that fat consumption increases vulnerability to drug abuse. In addition, preclinical reports show that palatable food may relieve craving for drugs, showing that an ad libitum access to a high-fat diet (HFD) can reduce cocaine-induced reinstatement.

Objective The main aim of the present study was to evaluate the effect of a limited and intermittent exposure to HFD administered during the extinction and reinstatement processes of a cocaine-induced conditioned place preference (CPP).

Methods Male and female mice underwent the 10 mg/kg cocaine CPP. From post-conditioning onwards, animals were divided into four groups: SD (standard diet); HFD-MWF with 2-h access to the HFD on Mondays, Wednesdays, and Fridays; HFD-24h, with 1-h access every day; and HFD-Ext with 1-h access to the HFD before each extinction session.

Results Our results showed that all HFD administrations blocked reinstatement in males, while only the HFD-MWF was able to inhibit reinstatement in females. In addition, HFD-Ext males needed fewer sessions to extinguish the preference, which suggests that administration of fat before being exposed to the environmental cues is effective to extinguish drug-related memories. HFD did not affect Oprμ gene expression but increased CB1r gene expression in the striatum in HFD-Ext males.

Conclusions These results support that palatable food could act as an alternative reward to cocaine, accelerating extinction and blocking reinstatement, these effects being sex specific.

Keywords Extinction · Cocaine · Reinstatement · High-fat diet · Conditioned place preference

Introduction

Drug addiction is defined as a chronic disorder characterized by relapse accompanied by the compulsion to seek and take the drug and the loss of control in limiting intake (Koob and Le Moal 1997). When access to the drug is prevented, a negative emotional state emerges, reflecting a motivational withdrawal syndrome (Koob and Volkow 2010). Due to this

Francisco Ródenas-González and María del Carmen Blanco-Gandía contributed equally to this work.

✉ Marta Rodríguez-Arias
marta.rodriguez@uv.es

[1] Unit of Research Psychobiology of Drug Dependence, Department of Psychobiology, Facultad de Psicología, Universitat de Valencia, Avda. Blasco Ibáñez, 21, 46010 Valencia, Spain

[2] Department of Psychology and Sociology, University of Zaragoza, C/ Ciudad Escolar s/n, 44003 Teruel, Spain

[3] Department of Molecular and Cellular Pathology of Alcohol, Principe Felipe Research Center, C/Eduardo Primo Yúfera 3, 46012 Valencia, Spain

[4] Department of Physiology, School of Medicine, Universitat de Valencia, Valencia, Spain

[5] Red Temática de Investigación Cooperativa en Salud (RETICS-Trastornos Adictivos), Instituto de Salud Carlos III, MICINN and FEDER, Madrid, Spain

negative emotional state, drugs of abuse become negative reinforcement during withdrawal (Koob and Le Moal 2001), leading to relapse due to the impelling need to consume (Koob and Volkow 2010). Therefore, it is not surprising that patients who undergo an addiction treatment tend to seek alternative reinforcements, including natural rewards, such as palatable food (high-fat and/or sugar-rich food), in order to stimulate brain circuits of reward (Salamone et al. 2005). In fact, clinical evidence emphasizes the frequent use of palatable food to decrease drug craving during withdrawal (Cowan and Devine 2008).

Preclinical studies have also pointed to this relation. Orsini et al. (2014) reported that rats with a history of chronic amphetamine exposure increased their food consumption. In addition, Loebens and Barros (2003) observed that animals fed with a high-fat diet (HFD) are more prone to depression during cocaine withdrawal in the forced swimming test (Loebens and Barros 2003). Moreover, other studies suggest that fat intake may represent a competitive reward for drugs. The conditioned place preference (CPP) procedure evaluates the role of environmental cues associated with the rewarding effects of drugs of abuse, such as cocaine, which were decreased by previous exposure to HFD (Morales et al. 2012). In this line, the present work is a follow-up of our previous study reporting that continuous HFD administration during the extinction of cocaine-induced CPP reduced the sessions required to extinguish the preference and decreased the sensitivity to drug priming-induced reinstatement (Blanco-Gandía et al. 2017a).

Epidemiological studies have shown high levels of comorbidity between eating disorders (bulimia and binge eating disorder) and substance abuse (Becker and Grilo 2016; Conason et al. 2006; Holderness et al. 1994; Nøkleby 2012; Flores-Fresco et al. 2018). We speculate that this high comorbidity could in part be due to shared reinforcing properties between palatable foods and drugs of abuse. For example, certain foods, particularly those rich in sugar and fat, are potent rewards that promote eating even in the absence of energetic requirements (Lenoir et al. 2007), being able to trigger learned associations between environmental stimulus and reward (Volkow et al. 2011). In fact, several studies have pointed out that a continuous access to fat diminishes the rewarding effects of cocaine (Morales et al. 2012; Thanos et al. 2010; Blanco-Gandía et al. 2017a). Palatable food activates the reward system (DiLeone et al. 2012; Narayanaswami et al. 2013) through the activation of the mu-opioid receptor pathway in the VTA (Pitman and Borgland 2015) and the cannabinoid system (Parylak et al. 2012).

The present work relates to the idea of palatable food as an alternative reward. In the previous studies, a continuous high-fat diet produced harmful metabolic effects (Blanco-Gandía et al. 2017b). Here, we aim to study if an intermittent and limited access to a HFD could also diminish cocaine-associated memories without causing changes on bodyweight or metabolism, proving that a sporadic exposure could be sufficient to extinguish the preference and block reinstatement. Our study will be the first to evaluate the possible counteracting effects of intermittent and limited access to a HFD on the extinction and reinstatement of cocaine-induced CPP. Our general hypothesis is that the limited access to a HFD will accelerate the extinction of cocaine-associated memories and will reduce cocaine priming reinstatement. To assess metabolic disturbances, we will measure bodyweight and leptin and ghrelin changes after HFD exposure. Because the opioid and cannabinoid systems play a crucial role in food and drug reward (de Macedo et al. 2016), we also evaluated the effects of HFD administrations on the opioid mu receptor (Oprμ) and CB1 receptor gene expression (CB1r) in the striatum. Oprμ and CB1r are implicated in food reward processes and palatability (Kessler et al. 2016; Bello et al. 2014), as well as in various forms of learning and memory, including acquisition and reinstatement of cocaine-associated memory (Sticht et al. 2010; Hu et al. 2015). Given that sex differences in the vulnerability to drug seeking have been scarcely studied (Carroll et al. 2002), we will conduct our study in both male and female mice. For example, several data suggest a more intense response to cocaine in female rodents, with more psychomotor sensitization (Holly et al. 2012), faster acquisition of cocaine self-administration (Martini et al. 2014), and higher a breaking point of the progressive ratio and cocaine reinstatement (Lynch 2006). Sex-specific differences have also been described in response to HFD, with male rodents being more susceptible to physiological changes (Grove et al. 2010; Mela et al. 2012; Wang et al. 2018; Gelineau 2017).

Material and methods

Subjects

A total of 60 female and 47 male mice of the OF1 outbred strain were acquired commercially from Charles River (Barcelona, Spain). Animals were 42 days old when they arrived at the laboratory and were all housed under standard conditions in groups of 4–5 (cage size 28 × 28 × 14.5 cm). Mice were exposed to a reverse light cycle (white lights on from 19:30 to 7:30), and the vivarium was controlled for constant temperature (21 ± 2 °C). Food (standard diet) and water were available ab libitum except during the 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.

Drug treatment

For CPP, animals were injected intraperitoneally (IP) with 10 mg/kg of cocaine hydrochloride (Laboratorios Alcaliber S.A., Madrid, Spain) diluted in 0.9% NaCl (saline) in a volume of 0.1 mL/10 g bodyweight.

Experimental design

Animals first underwent the 10 mg/kg cocaine-induced CPP procedure from postnatal day (PND) 43. From PND 53 onwards, all mice were, from this moment on, exposed twice a week to extinction sessions (Table 1). Female and male mice were randomly divided into four groups: standard diet (SD); daily high-fat diet (HFD-24h); Monday, Wednesday, and Friday high-fat diet (HFD-MWF); and high-fat diet 1h before extinction (HFD-Ext).

Apparatus and procedure

Conditioned place preference

For place conditioning, we employed sixteen identical Plexiglas boxes with two equally sized compartments (30.7 cm length × 31.5 cm width × 34.5 cm height) separated by a gray central area (13.8 cm length × 31.5 cm width × 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 position of the animal and its crossing from one compartment to the other. The equipment was controlled by two IBM PC computers using MONPRE 2Z software (CIBERTEC S.A., Spain).

Acquisition of CPP The procedure of place conditioning, unbiased in terms of initial spontaneous preference, was performed as described previously (Maldonado et al. 2006) and consisted in three phases. To summarize the main aspects, in the first phase, known as Pre-C, mice were allowed access to both compartments of the apparatus for 15 min (900 s) per day for 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 for the rest of the experiment (total excluded: 4). 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 between the time spent in the drug-paired and vehicle-paired compartments during the pre-conditioning 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 an interval of 4 h, 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. During the third phase, known as Post-C, the guillotine door separating the two compartments was removed (day 8), and the time spent by the untreated mice in each compartment during a 900-s observation period was recorded. 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, while the opposite indicates that an aversion has been developed.

Extinction of CPP When the preference for the drug-paired compartment was established, mice underwent twice a week (Monday and Thursday) an extinction session that consisted of placing the animals in the apparatus (without the guillotine doors separating the compartments) for 15 min. The extinction condition was fulfilled when there was a significant difference between CPP scores and Post-C scores in two consecutive sessions and a lack of significant difference between CPP and Pre-C test values.

Reinstatement of CPP Twenty-four hours after extinction had been confirmed, the effects of a priming dose of cocaine were

Table 1 Experimental design. *PND* postnatal days, *HFD* high-fat diet

			PND 53 onwards				
	Male	Female	Monday	Tuesday	Wednesday	Thursday	Friday
SD	*n*=12	*n*=15	Standard diet	Standard diet	Standard diet	Standard diet	Standard diet
HFD-24h	*n*=11	*n*=15	HFD 1h	HFD 1h	HFD 1h	HFD 1h	HFD 1h
HFD-MWF	*n*=12	*n*=15	HFD 2h		HFD 2h		HFD 2h
HFD-Ext	*n*=12	*n*=15	HFD 1h before EXT			HFD 1h before EXT	

evaluated. Reinstatement tests were the same as those carried out in Post-C (free ambulation for 15 min), except that animals were tested 15 min after administration of the respective dose of cocaine. When reinstatement of the preference was achieved, after a subsequent weekly extinction process, a new reinstatement test was conducted with progressively lower doses of the drug until the CPP was completely extinguished. This procedure of extinction-reinstatement was repeated with decreasing doses (half the previous dose) until a priming dose was confirmed to be ineffective (5 mg/kg after extinction of CPP induced by 10 mg/kg and 2.5 mg/kg after extinction if animals showed reinstatement with 5 mg/kg). HFD conditions were maintained until the end of the experiment. Priming injections were administered in the vivarium, which constituted a non-contingent place to that of the previous conditioning procedure.

Feeding conditions

After the Post-C test in the CPP, each group began their intermittent access to the different HFD patterns. Our feeding procedure is based on the limited access model described by Corwin et al. (1998), in which non-food-deprived animals have sporadic and limited access to a HFD. Two different types of diet were used in this study: a standard diet (Teklad Global Diet 2014, 13 Kcal % fat, 67 Kcal % carbohydrates, and 20 Kcal % protein; 2.9 kcal/g) and the HFD (TD.06415, 45 Kcal % fat, 36 Kcal % carbohydrates and 19% Kcal protein; 4.6 kcal/g). Both diets were supplied by Harlan Laboratories Models, S. L. (Barcelona, Spain) and will be referred to from now on as the standard diet and the high-fat diet (HFD).

As we described on Table 1, on postnatal day (PND) 53, mice were randomly divided into 4 groups of males and 4 groups of females with similar average bodyweights and assigned to one of the following conditions: standard diet (SD); daily high-fat diet (HFD-24h); Monday, Wednesday, and Friday high-fat diet (HFD-MWF); and high-fat diet before extinction (HFD-Ext). All the groups had standard diet access during the whole procedure, and the HFD-24h group had a 1-h access to HFD from Monday to Friday; the HFD-MWF had a 2-h access to HFD on Monday, Wednesday, and Friday; and lastly, animals in the HFD-Ext had a 1-h HFD access prior to each extinction session (twice a week). The SD group remained undisturbed in their home cage.

All groups were fed ad libitum with the standard diet (Teklad Global Diet 2014) in their own cages, and water was freely available. After acquiring cocaine preference, during the extinction process, animals continued with SD in their home cages, but only the animals in the HFD groups were taken for a limited time into a separated plastic cage with access to the HFD. Exposure to the HFD took place in different individual plastic cages 2–3 h after the beginning of the dark phase. HFD intake was measured after each session. Animals were weighed every week throughout the study, at which point their intake of the standard diet in their home cage was also measured in grams.

Determination of plasma leptin and ghrelin levels

For leptin and ghrelin plasma quantification, an ELISA kit was employed for leptin and ghrelin (Merck-Sigma Aldrich, Saint Louis, USA) following the manufacturer's instructions. The sensitivity of the test is 0.2. All samples were run in duplicate.

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 plaque. Cerebellum and olfactory bulbs were eliminated, and the striatum was dissected. Brain tissue samples were immediately stored at −80°C until the RT-PCR assay was performed. The whole striatum was employed for this analysis.

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 are Mm01212171_s1, Mm01188089_m1, and Mm00446953_m1 corresponding to CB1r, Oprμ, and Gusb, respectively. Data were analyzed using the LightCycler 480 relative quantification software and were normalized to the amplification product of b-glucuronidase.

Statistics

To test for the acquisition of CPP, the time spent in the drug-paired compartment was analyzed with a (2)×2×4 mixed ANOVA. The two between factors were sex (male and female) and diet (SD, HFD-24h, HFD-MWF, and HFD-Ext). The within subjects factors tested the measurement differences between the pre- and post-CPP phases (Pre-C and Post-C). Since at this point of measurement all the animals had been maintained with the standard diet, the diet factor simply functions as a control check for the effectiveness of the random assignment to produce equivalent groups prior to exposure to the extinction-reinstatement manipulation (i.e.,

the expectation is that there will not be an effect for Diet). To compare whether extinction/reinstatement is achieved within the same group, data related to extinction, 2.5 mg/kg reinstatement, and 5 mg/kg reinstatement were analyzed by means of Student's *t*-test. The time required for the preference to be extinguished was analyzed by means of the Kaplan-Meier test, with Breslow (generalized Wilcoxon) comparisons when appropriate. The extinction analyses were performed within every group; therefore, no comparisons among groups were made. Ghrelin and leptin plasma levels and CB1r and Oprμ gene expression values were analyzed by a one-way ANOVA, considering the between variable –Sex–, with two levels (male and female), and the between variable –Diet–, with 4 levels (SD, HFD-24h, HFD-MWF, HFD-Ext). 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]

Conditioned place preference

Results of the 10 mg/kg cocaine-induced CPP are presented in Fig. 1a (males) and b (females). Regarding the main effects, the ANOVA for the time spent in the drug-paired compartment revealed an effect of the variable days [$F(1,99)=138{,}410$; $p<0.001$], which indicates that all animals developed conditioned place preference (Post-C vs Pre-C). Bonferroni's post hoc comparisons showed that in all cases, males and females spent significantly more time in the drug-paired compartment in Post-C than in Pre-C ($p<0.001$ in all cases). No effect was found in the variables sex nor diet separately. Regarding the interactions, there was no significant effect in the three-way interaction days × sex × diet, but the ANOVA did reveal a significant effect of the interaction days × sex [$F(1,99)=3833$; $p<0.05$]. Bonferroni's post hoc comparisons showed that female mice spent more time in the drug-paired compartment in Post-C than male mice ($p<0.05$), showing a stronger CPP but only in two groups: those that will receive the HFD tree days a week (HFD-MWF) or previously to each extinction sessions (HFD-Ext).

To compare if there was a reinstatement into drug seeking after achieving extinction within the same group, Student's *t*-tests were performed. Reinstatement with a priming dose of 5 mg/kg cocaine (Fig. 1a) was achieved in the male SD group ($t=-2.772$; d.f. 11; $p=0.018$), but after subsequent extinction sessions, the Student's *t*-test showed that no reinstatement with a priming dose of 2.5 mg/kg cocaine was achieved ($t=-0.078$; d.f. 11; $p=0.939$). In females (Fig. 1b), the Student's *t*-test showed reinstatement with a priming dose of 5 mg/kg cocaine in SD ($t=-2.297$; d.f. 14; $p=0.038$), HFD-24h ($t=-2.529$; d.f. 14; $p=0.024$), and HFD-Ext ($t=-2.282$; d.f. 14; $p=0.039$). Extinction was confirmed with the Student's *t*-test, where no group of males and females showed any differences with respect to the Pre-C test (data not shown). After two subsequent extinction sessions, the Student's *t*-test showed that no reinstatement with a priming dose of 2.5 mg/kg cocaine was achieved in any group (SD: $t=-1.241$; d.f. 14; $p=0.235$; HFD-24h: $t=-0.684$; d.f. 14; $p=0.505$; and HFD-Ext: $t=-0.303$; d.f. 14; $p=0.767$).

With regard to the time required to extinguish the preference, we found that in males (Fig. 2), the SD, HFD-MWF, and HFD-24h groups required a total of 16, 21, and 17 sessions, respectively, to achieve extinction, while HFD-Ext required only 8 sessions to extinguish the preference. The Kaplan-Meier analysis showed that the HFD-Ext male group required significantly less time to achieve extinction than the SD group ($\chi^2=4.336$; $p<0.05$), with no significant differences with respect to the other groups.

In female groups, the SD, HFD-MWF, and HFD-Ext groups required 9 sessions to achieve extinction, while the HFD-24h group required a total of 15 sessions to achieve extinction (Fig. 2). The Kaplan-Meier analysis revealed that the HFD-24h group required significantly more time to achieve extinction than the SD group ($\chi^2=8.431$; $p<0.01$), HFD-MWF ($\chi^2=4.250$; $p<0.05$), and HFD-Ext ($\chi^2=4.289$; $p<0.05$).

Effects of different HFD eating patterns and sex on plasma leptin and ghrelin levels and CB1r and Oprμ gene expression

There were no significant effects of the different intermittent eating patterns or sex on circulating leptin [$F(3,56)=0.975$; $p=0.411$] and ghrelin levels [$F(3,56)=0.440$; $p=0.725$) (Table 2). Regarding the real-time PCR analyses, the ANOVA indicated in the CB1r gene expression (Fig. 3a) an effect of the interaction diet × sex [$F(3,56)=3.340$; $p<0.05$]. There was an increased CB1r gene expression only in males of the HFD-Ext group with significant differences with respect to the SD group ($p<0.01$), HFD-MWF group ($p<0.01$), and HFD-24h group ($p<0.001$). Moreover, the HFD-Ext male group showed a significant increase against their corresponding HFD-Ext female group ($p<0.05$).

Regarding Oprμ gene expression (Fig. 3b), the ANOVA revealed a significant effect in the variable sex [$F(1,55)=7{,}604$; $p<0.01$], as overall, HFD male mice overexpressed Oprμ with respect to females ($p<0.01$).

[1] Information relating to bodyweight and food intake can be found in the supplementary material S1. No bodyweight and food intake differences were found between the four diet groups within each sex group.

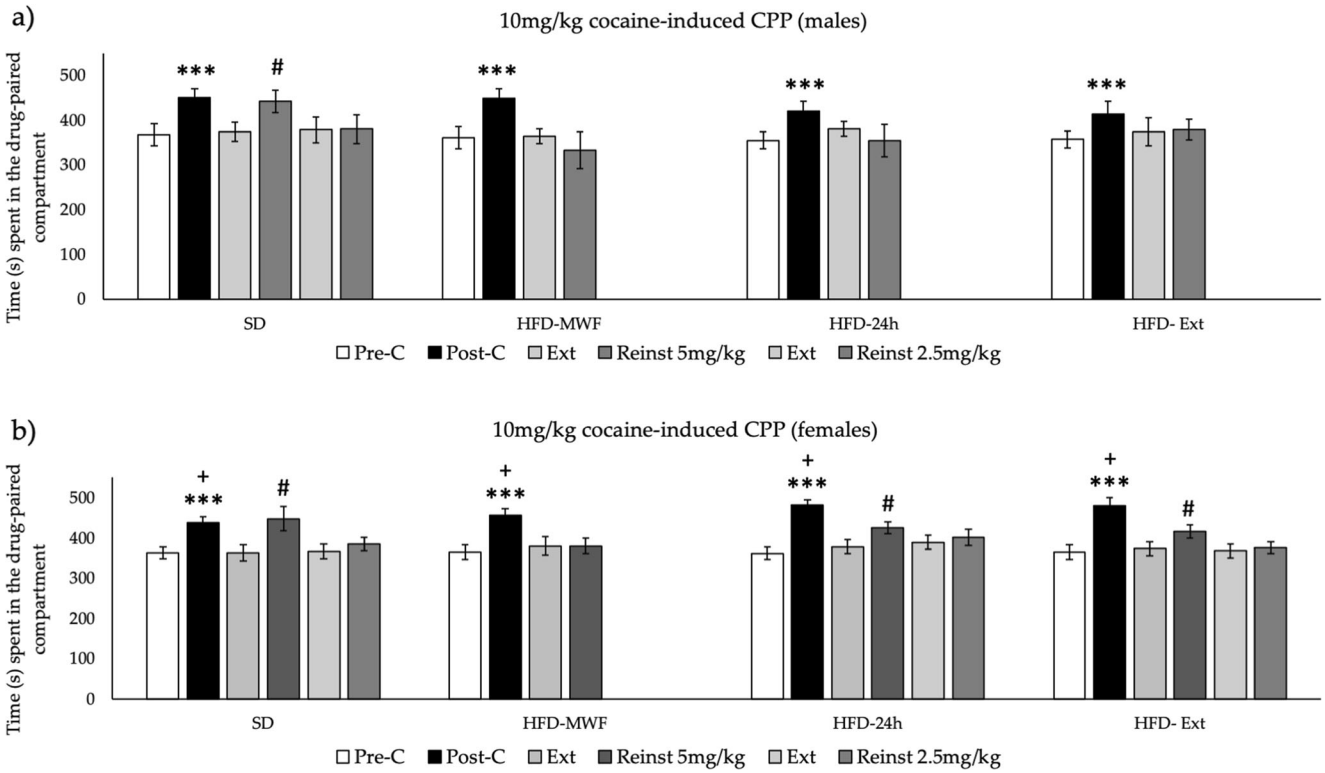

Fig. 1 Effects of HFD during the extinction-reinstatement process in conditioned place preference (CPP) in males (**a**) and females (**b**). CPP was induced by 10 mg/kg of cocaine in male and female mice fed with a standard diet and exposed after Post-C to different dietary conditions: SD group (standard diet throughout the procedure), HFD-24h group (1-h access to HFD from Monday to Friday), in HFD-MWF group (2-h access to high-fat diet on Monday, Wednesday, and Friday), and in the HFD-Ext group (1-h high-fat diet access twice a week, prior to extinction sessions). Bars represent the time (± SEM) in seconds spent in the drug-paired compartment in the pre-conditioning test (white bars), the post-conditioning test (black bars), in the last extinction session (light gray bars), and in the reinstatement test (dark gray bars). The first reinstatement test was evaluated 15 min after a priming dose of 5 mg/kg of cocaine, while the second reinstatement test was evaluated 15 min after a priming dose of 2.5 mg/kg of cocaine. ***$p<0.001$ significant difference with respect to the Pre-C (ANOVA); +$p<0.05$ significant difference in female Post-C vs male Post-C. #$p<0.05$ significant difference with respect to extinction (Student's *t* test)

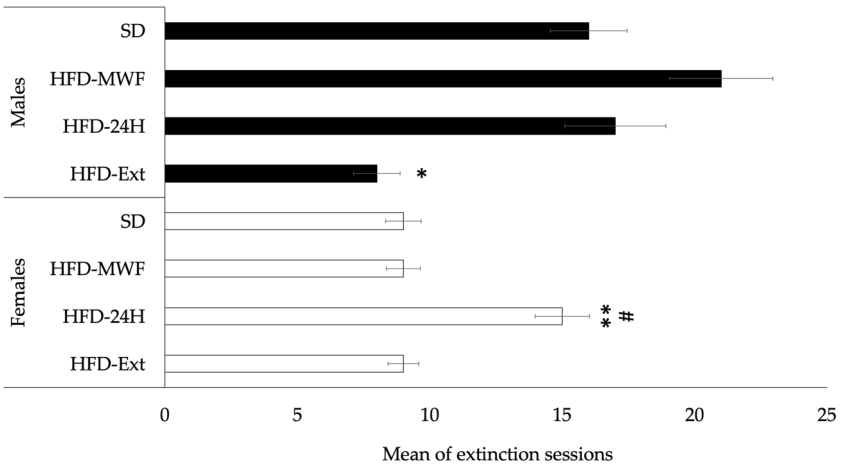

Fig. 2 Mean of extinction sessions. The bars represent the mean value (± SEM) of the number of sessions required for the preference to be extinguished after the Post-C test. Preference was considered to be extinguished when an animal spent 370s or less in the drug-paired compartment on two consecutive days. When the preference was not extinguished in a mouse, the number of days needed to achieve extinction in the whole group was assigned to that animal. *$p<0.05$, **$p<0.01$ with respect to the respective standard diet group (SD); #$p<0.05$ with respect to HFD-MWF and HFD-Ext

Table 2 Plasma leptin (ng/ml) and ghrelin (pg/ml) levels. Data are presented as mean values ± SEM (n=8/condition)

	Plasma leptin (ng/ml)		Plasma ghrelin (pg/ml)	
	Males	Females	Males	Females
SD	3.87 ± 0.49	3.64 ± 0.46	487 ± 51	356 ± 53
HFD-MWF	2.46 ± 0.77	4.03 ± 0.53	477 ± 78	471 ± 51
HFD-24h	3.07 ± 0.61	3.03 ± 0.70	475 ± 76	437 ± 60
HFD-Ext	3.01 ± 0.49	3.18 ± 0.79	482 ± 69	398 ± 50

Discussion

The present study noticed that the intermittent and limited access to a HFD may prevent reinstatement of the conditioned rewarding effects of cocaine in males, and specific administration schedules can facilitate or disrupt the extinction of the cocaine-associated memories in males and females. Related to this, this study highlights the important role of sex in these effects, since there were great differences between the results obtained in male and female mice. Once 10 mg/kg cocaine-induced CPP was acquired, all the mice were exposed to a different intermittent administration of HFD. The main results of the present work indicate that in males, exposure to the HFD in any of the three patterns employed blocked the reinstatement of the preference with a priming dose of 5 mg/kg of cocaine. However, in female mice, only one HFD administration (HFD-MWF) was effective in blocking the reinstatement of cocaine-induced preference. Extinction of the memories associated with cocaine was faster when access to the HFD was prior to each extinction session, but this phenomenon occurred only in males.

As we mentioned in the "Introduction," this is a follow-up of a previous study where we confirmed that a continuous HFD administration during cocaine withdrawal undermined reinstatement of cocaine-induced CPP, thereby acting as an alternative reward. However, that administration pattern induced several metabolic consequences (Blanco-Gandía et al. 2017a). Therefore, the aim of the present study was to evaluate a reduced administration pattern of HFD that could have effects on cocaine reward without inducing metabolic disturbances, such as increased bodyweight or changes in circulating leptin or ghrelin levels. We have shown that the metabolic harm induced by HFD is not necessary to disrupt the extinction and reinstatement of the CPP induced by cocaine, given that a limited and intermittent exposure was sufficient to block cocaine-related effects in a sex-specific manner. Although the HFD did not modify these parameters or affect the Oprμ gene expression, we found changes in the CB1r gene expression in the striatum of male animals. Surprisingly, we observed that only males that showed a faster extinction of cocaine-related memories (HFD-Ext) exhibited an overexpression in CB1r.

Conditioned rewarding effects of cocaine

Most of the studies performed to date focus on the role of palatable food on the acquisition of the self-administration/CPP of drugs (Davis et al. 2008; Morales et al. 2012; Blanco-Gandía et al. 2017a, 2017b). Prevention of the reinstatement of cocaine self-administration in rats has been obtained by pairing cocaine-related stimuli with food (Kearns and Weiss 2007). In that study, one of the groups was submitted to extinction by pairing a tone with the presentation of food in a different context. When this group was exposed to the tone in the original context, their renewal was significantly lower than that observed in the group exposed to the tone but without alternative reward to cocaine. Kearns and Weiss (2007) suggested that pairing a drug-related stimulus, such as a tone, to another reward different from the drug enhances

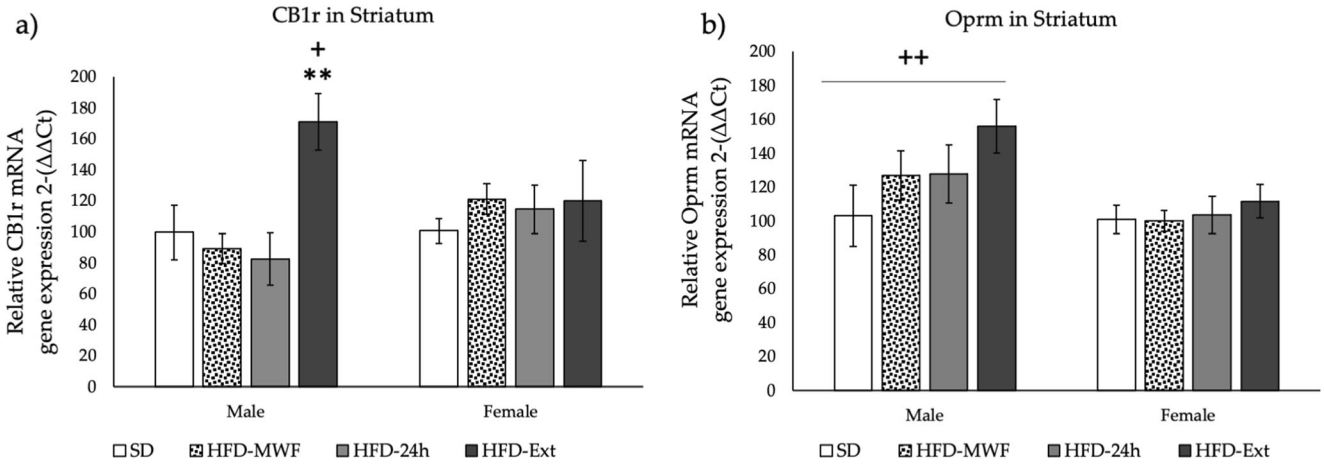

Fig. 3 Real-time PCR gene expression in the striatum. (**a**) CB1r relative gene expression evaluation in the striatum region (n = 8/condition). (**b**) Oprμ relative gene expression evaluation in the striatum region (n=8/condition). The columns represent means and the vertical lines ± SEM of relative (2-ΔΔCt method) gene expression in the striatum of OF1 mice. **p<0.01 significant differences with respect to the rest of the groups. +p<0.05; ++p<0.01 significant differences with respect to their corresponding female group

the reduction of the reinstatement into drug seeking and prevents relapse. To date, no data regarding food administration before being exposed to a drug-related context are available. In our study, we evaluated for the first time how intermittent access to HFD may modulate the extinction/reinstatement process.

We have previously shown that ad libitum access to a HFD accelerated the extinction process and blocked the reinstatement of cocaine seeking in adult mice (Blanco-Gandía et al. 2017a). However, an important weakness of that study was that continuous access to HFD induced bodyweight gain and dysregulation of hormone levels, with an increase in leptin and a decrease in ghrelin signaling, pointing to a metabolic syndrome and discarding the possibility of employing palatable food as an alternative reward to cocaine. However, in the present study, none of the intermittent and limited access to HFD schedules employed affected bodyweight, confirming that limited access to a HFD does not promote obesity (Corwin et al. 1998; Hudson et al. 2007; Blanco-Gandía et al. 2017b). In addition, there were no changes in leptin or ghrelin signaling in any of the groups, independently of HFD administration. These results confirmed previous studies (Blanco-Gandía et al. 2017b), showing that intermittent access to palatable food does not induce the negative consequences that were observed after ad libitum access (Davis et al. 2008; Morales et al. 2012; Blanco-Gandía et al. 2017a).

In agreement with previous reports indicating sex differences in the response to cocaine, we have observed a marked sex difference in the establishment of cocaine-induced CPP. Female mice spent more time in the drug-paired compartment during Post-C than males, suggesting a stronger sensitivity to the rewarding effects of cocaine. In line with our results, female rodents exhibit an increased sensitization to the locomotor effects of cocaine (Holly et al. 2012), faster acquisition of cocaine self-administration with persistence in the progressive ratio schedule (Martini et al. 2014; Lynch 2006), and develop cocaine-induced CPP with less pairing sessions than males (Russo et al. 2010).

However, after Post-C, female mice took less time to extinguish the preference than males, which suggests that cocaine-related memories are stronger in males. These results are in the line with previous studies showing that female mice require fewer extinction sessions than males to extinguish the CPP (Hilderbrand and Lasek 2014) and that estradiol administration facilitates extinction of cocaine CPP in female rats (Twining et al. 2013). However, no positive effects of the diet on the extinction process were observed in females, conversely to the results in males. Male mice exposed to HFD prior to each extinction session (HFD-Ext) exhibited a faster extinction of the drug-related memories. The HFD-Ext male group required significantly fewer sessions than the control group as well as fewer sessions than the HFD-MWF and HFD-24h groups. This effect could be related to the administration of HFD before every exposure to the context associated with cocaine reward. This is supported by previous data, where it has been suggested that pairing food with the old contextual cues related to the drug can prevent relapse (Kearns and Weiss 2007). An additional explanation is that the more rapid extinction in the HFD-Ext male group could be due to satiety and not be specific to HFD, as some studies have found that caloric restriction lowers the threshold dose for cocaine CPP and increases the persistence of extinction (Zheng et al. 2012; Jung et al. 2016). Thus, we cannot rule out that satiation in this group modulates the extinction process.

Hence, it can be argued that in order to diminish drug seeking in male mice, the moment in which HFD is administered plays a key role. Extinction recruits a new learning process (Lattal et al. 2006; Nic Dhonnchadha et al. 2013), especially in the hippocampus, which is particularly involved in the extinction of drug-associated memories (Szalay et al. 2013). Exposure to fat before each extinction session became a stimulus that predicted a non-reinforced context without cocaine and therefore accelerated the extinction of the preference. This effect is clear in males (HFD-Ext), but not in females, maybe due to their faster extinction of the preference. It is important to note that several studies have shown that HFDs lead to impairments in cognitive function such as memory or learning (Hwang et al. 2010; Valladolid-Acebes et al. 2013). In a previous study from our laboratory, we evaluated if a limited and intermittent access (exposed to the same conditions as the HFD-MWF group in this study) produced comparable impairments as the continuous access to a HFD (Blanco-Gandía et al. 2019). Our results showed that animals exposed to a limited and intermittent access to HFD showed no differences with respect to animals fed with a standard diet, which supports that the data obtained in the male HFD-Ext group are not due to a recall impairment.

As expected, 5 mg/kg of cocaine induced reinstatement in male and female mice fed with the standard diet. All three of the HFD administrations were effective in males, which did not reinstate their preference after a priming dose of cocaine. With a similar or lower number of extinction sessions than the control group, none of the male groups exposed to HFD reinstated the preference, suggesting that intermittent and limited HFD administration is a good alternative reinforcer. Therefore, the fact that the HFD blocked the reinstatement of preference in males, in all the schedules employed, independently of its administration schedule, suggests that fat could also act as an alternative reinforcer competing with cocaine.

Different results were observed in female mice, with only one group not reinstating the preference with 5 mg/kg cocaine, the female HFD-MWF group. The sex differences found in the response to HFD could be explained through the fact that female rats exhibited a higher cocaine priming-induced reinstatement response than males (Lynch 2006) with a greater

magnitude of reinstatement to cocaine-induced CPP (Bobzean et al. 2010). Several studies have suggested that the neural systems mediating cocaine reinforcement could also show sex differences, with dopamine response induced by cocaine in several brain areas being greater in female (Becker 1999; Becker and Ramirez 1981; Walker et al. 2001). Results even showed that this higher dopaminergic sensitivity in females could be independent of gonadal hormones (Bazzett and Becker 1994; Castner et al. 1993; McDermott et al. 1994). However, the remaining question is why only the HFD-MWF pattern was a protective pattern to reinstate cocaine preference in females. Firstly, it was only in this group where females ate significantly more fatty food. Secondly, we have previously shown that administration for several weeks is a risky pattern that induces neurobiological changes similar to those produced by chronic drug administration and could interfere in the reward system (Blanco-Gandía et al. 2017a; Corwin et al. 1998; Puhl et al. 2011). We can hypothesize that HFD-MWF females were protected from reinstatement into cocaine seeking because they may have developed another preference for HFD. Some studies have reported that, after drug withdrawal, there is increased overeating, and it is even recommended to counteract craving (Bane et al. 1993; Orsini et al. 2014). In this context, authors propose the concept of "addiction transfer," where one addiction is replaced by another, and could explain the behavioral outcomes exhibited by the HFD-MWF female group (Chechlacz et al. 2009).

Based on our results, we hypothesize that the administration of a natural reward, such as food, was not enough to block the potent effect of cocaine on female mice. However, in the case of males, who acquired the preference with less intensity than females, HFD became a good alternative reinforcer. Although preclinical studies are limited, several reports show that drug withdrawal induces an increase in food consumption. Orsini et al. (2014) showed that chronic exposure to amphetamine (9 injections) increased food consumption in male rats after cessation, discarding the possibility of a rebound from amphetamine-induced anorexia, as all the animals, control and amphetamine-treated, weighted the same when withdrawal began. In the same line, there is a reduction in the rewarding properties of drugs when a HFD is administered. For example, Wellman et al. (2007) demonstrated that a free access to HFD for 45 days diminished the acquisition of cocaine self-administration in male rats. Other findings on female rats showed that, after a 14-day exposure to cocaine, a specific increase in fat and carbohydrate consumption occurred, which was not seen in protein consumption (Bane et al. 1993). Most of these studies have been performed in male rodents, and our results highlighted the necessity of studying the response to palatable food in females as well as the limitation of the abovementioned results.

The different schedules of intermittent accesses to the HFD caused animals to receive a different number of rewarding experiences, which can be considered a limitation of this study. Those groups needing more sessions to extinguish the preference consequently were exposed to a higher number of fat administrations. However, a lack of reinstatement did not correlate to the number of HFD sessions in male or female mice. In addition, another important limitation to take into account in future studies is the variety of manipulations per week during the extinction process, given that, during this period, the SD groups were only moved to perform the extinction sessions, while the HFD groups were also moved for HFD access.

Neurobiology changes induced by intermittent and limited access to HFD

The endocannabinoid and the endogenous opioid systems are crucial in the addiction process and regulate feeding behaviors (Kessler et al. 2016; Bello et al. 2014). Opioid signaling is closely related to the rewarding properties of food, regulating palatability (Esch and Stefano 2004). For example, a continuous access to a HFD induces a significant reduction in Oprμ gene expression in the VTA (Blendy et al. 2005; Vucetic et al. 2011). Moreover, some studies point that CB1 activation in the NAcc and VTA modulates both dopaminergic and opioidergic pathways (Mellis et al. 2007). CB1 receptor antagonists are capable of reducing binge eating and mediate the extracellular dopamine release produced by a HFD (Parylak et al. 2012; Mellis et al. 2007). All these results support the idea that intermittent fat ingestion can modify reward pathways through different systems such as the opioid and cannabinoid systems. While the endogenous opioid system is related to the hedonic properties of food and modulates the release of DA-anticipating food, the endocannabinoid system is related to the homeostatic control of intake and positive feedback on the specific intake of fatty food (Koch 2001). In contrast with the numerous changes in gene expression induced by ad libitum administration of HFD (Blanco-Gandía et al. 2017a), the intermittent and the limited access to HFD during the extinction process practically did not induce variations. HFD administration did not induce any changes in the Oprμ gene expression, with the exception of a higher expression in males with respect to females. Results from previous studies are still controversial and depend on many factors, as some studies have reported that intermittent access to HFD for several weeks decreases mRNA expression of the Oprμ receptor in the NAcc in male mice (Blanco-Gandía et al. 2017b), while others reported the same reduction after a continuous access to a HFD or cafeteria diet in male mice (Ong et al. 2013; Vucetic et al. 2011) with no changes in females (Ong et al. 2013). The present results do not confirm that HFD administration changes Oprm gene expression, since we only found differences between sexes but not due to HFD intake. A previous study by Kawahara et al. (2013) showed that consumption of

palatable food increased DA release in the NAcc via activation of the Oprm pathway in the VTA, and it is well known that this projection has an influence on learning or performance of behaviors based on drug reward (Koob and Le Moal 2005). Regarding CPP studies, the Oprm antagonist naloxone was effective in blocking the reacquisition of a cocaine-induced CPP (Sticht et al. 2010). Although there are very few studies that focus on this relationship, this could account for the difference between males and females, indicating that male mice are modifying their learning processes during extinctions more efficiently than females.

Although HFD did not induce any changes in CB1r gene expression in females, an increase was detected in the HFD-Ext male group. Some studies have reported that HFD upregulates endocannabinoid levels (Massa et al. 2010; Higuchi et al. 2012) and that CB1 antagonists reduce binge eating (Parylak et al. 2012). We have only observed this upregulation in the HFD-Ext group, which could be related to the time required to extinguish the preference, and thus, males in this group could have quickly learned to notice the absence of the conditioned drug in the CPP. This would support that CB1 receptors are modulating the extinction and reinstatement processes, as previous studies show that CB1 antagonists such as rimonabant or AM251 are able to block cocaine and morphine extinction and CPP reinstatement (Yu et al. 2011; Khaleghzadeh-Ahangar and Haghparast 2015). A limitation of the present work is in the analysis of the complete striatum without differentiating the ventral from the dorsal part, which could have offered more specific changes.

Conclusion

The results of the present work support our initial hypothesis, showing that palatable food could act as an alternative reward to cocaine by decreasing its conditioned rewarding memories and blocking cocaine priming-induced reinstatement. These effects are conditioned by sex, as females were less sensitive to the protective action of HFD. Taken together, the present results point out that a sporadic access to HFD stimulates the same pathways activated by drugs, as well as decreasing craving and drug-related memories.

Currently, no controlled studies in humans have been performed to test the role of palatable food in attenuating drug withdrawal. It is well known that palatable food is generally used as self-medication to escape from a negative mood state or stressful situations (Groesz et al. 2012; Ifland et al. 2009; Kim et al. 2013). In 1989, Hatcher reported that substances such as sugar, aspartame, chocolate, and nutritional supplements were compulsively used by patients in rehabilitation centers (Hatcher 1989). Several reports highlighted that during drug withdrawal and abstinence, overeating is a well-known problem in rehabilitation centers (Edge and Gold 2011). For example, Cowan and Devine (2008) found that patients at different stages of recovery from substance addictions experienced an increase in food intake, weight changes, and used food in recovery. Overeating and post-addiction obesity are so common that most abstinence-oriented drug treatment programs schedule diet counseling and mandatory exercise programs (Cowan and Devine 2008). Our results support these clinical reports and suggest that, acting as an alternative reward, palatable food may attenuate drug craving and the vulnerability to relapse. In particular, a more effective reduction in the extinction of drug-related memories occurs when a HFD is consumed temporally close to a drug-related cue exposure.

Contrary to an ad libitum access, our feeding conditions do not have significant consequences on bodyweight or hormonal levels, with minimal changes in opioid and cannabinoid receptors gene expression. These results indicate that it would be beneficial to introduce the intermittent use of palatable food as a "rehabilitation tool" in drug treatment programs, allowing patients to eat it when drug craving is happening. The translational value of this study relies on the lack of metabolic adverse effects of any of the three HFD administrations. However, and no less important, this treatment was significantly less effective in females, which indicates the necessity of conducting more studies in females, since we cannot assume that environmental or nutritional interventions are equally effective in both sexes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00213-021-05834-7.

Acknowledgements We wish to thank Guillem Chulià for his English language editing.

Funding This study was supported by the Spanish Ministry of Health, Social Affairs and Equality, Government Delegation for the National Drugs Plan (2018/013); Generalitat Valenciana, Conselleria de Educación, Dirección General de Universidades, Grupos de Investigación de excelencia, PROMETEOII/2018/132; Instituto de Salud Carlos III, Red de Trastornos Adictivos (RD16/0017/0007 and RD16 0017 0004); and Unión Europea, Fondos FEDER "una manera de hacer Europa".

Declarations

Conflict of interest The authors declare no competing interests.

References

Bane AJ, McCoy JG, Stump BS, Avery DD (1993) The effects of cocaine on dietary self-selection in female rats. Physiol Behav 54(3):509–513. https://doi.org/10.1016/0031-9384(93)90244-A

Bazzett TJ, Becker JB (1994) Sex differences in the rapid and acute effects of estrogen on striatal D2 dopamine receptor binding. Brain Res 637:163–172. https://doi.org/10.1016/0006-8993(94)91229-7

Becker JB (1999) Gender differences in dopaminergic function in striatum and nucleus accumbens. Pharmacol Biochem Behav 64(4): 803–812. https://doi.org/10.1016/S0091-3057(99)00168-9

Becker DF, Grilo CM (2016) Comorbidity of mood and substance use disorders in patients with binge-eating disorder: associations with personality disorder and eating disorder pathology. J Psychosom Res 79(2):159–164. https://doi.org/10.1016/j.jpsychores.2015.01.016

Becker JB, Ramirez VD (1981) Experimental studies on the development of sex differences in the release of dopamine from striatal tissue fragments in vitro. Neuroendocrinology 32(3):168–173. https://doi.org/10.1159/000123151

Bello NT, Yeh CY, Verpeut JL, Walters AL (2014) Binge-like eating attenuates nisoxetine feeding suppression, stress activation, and brain norepinephrine activity. PLoS One 9(4):e93610. https://doi.org/10.1371/journal.pone.0093610

Blanco-Gandía MC, Aracil-Fernández A, Montagud-Romero S, Aguilar MA, Manzanares J, Miñarro J, Rodríguez-Arias M (2017a) Changes in gene expression and sensitivity of cocaine reward produced by a continuous fat diet. Psychopharmacology 234(15):2337–2352. https://doi.org/10.1007/s00213-017-4630-9

Blanco-Gandía MC, Cantacorps L, Aracil-Fernández A, Montagud-Romero S, Aguilar MA, Manzanares J, Valverde O, Miñarro J, Rodríguez-Arias M (2017b) Effects of bingeing on fat during adolescence on the reinforcing effects of cocaine in adult male mice. Neuropharmacology 113:31–44. https://doi.org/10.1016/j.neuropharm.2016.09.020

Blanco-Gandía MC, Miñarro J, Rodríguez-Arias M (2019) Behavioral profile of intermittent vs continuous access to a high fat diet during adolescence. Behav Brain Res 368:111891. https://doi.org/10.1016/j.bbr.2019.04.005

Blendy JA, Strasser A, Walters CL, Perkins KA, Patterson F, Berkowitz R, Lerman C (2005) Reduced nicotine reward in obesity: cross-comparison in human and mouse. Psychopharmacology 180(2): 306–315. https://doi.org/10.1007/s00213-005-2167-9

Bobzean SAM, Dennis TS, Addison BD, Perrotti LI (2010) Influence of sex on reinstatement of cocaine-conditioned place preference. Brain Res Bull 83(6):331–336. https://doi.org/10.1016/j.brainresbull.2010.09.003

Carroll ME, Morgan AD, Lynch WJ, Campbell UC, Dess NK (2002) Intravenous cocaine and heroin self-administration in rats selectively bred for differential saccharin intake: phenotype and sex differences. Psychopharmacology 161(3):304–313. https://doi.org/10.1007/s00213-002-1030-5

Castner SA, Xiao L, Becker JB (1993) Sex differences in striatal dopamine: in vivo microdialysis and behavioral studies. Brain Res 610(1):127–134. https://doi.org/10.1016/0006-8993(93)91225-H

Chechlacz M, Rotshtein P, Klamer S, Porubska K, Higgs S, Booth D et al (2009) Diabetes dietary management alters responses to food pictures in brain regions associated with motivation and emotion: a functional magnetic resonance imaging study. Diabetologia 52(3): 524–533. https://doi.org/10.1007/s00125-008-1253-z

Conason AH, Brunstein Klomek A, Sher L (2006) Recognizing alcohol and drug abuse in patients with eating disorders. J Assoc Phys 99(5): 335–339. https://doi.org/10.1093/qjmed/hcl030

Corwin RL, Wojnicki FH, Fisher JO, Dimitriou SG, Rice HB, Young MA (1998) Limited access to a dietary fat option affects ingestive behavior but not body composition in male rats. Physiol Behav 65(3):545–553. https://doi.org/10.1016/S0031-9384(98)00201-7

Cowan J, Devine C (2008) Food, eating, and weight concerns of men in recovery from substance addiction. Appetite 50(1):33–42. https://doi.org/10.1016/j.appet.2007.05.006

Davis JF, Tracy AL, Schurdak JD, Tschöp MH, Lipton JW, Clegg DJ, Benoit SC (2008) Exposure to elevated levels of dietary fat attenuates psychostimulant reward and mesolimbic dopamine turnover in the rat. Behav Neurosci 122(6):1257–1263. https://doi.org/10.1037/a0013111

de Macedo IC, de Freitas JS, da Silva Torres IL (2016) The influence of palatable diets in reward system activation: a mini review. Adv Pharmacol Sci 2016:1–7. https://doi.org/10.1155/2016/7238679

DiLeone RJ, Taylor JR, Picciotto MR (2012) The drive to eat: comparisons and distinctions between mechanisms of food reward and drug addiction. Nat Neurosci 15(10):1330–1335. https://doi.org/10.1038/nn.3202

Edge PJ, Gold MS (2011) Drug withdrawal and hyperphagia: lessons from tobacco and other drugs. Curr Pharm Des 17(12):1173–1179. https://doi.org/10.2174/138161211795656738

Esch T, Stefano GB (2004) The neurobiology of pleasure, reward processes, addiction and their health implications. Neuroendocrinol Lett 25(4):235–251

Flores-Fresco MJ, Blanco-Gandía MC, Rodríguez-Arias M (2018) Alteraciones de la Conducta Alimentaria en Pacientes con Trastorno por Abuso de Sustancias. Clin Salud 29(3):125–132. https://doi.org/10.5093/clysa2018a18

Gelineau R (2017) Combined consumption of alcohol and a high-fat diet: effects on behavior and health in male and female C57B1/6J mice.

Groesz LM, McCoy S, Carl J, Saslow L, Stewart J, Adler N, Laraia B, Epel E (2012) What is eating you? Stress and the drive to eat. Appetite 58(2):717–721. https://doi.org/10.1016/j.appet.2011.11.028

Grove KL, Fried SK, Greenberg AS, Xiao XQ, Clegg DJ (2010) A microarray analysis of sexual dimorphism of adipose tissues in high-fat-diet-induced obese mice. Int J Obes 34(6):989–1000. https://doi.org/10.1038/ijo.2010.12

Hatcher AS (1989) From one addiction to another: life after alcohol and drug abuse. Nurse Pract 14(11):13–14

Higuchi S, Irie K, Yamaguchi R, Katsuki M, Araki M, Ohji M, Hayakawa K, Mishima S, Akitake Y, Matsuyama K, Mishima K, Mishima K, Iwasaki K, Fujiwara M (2012) Hypothalamic 2-arachidonoylglycerol regulates multistage process of high-fat diet preferences. PLoS One 7(6):e38609. https://doi.org/10.1371/journal.pone.0038609

Hilderbrand ER, Lasek AW (2014) Sex differences in cocaine conditioned place preference in C57BL/6J mice. Neuroreport 25(2): 105–109. https://doi.org/10.1097/WNR.0000000000000053

Holderness CC, Brooks-Gunn J, Warren MP (1994) Co-morbidity of eating disorders and substance abuse review of the literature. Int J Eat Disord 16(1):1–34. https://doi.org/10.1002/1098-108X(199407)16:1<1::AID-EAT2260160102>3.0.CO;2-T

Holly EN, Shimamoto A, DeBold JF, Miczek KA (2012) Sex differences in behavioral and neural cross-sensitization and escalated cocaine taking as a result of episodic social defeat stress in rats. Psychopharmacology 224(1):179–188. https://doi.org/10.1007/s00213-012-2846-2

Hu SSJ, Liu YW, Yu L (2015) Medial prefrontal cannabinoid CB 1 receptors modulate consolidation and extinction of cocaine-associated memory in mice. Psychopharmacology 232(10):1803–1815. https://doi.org/10.1007/s00213-014-3812-y

Hudson JI, Hiripi E, Pope HG Jr, Kessler RC (2007) The prevalence and correlates of eating disorders in the national comorbidity survey replication. Biol Psychiatry 61(3):348–358. https://doi.org/10.1016/j.biopsych.2006.03.040

Hwang LL, Wang CH, Li TL, Chang SD, Lin LC, Chen CP, Chen CT, Liang KC, Ho IK, Yang WS, Chiou LC (2010) Sex differences in high-fat diet-induced obesity, metabolic alterations and learning, and synaptic plasticity deficits in mice. Obesity 18(3):463–469. https://doi.org/10.1038/oby.2009.273

Ifland JR, Preuss HG, Marcus MT, Rourke KM, Taylor WC, Burau K, Jacobs WS, Kadish W, Manso G (2009) Refined food addiction: a classic substance use disorder. Med Hypotheses 72(5):518–526. https://doi.org/10.1016/j.mehy.2008.11.035

Jung C, Rabinowitsch A, Lee WT, Zheng D, de Vaca SC, Carr KD (2016) Effects of food restriction on expression of place conditioning and biochemical correlates in rat nucleus accumbens. Psychopharmacology 233(17):3161–3172. https://doi.org/10.1007/s00213-016-4360-4

Kawahara Y, Kaneko F, Yamada M, Kishikawa Y, Kawahara H, Nishi A (2013) Food reward-sensitive interaction of ghrelin and opioid receptor pathways in mesolimbic dopamine system. Neuropharmacology 67:395–402. https://doi.org/10.1016/j.neuropharm.2012.11.022

Kearns DN, Weiss SJ (2007) Contextual renewal of cocaine seeking in rats and its attenuation by the conditioned effects of an alternative reinforcer. Drug Alcohol Depend 90(2-3):193–202. https://doi.org/10.1016/j.drugalcdep.2007.03.006

Kessler RM, Hutson PH, Herman BK, Potenza MN (2016) The neurobiological basis of binge-eating disorder. Neurosci Biobehav Rev 63:223–238. https://doi.org/10.1016/j.neubiorev.2016.01.013

Khaleghzadeh-Ahangar H, Haghparast A (2015) Intra-accumbal CB1 receptor blockade reduced extinction and reinstatement of morphine. Physiol Behav 149:212–219. https://doi.org/10.1016/j.physbeh.2015.06.005

Kim Y, Yang HY, Kim AJ, Lim Y (2013) Academic stress levels were positively associated with sweet food consumption among Korean high-school students. Nutrition 29(1):213–218. https://doi.org/10.1016/j.nut.2012.08.005

Koch JE (2001) Δ9-THC stimulates food intake in Lewis rats: effects on chow, high-fat and sweet high-fat diets. Pharmacol Biochem Behav 68(3):539–543. https://doi.org/10.1016/S0091-3057(01)00467-1

Koob GF, Le Moal M (1997) Drug abuse: hedonic homeostatic dysregulation. Science 278(5335):52–58. https://doi.org/10.1126/science.278.5335.52

Koob GF, Le Moal M (2001) Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24(2):97–129. https://doi.org/10.1016/S0893-133X(00)00195-0

Koob GF, Le Moal M (2005) Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. Nat Neurosci 8(11):1442–1444. https://doi.org/10.1038/nn1105-1442

Koob GF, Volkow ND (2010) Neurocircuitry of addiction. Neuropsychopharmacology 35(1):217–238. https://doi.org/10.1038/npp.2009.110

Lattal KM, Radulovic J, Lukowiak K (2006) 9YExtinction: does it or doesn't it? The requirement of altered gene activity and new protein synthesis. Biol Psychiatry 60(4):344–351. https://doi.org/10.1016/j.biopsych.2006.05.038

Lenoir M, Serre F, Cantin L, Ahmed SH (2007) Intense sweetness surpasses cocaine reward. PLoS One 2(8):e698. https://doi.org/10.1371/journal.pone.0000698

Loebens M, Barros HMT (2003) Diet influences cocaine withdrawal behaviors in the forced swimming test. Pharmacol Biochem Behav 74(2):259–267. https://doi.org/10.1016/S0091-3057(02)00924-3

Lynch WJ (2006) Sex differences in vulnerability to drug self-administration. Exp Clin Psychopharmacol 14(1):34–41. https://doi.org/10.1037/1064-1297.14.1.34

Maldonado C, Rodríguez-Arias M, Castillo A, Aguilar MA, Miñarro J (2006) Gamma-hydroxybutyric acid affects the acquisition and reinstatement of cocaine-induced conditioned place preference in mice. Behav Pharmacol 17(2):119–131. https://doi.org/10.1097/01.fbp.0000190685.84984.ec

Martini M, Pinto AX, Valverde O (2014) Estrous cycle and sex affect cocaine-induced behavioural changes in CD1 mice. Psychopharmacology 231(13):2647–2659. https://doi.org/10.1007/s00213-015-3867-4

Massa F, Mancini G, Schmidt H, Steindel F, Mackie K, Angioni C, Oliet SHR, Geisslinger G, Lutz B (2010) Alterations in the hippocampal endocannabinoid system in diet-induced obese mice. J Neurosci 30(18):6273–6281. https://doi.org/10.1523/JNEUROSCI.2648-09.2010

McDermott JL, Liu B, Dluzent DE (1994) Sex differences and effects of estrogen on dopamine and DOPAC release from the striatum of male and female CD-1 mice. Exp Neurol 125(2):306–311. https://doi.org/10.1006/exnr.1994.1034

Mela V, Llorente-Berzal Á, Díaz F, Argente J, Viveros MP, Chowen JA (2012) Maternal deprivation exacerbates the response to a high fat diet in a sexually dimorphic manner. PLoS One 7(11):e48915. https://doi.org/10.1371/journal.pone.0048915

Mellis T, Succu S, Sanna F, Boi A, Argiolas A, Melis MR (2007) The cannabinoid antagonist SR 141716A (Rimonabant) reduces the increase of extra-cellular dopamine release in the rat nucleus accumbens induced by a novel high palatable food. Neurosci Lett 419(3):231–235. https://doi.org/10.1016/j.neulet.2007.04.012

Morales L, Del Olmo N, Valladolid-Acebes I, Fole A, Cano V, Merino B et al (2012) Shift of circadian feeding pattern by high-fat diets is coincident with reward deficits in obese mice. PLoS One 7(5):e36139. https://doi.org/10.1371/journal.pone.0036139

Narayanaswami V, Thompson AC, Cassis LA, Bardo MT, Dwoskin LP (2013) Diet-induced obesity: dopamine transporter function, impulsivity and motivation. Int J Obes 37(8):1095–1103. https://doi.org/10.1038/ijo.2012.178

Nic Dhonnchadha BA, Lin A, Leite-Morris KA, Kaplan GB, Man HY, Kantak KM (2013) Alterations in expression and phosphorylation of GluA1 receptors following cocaine-cue extinction learning. Behav Brain Res 238:119–123. https://doi.org/10.1016/j.bbr.2012.10.012

Nøkleby H (2012) Comorbid drug use disorders and eating disorders: a review of prevalence studies. Nordic Stud Alcohol Drugs 29(3):303–314. https://doi.org/10.2478/v10199-012-0024-9

Ong ZY, Wanasuria AF, Lin MZ, Hiscock J, Muhlhausler BS (2013) Chronic intake of a cafeteria diet and subsequent abstinence. Sex-specific effects on gene expression in the mesolimbic reward system. Appetite 65:189–199. https://doi.org/10.1016/j.appet.2013.01.014

Orsini CA, Ginton G, Shimp KG, Avena NM, Gold MS, Setlow B (2014) Food consumption and weight gain after cessation of chronic amphetamine administration. Appetite 78:76–80. https://doi.org/10.1016/j.appet.2014.03.013

Parylak SL, Cottone P, Sabino V, Rice KC, Zorrilla EP (2012) Effects of CB1 and CRF1 receptor antagonists on binge-like eating in rats with limited access to a sweet fat diet: lack of withdrawal-like responses. Physiol Behav 107(2):231–242. https://doi.org/10.1016/j.physbeh.2012.06.017

Pitman KA, Borgland SL (2015) Changes in mu-opioid receptor expression and function in themesolimbic system after long-term access to a palatable diet. Pharmacol Ther 154:110–119. https://doi.org/10.1016/jpharmthera.2015.07.005

Puhl MD, Cason AM, Wojnicki FH, Corwin RL, Grigson PS (2011) A history of bingeing on fat enhances cocaine seeking and taking. Behav Neurosci 125(6):930–942. https://doi.org/10.1037/a0025759

Russo SJ, Sun WL, Minerley ACE, Weierstall K, Nazarian A, Festa ED et al (2010) Progesterone does not affect cocaine-induced conditioned place preference or locomotor activity in male rats. Ethn Dis 20(1):73

Salamone JD, Correa M, Mingote SM, Weber SM (2005) Beyond the reward hypothesis: alternative functions of nucleus accumbens dopamine. Curr Opin Pharmacol 5(1):34–41. https://doi.org/10.1016/j.coph.2004.09.004

Sticht M, Mitsubata J, Tucci M, Leri F (2010) Reacquisition of heroin and cocaine place preference involves a memory consolidation process sensitive to systemic and intra-ventral tegmental area naloxone.

Neurobiol Learn Mem 93(2):248–260. https://doi.org/10.1016/j.nlm.2009.10.005

Szalay JJ, Jordan CJ, Kantak KM (2013) Neural regulation of the time course for cocaine-cue extinction consolidation in rats. Eur J Neurosci 37:269–277. https://doi.org/10.1111/ejn.12035

Thanos PK, Kim R, Cho J, Michaelides M, Anderson BJ, Primeaux SD, Bray GA, Wang GJ, Robinson JK, Volkow ND (2010) Obesity-resistant S5B rats showed greater cocaine conditioned place preference than the obesityprone OM rats. Physiol Behav 101(5):713–718. https://doi.org/10.1016/j.physbeh.2010.08.011

Twining RC, Tuscher JJ, Doncheck EM, Frick KM, Mueller D (2013) 17β-estradiol is necessary for extinction of cocaine seeking in female rats. Learn Mem 20(6):300–306. https://doi.org/10.1101/lm.030304.113

Valladolid-Acebes I, Fole A, Martín M, Morales L, Cano MV, Ruiz-Gayo M, Del Olmo N (2013) Spatial memory impairment and changes in hippocampal morphology are triggered by high-fat diets in adolescent mice. Is there a role of leptin? Neurobiol Learn Mem 106:18–25. https://doi.org/10.1016/j.nlm.2013.06.012

Volkow ND, Wang GJ, Baler RD (2011) Reward, dopamine and the control of food intake: implications for obesity. Trends Cogn Sci 15(1):37–46. https://doi.org/10.1016/j.tics.2010.11.001

Vucetic Z, Kimmel J, Reyes TM (2011) Chronic high-fat diet drives postnatal epigenetic regulation of m-opioid receptor in the brain. Neuropsychopharmacology 36(6):1199e1206–1199e1206. https://doi.org/10.1038/npp.2011.4

Walker QD, Francis R, Cabassa J, Kuhn CM (2001) Effect of ovarian hormones and estrous cycle on stimulation of the hypothalamo-pituitary-adrenal axis by cocaine. J Pharmacol Exp Ther 297(1):291–298. https://doi.org/10.1007/978-3-540-29678-2_2319

Wang J, Hodes GE, Zhang H, Zhang S, Zhao W, Golden SA, Bi W, Menard C, Kana V, Leboeuf M, Xie M, Bregman D, Pfau ML, Flanigan ME, Esteban-Fernández A, Yemul S, Sharma A, Ho L, Dixon R, Merad M, Han MH, Russo SJ, Pasinetti GM (2018) Epigenetic modulation of inflammation and synaptic plasticity promotes resilience against stress in mice. Nat Commun 9(1):477. https://doi.org/10.1038/s41467-017-02794-5

Wellman PJ, Nation JR, Davis KW (2007) Impairment of acquisition of cocaine self-administration in rats maintained on a high-fat diet. Pharmacol Biochem Behav 88(1):89–93. https://doi.org/10.1016/j.pbb.2007.07.008

Yu LL, Zhou SJ, Wang XY, Liu JF, Xue YX, Jiang W, Lu L (2011) Effects of cannabinoid CB1 receptor antagonist rimonabant on acquisition and reinstatement of psychostimulant reward memory in mice. Behav Brain Res 217(1):111–116. https://doi.org/10.1016/j.bbr.2010.10.008

Zheng D, de Vaca SC, Carr KD (2012) Food restriction increases acquisition, persistence and drug prime-induced expression of a cocaine-conditioned place preference in rats. Pharmacol Biochem Behav 100(3):538–544. https://doi.org/10.1016/j.pbb.2011.10.021