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Research article

Effects of ketosis on cocaine-induced reinstatement in male mice

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ABSTRACT

In recent years, the benefits of the ketogenic diet (KD) on different psychiatric disorders have been gaining attention, but the substance abuse field is still unexplored. Some studies have reported that palatable food can modulate the rewarding effects of cocaine, but the negative metabolic consequences rule out the recommendation of using it as a complementary treatment. Thus, the main aim of this study was to evaluate the effects of the KD on cocaine conditioned place preference (CPP) during acquisition, extinction, and reinstatement. 41 OF1 male mice were employed to assess the effects of the KD on a 10 mg/kg cocaine-induced CPP. Animals were divided into three groups: SD, KD, and KD after the Post-Conditioning test. The results revealed that, while access to the KD did not block CPP acquisition, it did significantly reduce the number of sessions required to extinguish the drug-associated memories and it blocked the priming-induced reinstatement.

1. Introduction

The ketogenic diet (KD) is a high-fat, low-carbohydrate, and protein-balanced diet [1] that induces a specific metabolic status named ketosis. A ketosis status involves a significant change in the main source of energy used by the body and the brain, in which the reduction in carbohydrate intake reduces glucose production, leading the body to use up fat stores [2]. When carbohydrates are reduced to less than 5–10%, fatty acids break down and create ketone bodies in the liver, such as β-hydroxybutyrate (βOHB), which are indicators of nutritional ketosis [3]. Due to this special metabolic status that KD induces, in the last years this diet has been employed as complementary treatment in several neurological disorders, such as epilepsy or neurodegenerative diseases [4–6]. However, there are other diseases like drug addiction, in which the role of diet is just beginning to be studied, but the role of a KD is hardly explored.

Drugs of abuse and palatable diets affect common brain mechanisms, namely the reward system [7]. Both stimulate common brain regions like the lateral hypothalamus, ventral tegmental area, prefrontal cortex or amygdala [8], reduce dopamine active transporter density [9] and activate dopaminergic neurons of the nucleus accumbens [10,11]. This dopaminergic activation caused by palatable food affects neural pathways involved in motivation and reward, such as drugs of abuse [12–14]. For example, the downregulation of dopaminergic receptors in the nucleus accumbens, which is characteristic of the addictive process, is also found in obesity [7].

In recent years, some nutritional interventions have proved to be a modulating factor in the addiction process. For example, in a series of studies, it was observed that a high-fat diet (HFD) can be an important modulating factor of the rewarding properties of cocaine. This effect seems to be dependent on the access pattern of palatable diets, such as intermittently or continuously. While intermittent access in a vulnerable period, such as adolescence, increases sensitivity to cocaine in the conditioned place preference paradigm (CPP) [15,16], continuous HFD access seems to reduce it [17]. Likewise, HFD administration after acquisition of CPP reduces the number of sessions needed to achieve extinction, suggesting that the diet had a role as an alternative reinforcer and diminished the drug-related memories [17]. Recently, it was demonstrated that a HFD administered in an intermittent schedule, which does not affect metabolic indicators like ghrelin, leptin or body-weight, also reduced the time required to achieve extinction and blocked reinstatement of cocaine preference in adult male and female mice [18]. To date, studies regarding a possible beneficial interaction of the KD with substance use disorders are scarce. Thus, with all these results regarding HFDs, in the present study we asked ourselves whether other types of diet, such as the KD, could exert a modulation on the

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conditioned rewarding effects of cocaine.

For example, regarding alcohol, a recently published preclinical - clinical study [19] confirmed that people with an alcohol use disorder maintained on a KD manifested fewer withdrawal symptoms than those on a standard (American) diet. The preclinical data showed that access to a KD reduced ethanol consumption in rats [19] and, more recently, it has also been demonstrated in mice [20]. It seems that the KD could also be advantageous in decreasing ethanol withdrawal symptoms in rats and mice [20,21]. Regarding cocaine, to date only one study has reported decreased cocaine-induced stereotypies and sensitization in male and female rats maintained on a KD, suggesting that this nutritional intervention may act on the dopaminergic system [22].

The present work employed the CPP procedure, which evaluates the contextual cues related to the rewarding effects of a drug. Considering the previous results obtained with a HFD, we hypothesized that a KD, which changes the metabolic status in the individual, would block the cocaine-induced CPP acquisition and accelerate the extinction of cocaine-related memories in the mice that acquired CPP. Finally, KD may be able to block reinstatement of cocaine-seeking behaviour.

2. Material and methods

2.1. Subjects

A total of 45 male mice of the OF1 strain were acquired commercially from Charles River (France). Animals were 21 days old on arrival at the laboratory and were all housed under standard conditions in groups of 4–5 (cage size 28 × 28 x1 4.5 cm) at a constant temperature (21 ± 2 °C), lights on from 8:00 to 20:00, and food and water available *ad libitum*. 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 Committee for the Use and Care of Animals of the University of Valencia approved the study (2019/VSC/PEA/0065).

2.2. Apparatus and procedure:

2.2.1. Experimental design

To avoid stressful social conditions in their home cages, animals arrived on PND 21 at the laboratory, but the experiment began during their young adulthood, on PND 42. Animals were randomly divided into 3 groups (Fig. 1) with similar average body weights (37–40 g): mice fed the standard diet throughout the whole procedure (SD, n = 12), mice fed the ketogenic diet throughout the procedure, from PND 42 (KD, n = 14), and mice fed the SD until the end of the CPP procedure and a KD after the Post-C test and until the end of the extinction sessions (PostCPP-KD, n = 15). Animals underwent a 10 mg/kg cocaine induced CPP procedure on PND 52, and then underwent an extinction session once a week in order to evaluate the effects of the KD on the extinction of the preference. Body weight and Beta-hydroxybutyrate (βOHB) plasma levels were measured before the Pre-C test, after the Post-C test, and 7 days after the Post-C.

2.2.2. Feeding conditions and ketosis

Two types of diet were administered in this study: the standard diet (SD) (Teklad Global Diet 2014, 13 kcal % fat, 67 kcal % carbohydrates and 20% kcal protein; 2,9kcal/g) and the ketogenic diet (KD) (TD.96355, 90.5 % kcal from fat, 0.3% kcal from carbohydrates and 9.1% kcal from protein; 6.7 kcal/g). Both diets were supplied by Envigo Teklad Diets (Barcelona, Spain).

To evaluate if animals were on a ketosis status, plasma β-hydroxybutyrate from the tail vein was measured weekly with an On Call GK Dual monitor and ketone test strips (ACON Laboratories, Inc., San Diego, CA).

2.2.3. 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 0.001 mL/kg body weight. The dose of 10 mg/kg cocaine has been demonstrated to be an effective dose that induces reinstatement with half the previous received dose in standard mice [18,23].

2.2.4. 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 grey central area (13.8 cm length × 31.5 cm width × 34.5 cm height). The compartments have different coloured 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 crossings from one compartment to the other. The equipment was controlled by two IBM PC computers using MONPRE 2Z software (CIBERTEC S.A., Spain).

2.2.5. Acquisition of CPP

The procedure of Place Conditioning, unbiased in terms of initial spontaneous preference, was performed as described previously [24] and consisted of 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 (<33% of the session time) or preference (more than 67%) for any compartment were excluded from the rest of the experiment (number of mice excluded: 4). The procedure of assignment is unbiased, assigning half of the animals in each group to the drug or vehicle in one compartment (e.g. white), and the other half in the other compartment (e.g. black). Additionally, half of the animals are assigned to the initially preferred compartment and the other half to their non-preferred compartment.

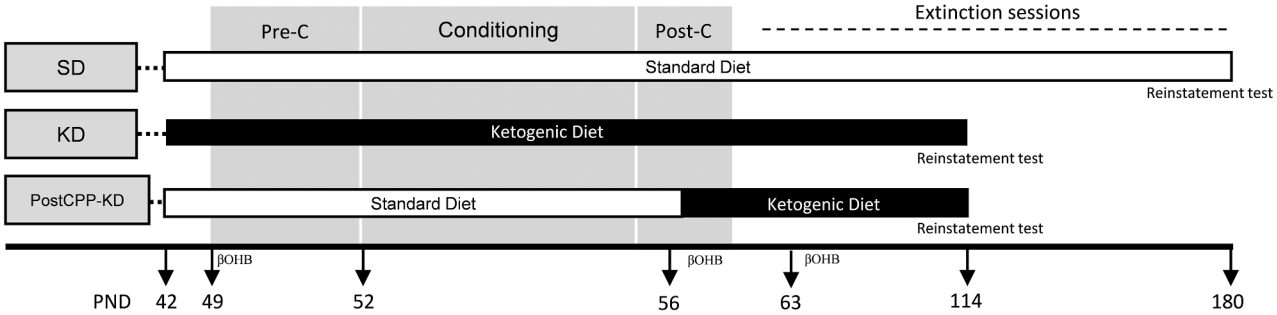


Fig. 1. Experimental design.

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 made possible in both cases by closing the guillotine door that separated the two compartments, rendering 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 developed.

2.2.6. Extinction of CPP

When preference for the drug-paired compartment had been established, all groups underwent a weekly extinction session in which they were placed in the apparatus (without the guillotine doors separating the compartments) for 15 min. Results were checked every week for each group to confirm if criteria had been satisfied. The extinction condition was fulfilled when there was a lack of a significant difference between CPP scores and Pre-C test values in two consecutive sessions.

2.2.7. Reinstatement of CPP

Twenty-four hours after extinction had been confirmed, the effects of a priming dose of cocaine were evaluated. The reinstatement test was 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 (5 mg/kg). Priming injections were administered in the vivarium, which constituted a non-contingent place to that of the previous conditioning procedure. If animals reinstated the preference, the extinction sessions continued in time and when the criteria were met again, the next half-dose (2.5 mg/kg) was administered. If they did not reinstate the preference, then the experiment finished. Therefore, each group can finish the procedure at different times.

2.3. Statistical analysis

Data relating to βOHB were analysed by a mixed ANOVA with one between-subjects variable – "Diet", with 3 levels (SD, KD and PostCPP-KD) - and a within variable – "Days", with 3 levels (Pre-C, Post-C and DAY7Post-C). Data relating to bodyweight were analysed by a mixed ANOVA with one between-subjects variable – "Diet", with 3 levels (SD, KD and PostCPP-KD) - and a within variable – "Weeks", with 8 levels (Baseline and Weeks 1–7). Body weight was compared until week 7 due to different extinction-reinstatement timings.

For the CPP procedure, the time spent in the drug-paired compartment was analysed by a repeated measures ANOVA, with the between-subjects variable - "Diet", with 3 levels (SD, KD and PostCPP-KD) - and a within variable – "Days", with two levels (Pre-C and Post-C). To compare whether extinction/reinstatement had been achieved within the same group, data relating to extinction and 5 mg/kg reinstatement were analysed by means of Student's *t*-test. The time required for the preference to be extinguished was analysed by means of the Kaplan-Meier test, with Breslow (generalized Wilcoxon) comparisons when appropriate. All results are expressed as mean ± S.E.M. Analyses were performed using SPSS v26.

3. Results

3.1. Increased β-hydroxybutyrate (βOHB) and body weight.

With respect to βOHB plasma levels (Fig. 2a), the ANOVA revealed a significant effect of the interaction "Days × Diet" [$F(4,76) = 34{,}714$; $p < 0.001$], as the KD group showed increased levels of βOHB with respect to SD and PostCPP-KD when measurements were taken in Pre-C ($p < 0.001$) and Post-C ($p < 0.001$). The KD and PostCPP-KD groups exhibited higher levels than the SD group 7 days after Post-C, ($p < 0{,}001$ in both cases). Moreover, the PostCPP-KD group's levels were higher 7 days after Post-C when compared to pre-C and post-C measures ($p < 0.001$ in both cases).

Regarding changes in body weight (Fig. 2b), the ANOVA revealed no significant differences in the variable "Diet" [$F(2,38) = 0.019$; $p = 0.981$], as all groups presented similar weight throughout the procedure. There was a significant effect of the variable "Week" [$F(7,266) = 254{,}571$; $p < 0.001$], since mice showed higher body weight in weeks 1 to 7 than at baseline ($p < 0.001$, in all cases).

3.2. Conditioned place preference

The ANOVA for the time spent in the drug-paired compartment (Fig. 3) revealed an effect of the variable "Days" [$F(1,38) = 111{,}919$; $p < 0.001$]. Bonferroni's post-hoc comparisons showed that the mice spent significantly more time in the drug-paired compartment in Post-C than in Pre-C ($p < 0.001$ in all cases). These results indicate that the three groups developed CPP.

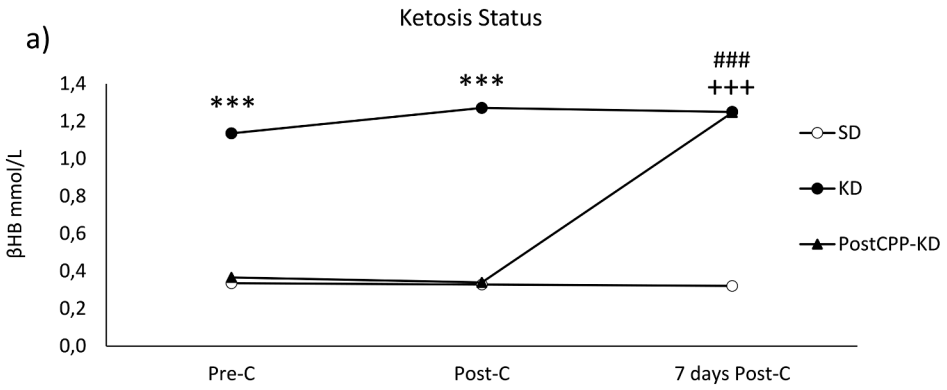
With regards to the time required to extinguish the preference (Fig. 4), the SD group required a total of 19 sessions, while the KD and the PostCPP-KD groups required only 8 sessions. The Kaplan-Meier analysis revealed that the SD group required significantly more sessions than the other two groups to extinguish the preference ($p < 0{,}05$ in both cases).

Reinstatement of drug-seeking after achievement of extinction was evaluated with Student's t-tests, which showed that reinstatement with a priming dose of 5 mg/kg cocaine was achieved only in the SD group ($t = -2.943$; d.f. 9; $p = 0.016$).

4. Discussion.

The aim of the present study was to evaluate whether a KD can modulate the conditioned rewarding effects of cocaine in two critical moments: during acquisition and/or during extinction/reinstatement of the preference. The results showed that all animals, regardless of being fed a KD or SD, developed a place preference for the cocaine-paired compartment after administration of 10 mg/kg of cocaine. However, during the extinction-reinstatement process both groups fed with the KD needed fewer sessions for the preference to be extinguished than the SD group. In the reinstatement test, induced by a priming dose of 5 mg/kg of cocaine (half the previously received dose), only the SD group exhibited preference for the drug-paired compartment, confirming that being on a KD blocked reinstatement with 5 mg/kg cocaine. To date, only one study has evaluated how access to a KD mediates the effects of cocaine. Martinez et al., [22] reported that access to a KD over three weeks reduced cocaine withdrawal symptoms in rats. In that study, rats received daily cocaine injections and after cessation, withdrawal symptoms such as stereotyped locomotor responses appeared. Their results showed that the animals fed a KD showed weaker cocaine-induced stereotyped response than those fed a SD.

Studies with other drugs of abuse, such as ethanol, have reported similar results, with rats or mice on KD displaying milder ethanol withdrawal symptoms [20,21]. As mentioned in the introduction, the KD reduces ethanol self-administration during acute withdrawal in rats and withdrawal symptoms during ethanol detoxification in humans [19]. In addition, previous studies by our research group have shown



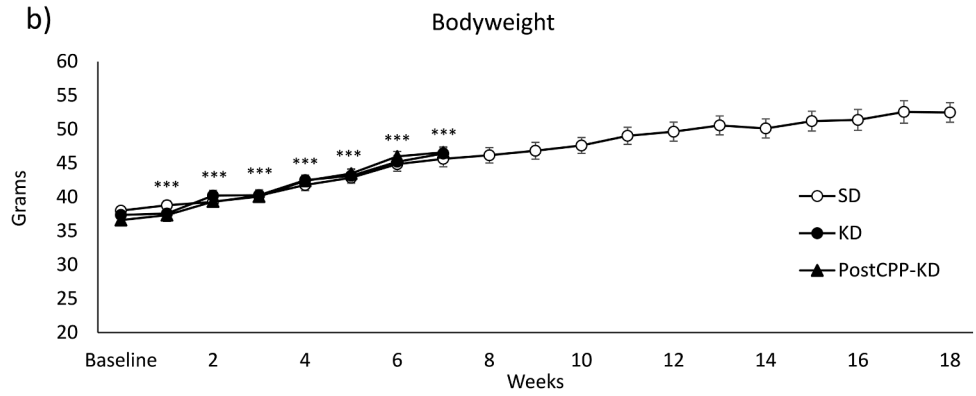


Fig. 2. β-hydroxybutyrate plasma levels and weekly body weight. (a) Ketosis status. Data are represented as the mean (±SEM) amount of βOHB. ***p < 0.001 significant difference with respect to the rest of the groups. +++p < 0.001 significant difference with respect to SD. ###p < 0.001 significant difference with respect to Pre-C and Post-C. **(b) Weekly body weight**. Data are represented as the mean (±SEM) body weight measured weekly. ***p < 0.001 significant difference with respect to Baseline.

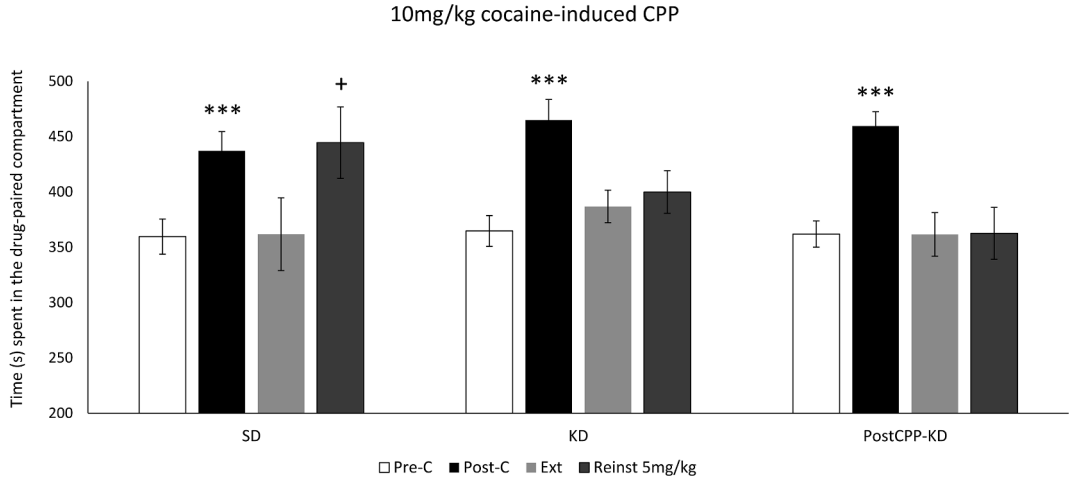


Fig. 3. Effects of KD during the extinction-reinstatement process in the Conditioned Place Preference (CPP) paradigm. Bars represent the time (±SEM) in seconds spent in the drug-paired compartment in the Pre-Conditioning test (white bars), the Post-conditioning test (black bars), the last extinction session (light gray bars) and the reinstatement test (dark gray bars). The reinstatement test was evaluated 15 min after a priming dose of 5 mg/kg of cocaine. ***p < 0.001 significant difference with respect to the Pre-C. + p < 0.05 significant difference with respect to Ext.

that access to a KD for 7 days prior to an ethanol self-administration test, and maintaining it for 4 weeks, reduces ethanol consumption compared to animals on a SD [25].

One of the main therapeutic effects of the KD is the increase that it produces in adenosine transmission, and one of the possible explanations for the effects of a KD on drug addiction is the relationship between adenosine and dopamine [22]. Several studies have demonstrated that there is an antagonistic interaction between the adenosine A1 - Dopamine D1 and adenosine A2A - dopamine D2 receptors [26], especially in GABAergic neurons. For example, D1 binding affinity is decreased by A1 agonists, suggesting that the A1 receptor modulates dopaminergic transmission [27]. It has been proposed that the response to drugs, such as psychostimulants, is also mediated by adenosine [28–30]. On the other hand, there are preclinical studies that have demonstrated that A2 agonists reduce cocaine and morphine locomotor sensitization [30,31] and decrease cocaine self-administration [32]. However, antagonist administration causes comparable effects to psychostimulants and enhances relapse into cocaine self-administration [33]. Thus, the main

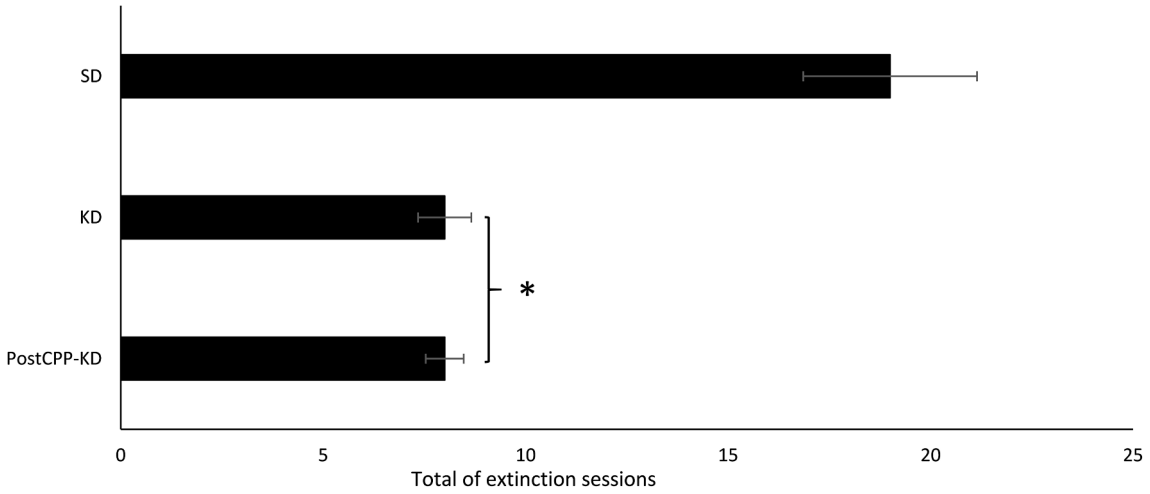


Fig. 4. Extinction. The bars represent the total value (±SEM) of the number of sessions required for the preference to be extinguished after the Post-C test. The Kaplan-Meyer analyses showed * $p < 0.05$ significant difference with respect to SD.

hypothesis of this work is that KD could attenuate dopaminergic transmission through activation of adenosine receptors [31,34]. In fact, in a previous study, we observed that a 4–5-week KD access led to alterations in the adenosine, dopamine and cannabinoid gene expression of mice [25]. Although the adenosine-dopamine modulation would not be strong enough to block the acquisition of cocaine-induced CPP, it could diminish the strength of the conditioning and therefore reduce the number of sessions needed to extinguish the preference, as well as the power of a cocaine-priming dose to reinstate drug-seeking behaviour. However, more extensive studies are needed to confirm the neurobiological mechanisms underlying these effects, especially ones considering female mice in them.

Our results, in line with those of Martínez et al., [22], also suggest another possible explanation for the KD modulation of addiction, which could be the role of differences in βOHB blood levels. Even when the KD contains more than double the calories as the SD, animals in the KD group did not gain more body weight than mice in the SD group. Previous results suggest differences in energy expenditure or lower food intake in KD-fed animals, with studies showing increases or decreases in body weight with respect to the control groups [21,25,35]. Nevertheless, some studies have reported that butyrate, which is a histone deacetylase inhibitor, keeps mice metabolically normal when maintained on a high-fat diet, with low glucose and insulin levels and normal body weight [36]. Butyrate is a product of bacterial anaerobic fermentation [37] and closely related to βOHB, the main source of energy for mammals during ketosis [38]. There are some studies that have reported that the overexpression of HDAC increases effects caused by cocaine [39]. Therefore, if βOHB could be acting as an endogenous HDAC inhibitor [40,41], it would contribute to the final effects of ketosis on cocaine extinction.

The KD may be considered as a promising nutritional approach in the treatment of cocaine addiction. Although the diet cannot be an exclusive treatment, it can contribute to the attenuation of the memories related to cocaine consumption, as well as the risk of relapse. This study supports what previous studies with other types of high-fat diets have suggested, and it is that nutritional interventions can modulate the conditioned effects of drugs like cocaine, which today does not yet have a definitive treatment.

CRediT authorship contribution statement

Francisco Ródenas-González: Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. **M. Carmen Blanco-Gandía:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **José Miñarro:** Funding acquisition, Investigation, Project administration, Resources, Writing – review & editing. **Marta Rodríguez-Arias:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

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