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Housing conditions modulate the reinforcing properties of cocaine in adolescent mice that binge on fat

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ABSTRACT

Binge eating is a specific form of overeating characterized by intermittent, excessive eating. To date, several studies have addressed the effects that bingeing on fat has on the rewarding effects of drugs of abuse, but they have found contradictory and highly variable results. Housing conditions could modulate these results, as most studies employ isolated animals to measure the exact amount of food that is ingested. The aim of this study was to evaluate the effects of housing conditions on the response of mice to cocaine, modulated by bingeing on a high-fat diet during adolescence.

After 40 days of binge-eating for 2 h, three days a week (PND 29–69), the reinforcing effects of a non-effective dose of cocaine (1 mg/kg) was evaluated using the conditioned place preference (CPP) paradigm. The anxiolytic profile using the Elevated Plus Maze and circulating leptin and corticosterone levels were also assessed.

Our results show a significant escalation in the consumption of a high-fat diet between the first and the last week in both types of housed mice. Among the grouped mice, only those exposed to high-fat binge (HFB) developed CPP. Conversely, isolated mice fed with standard diet were more sensitive to the rewarding effects of a subthreshold dose of cocaine than those fed with HFB. Plasma leptin levels were elevated in both groups that developed CPP. Although isolated animals presented higher corticosterone levels with respect to the grouped ones, anxiety levels did not differ. Therefore, our results highlight the importance of housing conditions on the effects that a high-fat diet exerts on cocaine reward.

1. Introduction

Adolescence is a period of brain maturation marked by structural alterations in many limbic and cortical regions, related to major changes in emotional and cognitive functions. Drug use during this critical period of development often predicts an increased likelihood of continued use into adulthood [1–3]. Currently, there is a growing high-fat "fast-food" culture and prevalence of obesity, particularly among adolescents [4–6]. Palatable food, like drugs of abuse, causes an increase in dopamine release that is linked with its pleasurable effect [7,8]. Recent research shows that hedonic eating, defined by Gold [9] as eating based on pleasure rather than energy needs, affects neural mechanisms connected with reward and maintains this behavior [6]. Binge eating is described as an intermittent, excessive, dysfunctional appetitive behavior that occurs in short periods of time [10]. Statistics suggest that binge eating is more common than other eating disorders [11], and there is evidence of a clinical overlap between binge-eating disorders and drug addiction [12,13].

Although some results point to the fact that nutritional status is a modulating factor for the development of drug addiction [6,14], and high-fat diets may work as a gateway for the development of drug addiction [10,15], other studies did not find the same results or found the opposite [16–18]. Therefore, many studies to date are contradictory and the results are highly variable. Two factors may explain these divergent results, the continuous vs binge fat intake and the housing conditions.

There are few studies of high-fat feeding that employ grouped animals, even if this condition is the only that provides the most valuable and translational results. For example, Loebens and Barros [19] observed that a high-fat diet decreased the withdrawal effects of cocaine. Although in the Morales and co-workers [18] study, continuous access to fat decreased the preference for cocaine in the CPP paradigm, we have previously reported that grouped mice exposed to continuous access to a high-fat diet showed an increase on the conditioned

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rewarding effects of cocaine only when the diet is abruptly interrupted [20]. In addition, exposure to a high-fat binge (HFB) in grouped mice increased cocaine-induced CPP during and after this fat exposure [21].

Most studies use isolated rodents, in order to control individual food intake and body weight. For example, France's group employs isolated animals in all their studies, demonstrating that animals with a continuous access to fat are more sensitive to the locomotor effects of cocaine [22,23] and methamphetamine [24]. Other groups have also demonstrated that prenatal exposure to high-fat diets lead to a higher vulnerability to the rewarding effects of ethanol or amphetamine in the individually-housed offspring [25]. With respect to binge-eating, Puhl and co-workers [10] observed that isolated adult rats bingeing on fat were more vulnerable to the rewarding effects of cocaine self-administration. Other studies have found the opposite, showing that obesity-prone rats fed on a high-fat diet were less sensitive to the rewarding effects of cocaine [26]. Equally, an impaired acquisition of the self-administration has been observed in isolated rats with ad libitum access to a high-fat diet [16,17].

Isolation is considered one of the most potent stressors, in both humans and animals [27–29], as it can lead to behavioral, anatomical and neurochemical changes that remain during adulthood [28,30]. Adolescence is a critical period for social experiences, and the interactions between social factors and addictive behavior have been well documented in human and animal studies, suggesting that impaired social attachment during early development can enhance the susceptibility to drug addiction [31–33]. Isolation in an early stage of life produces an increase in self-administration of low doses of cocaine and amphetamine [34–38], enhancing motivation for cocaine in the progressive ratio schedule [38]. A recent study shows that isolated rats evoke a greater dopamine release than grouped rats in response to cocaine, suggesting an enhanced cocaine reinforcement [39]. In addition, several studies have shown that social isolation is related to increased adiposity, as isolated mice exhibit augmented plasma leptin levels [40–42].

In light of these previous reports, we hypothesized that the different reported results regarding the effects of high-fat feeding on drugs of abuse may be due, at least in part, to the different housing conditions used in these studies. The aim of this study is to explore how these two factors may modulate the reinforcing effects of cocaine. To achieve this objective, mice housed in groups or in isolation will be fed only with a standard diet or exposed to a high-fat binge during adolescence. The rewarding effects of cocaine were evaluated using the Conditioned Place Preference (CPP) paradigm. As it is well known that housing conditions can affect anxiety [43], we also evaluated anxiety-like behaviors with the Elevated Plus Maze (EPM) and measured circulating corticosterone and leptin levels. Thus, we hypothesized that grouped animals fed with a standard diet would not develop CPP with this subthreshold cocaine dose, but those groups that binge on fat will develop preference confirming previous results from our laboratory [21]. On the other hand, isolated animals in standard diet conditions will exhibit increased sensitivity to cocaine developing CPP, but bingeing on fat will eliminate this effect of chronic stress, acting as comfort food [44,45].

2. Methods

2.1. Subjects

A total of 60 male mice of the OF1 outbred strain were acquired commercially from Charles River (France). Animals were 21 days old on arrival at the laboratory and then, half of them were housed under standard conditions in groups of 3–4 and the other half was isolated. All the experimental procedures are in agreement 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.

2.2. Drugs

For CPP, animals were injected i.p. with 1 mg/kg of cocaine hydrochloride (Laboratorios Alcaliber S. A. Madrid, Spain) that was diluted in physiological saline. The cocaine dose of 1 mg/kg to induce CPP was based on previous studies [46] where it was shown to be a subthreshold dose to induce CPP in grouped naïve mice with a standard diet.

2.3. Procedure and apparatus

2.3.1. Feeding conditions

Our feeding procedure is based on the limited access model described by Corwin et al. [47], in which non-food-deprived animals with sporadic and limited access to high-fat food developed binge-type behaviors. Two different diets were supplied by Harlan Laboratories Models, S. L. (Barcelona, Spain): the standard diet (Teklad Global Diet 2014, 13 Kcal% fat, 67 Kcal% carbohydrates and 20% Kcal protein; 2,9 Kcal/g) and the high-fat diet (TD.06415, 45 Kcal % fat, 36 Kcal % carbohydrates and 19% Kcal protein; 4,6 Kcal/g). The standard diet was always available at the home cage and the high-fat diet was administered in a sporadic and limited way to the high-fat diet binge group (HFB).

On PND 29, in each of the housing conditions, mice were randomly divided into groups (n = 15/condition) with similar average body weight (25–26 g) and assigned either a Control (C) diet or HFB (2 h access on Monday, Wednesday and Friday). All groups of mice were fed ad libitum with the standard diet in their own cages, and 3 days a week, they were exposed to a 2 h binge session in a different plastic cage (standard diet for the control group and high-fat diet for the HFB groups). Water was freely available at all times. Binge sessions took place 2–3 h after the beginning of the dark phase. Animals were weighed every Monday, Wednesday and Friday throughout the study, and their intake on the standard diet in their home cage was also measured.

2.3.2. Experimental design

Animals developed a binge-eating pattern from PND 29 to 69 with a total of 18 binge-eating sessions, and then behavioral tests were started. On PND 69 animals performed the EPM, and from PND 70 to 77 they were conditioned with 1 mg/kg cocaine. The outcomes of behavioral tests and biochemical measurements were evaluated at the beginning of the dark phase before the binge eating session of the corresponding day. After the end of the CPP, blood samples were taken in order to measure plasmatic corticosterone and leptin levels. An overall and more detailed description of the experimental procedure is provided in Table 1.

2.3.3. Elevated Plus Maze

The EPM consisted of two open arms and two enclosed arms and a central platform, elevated 45 cm above floor level. At the beginning of each trial, subjects were placed on the central platform so that they were facing an open arm, and were allowed to explore for 5 min. The behavior displayed by the mice was recorded automatically by an automated tracking control (EthoVision 3.1; Noldus Information Technology, Leesburg, VA). The measurements recorded during the test period are generally used to characterize the anxiolytic effects of drugs [48,49]. For more details, see the previously described protocol [50].

2.3.4. Conditioning place preference

For Place Conditioning, we employed twelve identical Plexiglas boxes with two equally sized compartments separated by a gray central area. 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). The equipment was controlled by two IBM PC

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