Physiology & Behavior 101 (2010) 713–718

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Obesity-resistant S5B rats showed greater cocaine conditioned place preference than the obesity-prone OM rats

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ARTICLE INFO

Article history:
Received 8 July 2010
Received in revised form 13 August 2010
Accepted 16 August 2010

Keywords:
Addiction
Psychostimulant
Bromocriptine
Conditioned place preference

ABSTRACT

Background: Dopamine (DA) and the DA D2 receptor (D2R) are involved in the rewarding and conditioned responses to food and drug rewards. Osborne–Mendel (OM) rats are genetically prone and S5B/P rats are genetically resistant to obesity when fed a high-fat diet. We hypothesized that the differential sensitivity of these two rat strains to natural rewards may also be reflected in sensitivity to drugs of abuse. Therefore, we tested whether OM and S5B/P rats showed a differential preference to cocaine using conditioned place preference (CPP). To also evaluate whether there is specific involvement of the D2R in this differential conditioning sensitivity, we then tested whether the D2R agonist bromocriptine (BC) would differentially affect the effects of cocaine in the two strains.
Methods: OM and S5B/P rats were conditioned with cocaine (5 or 10 mg/kg) in one chamber and saline in another for 8 days. Rats were then tested for cocaine preference. The effects of BC (0.5, 1, 5, 10, 20 mg/kg) on cocaine preference were then assessed in subsequent test sessions.
Results: OM rats did not show a significant preference for the cocaine-paired chamber on test day. Only the S5B/P rats showed cocaine CPP. Later treatment with only the highest dose of BC resulted in reduced cocaine CPP in S5B/P rats when treated with 5 mg/kg cocaine and in OM rats treated with 10 mg/kg cocaine.
Conclusion: Our results indicated that obesity-resistant S5B rats showed greater cocaine CPP than the obesity-prone OM rats. These findings do not support a theory of common vulnerability for reinforcer preferences (food and cocaine). However, they show that BC reduced cocaine conditioning effects supporting at least a partial regulatory role of D2R in conditioned responses to drugs.

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1. Introduction

Obesity is one of the fastest growing public health problems worldwide. Nearly 30% of the adult US population is obese; an alarming statistic considering the increased morbidity and mortality linked with obesity, including an estimate of as many as 300,000 deaths per year in the US [1].

Similarly, drug addiction continues to be a pervasive problem worldwide. In the US alone it is estimated that 21.6 million people aged 12 or older (9.1% of the US population) need treatment for illicit drug or alcohol abuse [2]. Dopamine (DA) and more specifically DA D2 receptors (D2R) have been previously implicated in obesity as well as drug addiction and are specifically involved in the rewarding and conditioned responses to natural (food) and drug rewards [3–7].

In addition, the DA transporter (DAT) has also been implicated in both cocaine abuse and obesity. Cocaine has been known to block the action of DAT, therefore increasing levels of extra synaptic DA [8]. Clinical studies have shown that an intravenous dose of (0.3–0.6 mg/kg) cocaine produces a "high" and leads to a 60–77% blockade of DAT [8]. In obese individuals, age and body mass index were negatively correlated with DAT levels [9]. Similarly, lower levels of DAT were found in C57 mice that were fed a high-fat (40%) diet [10].

Therefore, both obesity and addiction have been linked with impaired brain DA function. Specifically for both conditions, clinical and preclinical studies have shown lower than normal levels of D2R in the striatum [11–17,2,18]. Similarly, when fed a high-fat diet, rats exhibited decreased DA turnover in the mesolimbic pathways and show reduced preference for amphetamines in the CPP paradigm [19].

Abbreviations: DA, Dopamine; D2R, Dopamine D2 receptors; OM, Osborne–Mendel rats; S5B, Obesity-resistant S5B rats; CPP, Conditioned place preference; BC, Bromocriptine.

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0031-9384/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.physbeh.2010.08.011

It follows from these observations that this shared mechanism may result in enhanced responses to natural rewards as well as drugs of abuse. We assessed this hypothesis by examining cocaine preference in two inbred rat strains with differing susceptibilities to diet-induced obesity. For this, we first examined cocaine conditioned place preference (CPP) in Osborne–Mendel (OM) rats, which favor high-fat diets over carbohydrates or proteins [20–23] and S5B/P (S5B) rats, which favor low-fat diets [20,21]. Because of these preferences, OM rats are considered susceptible to dietary obesity while S5B rats are considered obesity-resistant [20,21,23]. Furthermore, to be able to assess the role of D2R in cocaine CPP, we also assessed the effects of bromocriptine (BC), a D2R agonist drug that reduces food intake in leptin receptor deficient obese Zucker (fa/fa) and in diet-induced obese rats [24], on cocaine's reinforcing effects. We hypothesized that OM and S5B rats will show differences in CPP to cocaine and in their response to BC.

2. Methods and materials

2.1. Animals

This study used 13 OM and 13 S5B male 3–4 month old rats which were obtained from a colony at Pennington Biomedical Research Center. Rats were individually housed in clear plexi-glass cages with wire covers under standard laboratory conditions (22 ± 2 °C, 50 ± 10% relative humidity) and a reverse12 h/12 h light/dark cycle with lights on at 2000 h and off at 0800 h. All experimental sessions occurred during the rat's dark cycle. Rat chow (Lab Diet, St. Louis, MO; laboratory rodent diet 5001: 13.496% fat, 28.507% protein, 57.996% carbohydrates) and tap water were available *ad libitum*. Body weight and food intake was measured on a daily basis at 1000 h. All experiments were conducted in conformity with the National Academy of Sciences Guide for the Care and Use of Laboratory Animals [25] and Brookhaven National Laboratory Institutional Animal Care and Use Committee Protocols.

2.2. Drugs

Cocaine hydrochloride and BC were both purchased from Sigma-Aldrich (St. Louis, MO). Cocaine hydrochloride was calculated as a salt base and prepared by dissolving the cocaine in saline for doses of 5 mg/kg and 10 mg/kg. The rats were randomly assigned to the order of receiving these different cocaine doses. BC was prepared by dissolving it in an ethanol (10%), distilled water (10%) and peanut oil (80%) solution as previously described [26] to produce concentrations of 0.5 mg/kg, 1 mg/kg, 5 mg/kg, 10 mg/kg and 20 mg/kg. Both drugs were administered intraperitoneally (IP).

2.3. Apparatus

The CPP apparatus (Coulbourn Instruments, Whitehall, PA) contained three compartments. The two end compartments ($30.5 \times 26.5 \times 37$ cm) were connected by a central corridor ($12.75 \times 23 \times 15.25$ cm). The compartment on the left had black walls with a perforated stainless steel floor with round holes on staggered centers, the central corridor was transparent with a smooth plexi-glass floor, and the right compartment had white walls with a stainless steel mesh floor. Infrared activity monitors measured locomotor activity in each compartment for each session. The Graphic State 3.02 program (Coulbourn Instruments, Whitehall, PA) was used to collect the experimental variables.

2.4. Procedures: cocaine conditioned place preference (CPP)

2.4.1. Habituation

The CPP procedure consisted of the following phases: habituation, pretest, conditioning, test, reconditioning and retest (see Fig. 1 for timeline). To habituate the rats to the transportation from the animal facility to the room where the experiments were conducted, rats were brought from the animal facility to the CPP room. They were left inside the room with the lights off for 30 min prior to any experimental procedures.

2.4.2. Pretest

On day 1 of the experiment, a pretest was conducted to determine initial chamber preference. Rats were placed in the middle chamber with the doors open and were given 10 min access to all chambers without cocaine or saline. Data was recorded by photo beam breaks within each chamber to determine baseline chamber preferences.

2.4.3. Conditioning

Rats were split into randomized groups based on strain and cocaine dose resulting in 4 different groups: OM rats that received 5 mg/kg (OM 5 mg/kg; n = 6) or 10 mg/kg cocaine (OM 10 mg/kg (n = 7); and S5B rats that received 5 mg/kg (S5B 5 mg/kg; n = 7) or 10 mg/kg cocaine (S5B 10 mg/kg; n = 6). Using baseline preference measurements from pretest, rats were given cocaine in the opposite chamber of preference. Cocaine and saline were administered on alternate days just prior to the rats being placed in the CPP apparatus. Rats were only allowed access to one of the two chambers each day during the conditioning session which lasted for a total of 30 min each. This procedure continued for 8 alternating days. Locomotor activity was also measured and analyzed inside the CPP chambers during the conditioning sessions by an infrared locomotor activity sensor located in the middle of the tap panel of the chamber.

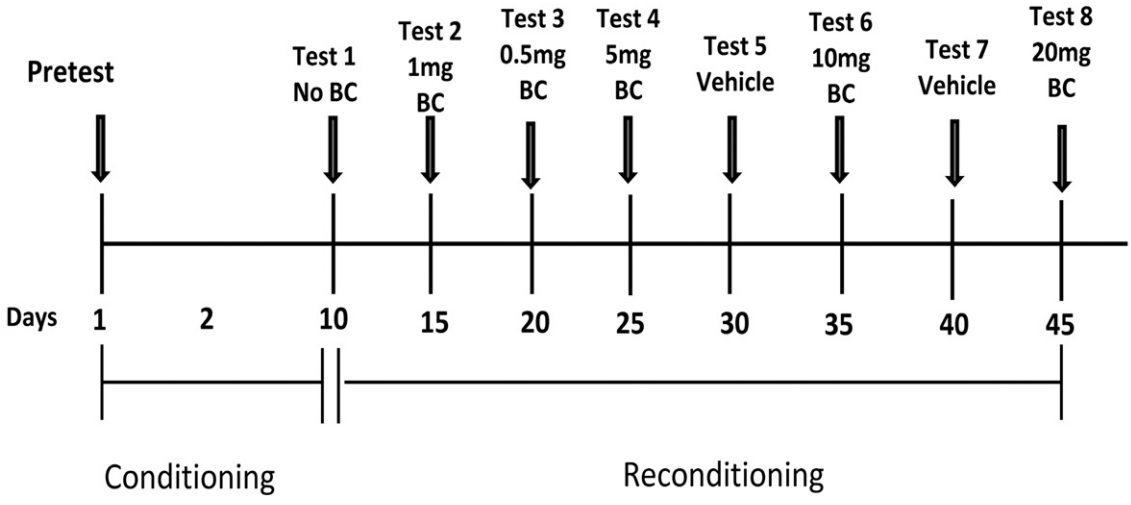

Fig. 1. Timeline of study.