



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

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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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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 ($22 \pm 2^\circ\text{C}$, $50 \pm 10\%$ relative humidity) and a reverse 12 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.

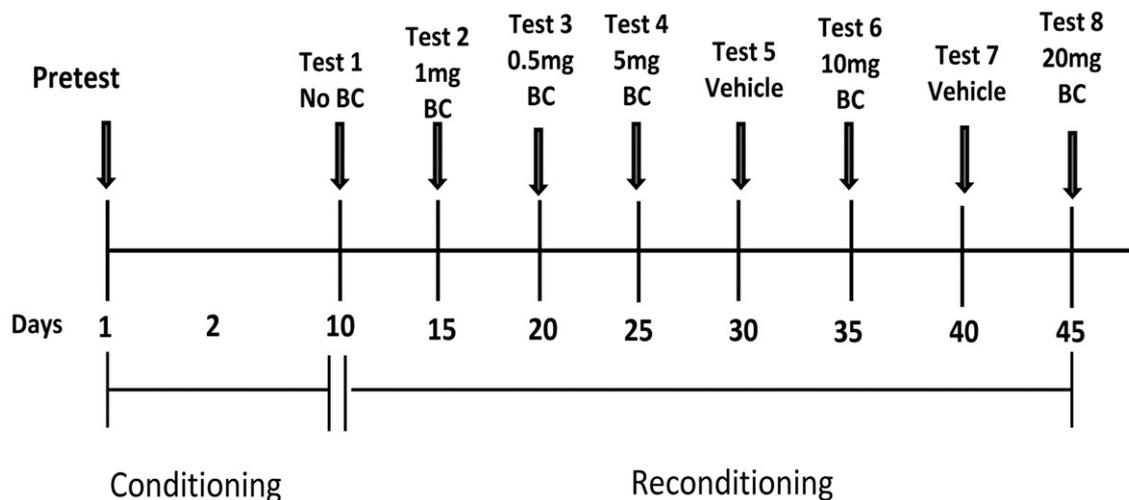


Fig. 1. Timeline of study.

2.4.4. Test

After the conditioning phase of the experiment, rats were tested for preference to cocaine. The procedure was similar to the pretest. Rats were placed in the middle chamber with doors open for 10 min and given access to both chambers. Preference to the cocaine-paired or saline paired chambers was measured by recording time spent in each box.

2.4.5. Reconditioning

After the first test session, rats were reconditioned using the same procedures as the conditioning phase of the experiment. However, instead of 8 alternating days, rats were only reconditioned for 4 alternating days.

2.4.6. Retest

After every 4 reconditioning days, rats were tested for cocaine CPP in response to different doses of BC (0.5, 1, 5, 10 and 20 mg/kg) which were administered 15 min prior to the test session. Retest procedures were identical to **Test** and **Pretest** procedures.

2.5. Data and statistical analysis

Time spent in each chamber (during testing) and locomotor activity (during conditioning sessions) was analyzed. Each rat was said to have established cocaine CPP if significantly more time was spent in the cocaine-paired chamber on test day compared to the pretest. In response to different doses of BC, time spent in the cocaine-paired chamber after BC administration was calculated and comparisons were made to the initial test day to examine if BC had any effects on the time each rat spent in the cocaine-paired chamber.

First, a two-way repeated measures analysis of variance (two-way RM ANOVA) was used to determine baseline cocaine preference (test) and subsequent cocaine preference in response to BC (retest). All pair-wise comparisons were assessed using the Holm–Sidak method. The statistical analyses were conducted using the SigmaPlot (v11.0) program.

3. Results

3.1. Cocaine conditioned place preference

A two-way RM ANOVA with test session (pretest vs. test) and group set as factors showed no significant difference between groups [$F(3, 51) = 0.594, p > .05$]; but a significant difference between test

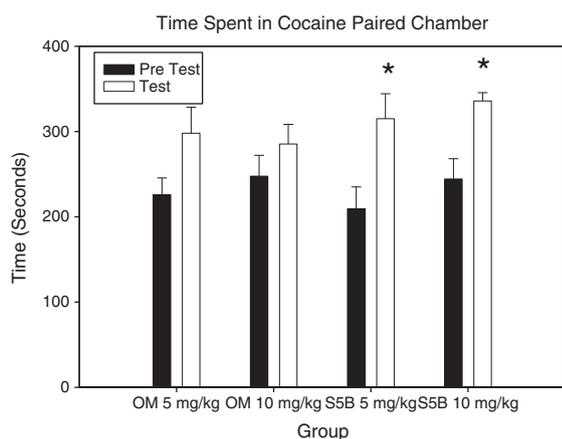


Fig. 2. Cocaine CPP. Mean time (+SEM) spent in the cocaine-paired chamber on pretest and test day. A pair-wise comparison of test sessions within each group show significant increases in time spent in the cocaine-paired chamber on test day compared to the pretest only in the S5B 5 mg/kg cocaine group ($t = 3.273, p < .05$) and the S5B 10 mg/kg cocaine group ($t = 2.624, p < .05$). *Denotes significant difference ($p < .05$) in time spent in the cocaine-paired chamber when compared to pretest.

sessions [$F(1, 51) = 20.855, p < .001$; Fig. 2]. A pair-wise comparison of test sessions within each group showed significant increases in time spent in the cocaine-paired chamber on test day compared to the pretest in the S5B rats both for the 5 mg/kg ($t = 3.273, p < .05$; Fig. 2) and the 10 mg/kg cocaine doses ($t = 2.624, p < .05$; Fig. 2). In the OM rats, cocaine only induced a trend for significance for CPP for the 5 mg/kg cocaine dose ($p = .051$; Fig. 2).

3.2. Cocaine CPP after BC treatment

A two-way RM ANOVA with test session and group set as factors showed no significant differences between groups [$F(3, 155) = 0.364, p > .05$] but showed a significant difference between test sessions [$F(5, 155) = 5.527, p < .001$ Fig. 3a and b]. Pair-wise comparisons made between test day, when BC was not administered, and subsequent test

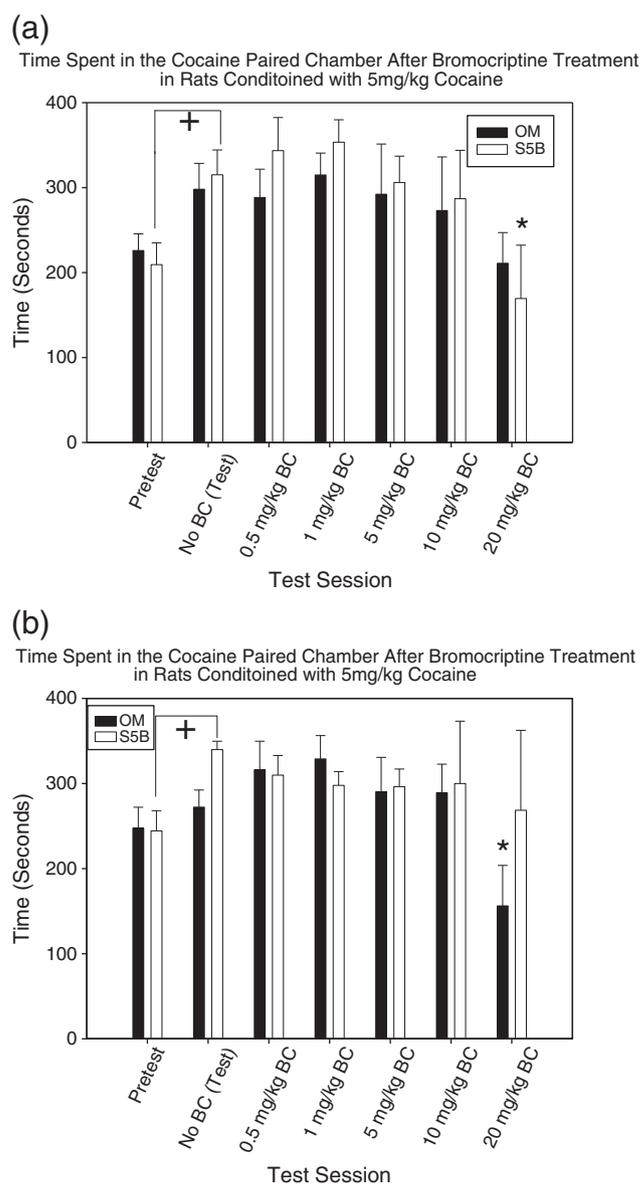


Fig. 3. (a) Mean time spent in the cocaine-paired chamber after BC treatment in rats conditioned with 5 mg/kg cocaine. Reduced CPP is only found in the S5B 5 mg/kg cocaine group ($t = 2.980, p < .05$) at the 20 mg/kg dose of BC. (b) Mean time spent in the cocaine-paired chamber after BC treatment in rats conditioned with 10 mg/kg cocaine. Reduced CPP is only found in the OM 10 mg/kg cocaine group ($t = 3.092, p < .05$) at the 20 mg/kg dose of BC.*Denotes significant difference ($p < .05$) in time spent in the cocaine-paired chamber when compared to test day (no BC). +Indicates significant increase in time spent in the cocaine-paired chamber on test day when compared to pretest.

sessions when BC was administered showed significant decreases in time spent in the cocaine-paired chamber only following the highest dose of BC (20 mg/kg) in the S5B rats when given 5 mg/kg cocaine ($t = 2.980, p < .05$; Fig. 3a) and in the OM rats when given 10 mg/kg cocaine ($t = 3.092, p < .05$; Fig. 3b).

3.3. Locomotor activity

A three-way ANOVA with strain, drug (saline or cocaine) and cocaine dose (5 vs. 10 mg/kg) set as factors show a significant difference in locomotor activity between strain [$F(1, 935) = 13.489, p < .001$; Fig. 4] and treatment [$F(1, 935) = 72.782, p < .001$; Fig. 4]. In contrast to the data on preference (Section 3.1), OM rats showed more activity than S5B rats when conditioned with 10 mg/kg but S5B rats showed more activity when conditioned with 5 mg/kg cocaine. This difference in locomotor activity was not seen when higher doses of BC

were administered. Both strains of rats showed more activity on cocaine conditioning days as opposed to saline conditioning days. The interaction between strain and drug was not significant [$F(1, 935) = 1.965, p > .05$].

3.4. Body weight and food intake

Body weight and food intake data confirmed that the two rat strains maintained their characteristic phenotypes throughout the study despite the conditioning procedures. A three-way ANOVA with test session, strain and cocaine dose set as factors show a significant difference between test session [$F(8, 35) = 70.567, p < .001$] and strain [$F(1, 35) = 1737.450, p < .001$; Fig. 5]. OM rats weighed more than S5B rats ($t = 41.683, p < .001$) and this difference was maintained throughout all test sessions (data not shown).

A three-way ANOVA with test session, strain and cocaine dose set as factors showed a significant difference between strains [$F(1, 35) = 44.328, p < .001$], as would be expected, OM rats exhibited greater food intake than S5B rats ($t = 6.658, p < .001$) (Fig. 6).

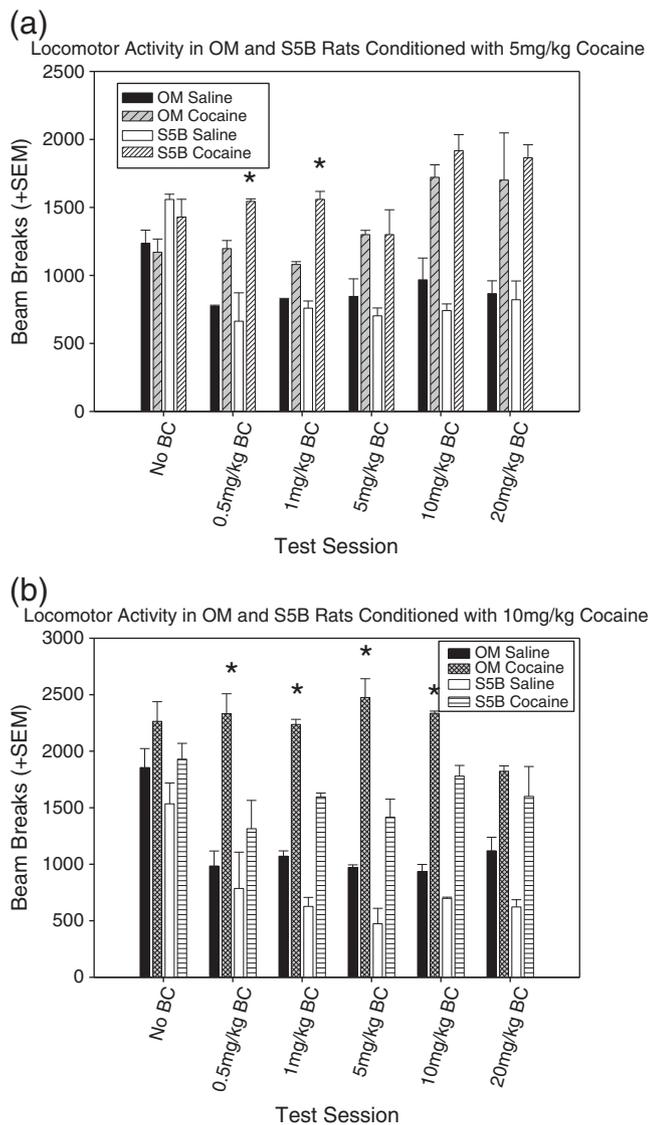


Fig. 4. (a) Locomotor activity on conditioning days in OM and S5B rats conditioned with 5 mg/kg cocaine. *Denotes significant difference ($p < .05$) compared to OM rats conditioned with the same drug. (b) Locomotor activity on conditioning days in OM and S5B rats conditioned with 10 mg/kg cocaine. OM rats showed more activity than S5B rats ($F(1, 935) = 15.255, p < .001$) and both strains of rats showed more activity on cocaine conditioning days as opposed to saline conditioning days ($F(1, 935) = 70.684, p < .001$). *Denotes significant difference ($p < .05$) compared to S5B rats conditioned with the same drug.

4. Discussion

The present study examined whether differential sensitivity to diet-induced obesity in non-obese rats would be mirrored by a similar differential sensitivity to the reinforcing motor stimulating effects of cocaine. The specific rat strains used express either genetic susceptibility or resistance to obesity and thus may serve as an appropriate model to make generalizations on drug abuse susceptibility in genetically susceptible and resistant obese populations.

Here we show that cocaine only induced a non-significant trend to CPP in the OM rats, but produced a robust CPP in the S5B rats. Despite the appeal of the notion of shared vulnerability for obesity and drug abuse, we found decreased CPP to cocaine in the obesity-prone OM rats in contrast to the CPP observed in the obesity-resistant S5B rats. Our findings are consistent with findings reported in the Fischer and Lewis rats, which also showed an opposite pattern in their sensitivity to cocaine than to food. Fischer rats, showed a greater motivation for food reward than Lewis rats whereas Lewis rats showed a greater motivation for cocaine than the Fischer rats [27]. This study together with the present study showed no cocaine preference in obesity-prone rats (OM) compared to obesity-resistant (S5B) rats. Thus, showing preference for

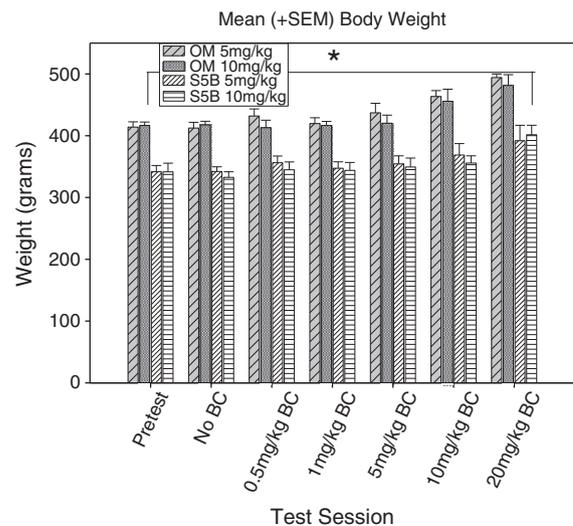


Fig. 5. Mean body weight (+SEM) between groups between test sessions. *Denotes significant ($p < .05$) difference in body weight between OM and S5B rats.

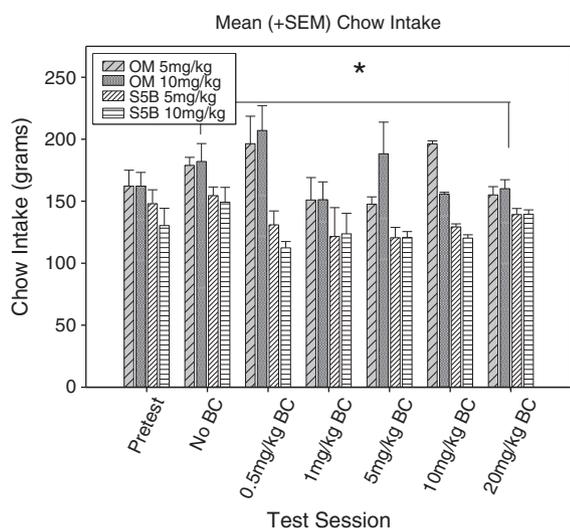


Fig. 6. Mean food intake (+SEM) between groups between test sessions. *Denotes significant ($p < .05$) difference in chow intake between OM and S5B rats.

food was associated with decreased preference for cocaine and vice-versa.

Although we used non-obese rats in this study, the two strains differed in body weight and such differences may have contributed to the CPP effects we observed. However, the strain differences in body weight between these two strains are evident across time, between sexes and even with different diets. OM rats show greater body weight than sex and age matched S5B rats at 10 weeks and 20 weeks of age, even when fed a grain diet (23.4% protein, 3% fat, 53.5 carbohydrate) [23]. However, when fed a high-fat diet (24.5% protein, 60% fat, 7.5% carbohydrate) this difference in body weight was superior and the OM rats weighed nearly twice as much as S5B rats [23]. Likewise, differences in body fat content between the two strains were only noticeable when given a high-fat diet [23].

Chronic food restriction has also been shown to lead to increased sensitivity to drug abuse [28]. Food restriction led to an increase in the reward magnitude of drugs and an increase in the locomotor inducing effects of drugs as a result of neuroadaptations and not changes in drug disposition [28]. Although OM and S5B rats in this study were not subject to food restriction, if these two strains were to be fed a different diet, one either high in fat or high in starch, as opposed to regular rat chow, the results in the CPP might have differed. Since the OM rats prefer a high-fat diet, if they were given this diet, we would predict that they would show a decrease in cocaine CPP; while an increase may be predicted in S5B rats. These predictions are based on previous studies in Sprague Dawley rats fed a high-fat diet that showed delayed acquisition of cocaine self-administration in contrast to those fed regular chow which showed cocaine self-administration acquisition in a shorter amount of time [29]. Similarly, when given a choice between water sweetened with saccharin and intravenous cocaine 94% of rats showed a preference for the water sweetened with saccharin [30]. Therefore, if OM and S5B rats were fed either a diet high in fat or starch, given their strain preferences for these diets, it is very possible that they may respond differently to cocaine.

Although OM rats did not show cocaine CPP, they were not insensitive to cocaine, showing enhanced activity during conditioning sessions to the 10 mg/kg cocaine dose. At the 5 mg/kg dose, this trend was reversed and S5B rats showed greater locomotor activity than OM rats. However, at both doses, the strain differences in locomotor activity were not seen with the highest dose of BC. This result was in contrast to previous studies where daily injections of 10 mg/kg BC for 4 weeks resulted in increased locomotor activity in diet-induced obese Sprague Dawley rats [24].

BC is a D2R agonist and previous studies have shown that it can decrease motivation for cocaine. Other studies have shown that BC may be beneficial in treating obesity and diabetes. For example, dose dependent decreases in cocaine self-administration were found if the rat was pretreated with BC [31]. Likewise, BC was found to attenuate the responding for cocaine associated stimuli [32]. In addition, BC has also been shown to decrease food intake, decrease body fat composition and increase locomotor activity in both obese Zucker rats as well as diet-induced obese rats [24,33]. In addition, BC reduced body fat composition in several different species including Djungarian hamsters, Swiss Webster mice and obese Zucker rats [26]. In the present study, it was only at the highest dose (20 mg/kg) of BC, that effects were observed, but a consistent differential effect across strain or cocaine dose was not evident. One possible explanation for this differential effect of BC is that OM and S5B rats differ in their response curve to cocaine and therefore, might be differentially affected by BC, based on the dose of cocaine. OM rats showed a greater preference for the lower dose, 5 mg/kg of cocaine. Perhaps for these rats the higher dose of 10 mg/kg cocaine was aversive or simply not as preferred. In contrast to the OM rats, S5B rats showed a preference for both doses of cocaine. These differential responses to cocaine may account for the differential effects of BC on both strain and cocaine dose. Conceivably BC efficacy is affected by specific genetic differences inherent between the two strains which remain to be defined.

This disruption of CPP is supportive of prior studies that have shown that selective DA agonists can disrupt cocaine self-administration [34–36] and CPP [37–39]. Thus, BC as shown in the present study to reduce cocaine preference should warrant further investigation with respect to clinical application, perhaps limited to only a relatively high dose. However, one is given pause in doing this as, clinical studies conducted to date have not shown a beneficial effect of BC in the treatment of cocaine addiction [40,41]. Future studies will examine the D2R availability in response to BC treatment as well as D2R levels between these two strains of rats. Furthermore, with advances in pharmacogenomics, future research may help us better understand and predict BC efficacy based on the genomic analysis of the patient.

In conclusion, our data highlight most the need to include in theoretical models of excess consumption several components of the brain's reinforcement pathways that may elicit both food and drug seeking appetitive behavior.

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