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Research report

Bromocriptine increased operant responding for high fat food but decreased chow intake in both obesity-prone and resistant rats

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ABSTRACT

Dopamine (DA) and DA D_2 receptors (D2R) have been implicated in obesity and are thought to be involved in the rewarding properties of food. Osborne–Mendel (OM) rats are susceptible to diet induced obesity (DIO) while S5B/P (S5B) rats are resistant when given a high-fat diet. Here we hypothesized that the two strains would differ in high-fat food self-administration (FSA) and that the D2R agonist bromocriptine (BC) would differently affect their behavior. Ad-libitum fed OM and S5B/P rats were tested in a FSA operant chamber and were trained to lever press for high-fat food pellets under a fixed-ratio (FR1) and a progressive ratio (PR) schedule. After sixteen days of PR sessions, rats were treated with three different doses of BC (1, 10 and 20 mg/kg). No significant differences were found between the two strains in the number of active lever presses. BC treatment (10 mg/kg and 20 mg/kg) increased the number of active lever presses (10 mg/kg having the strongest effect) whereas it decreased rat chow intake in the home cage with equivalent effects in both strains. These effects were not observed on the day of BC administration but on the day following its administration. Our results suggest that these two strains have similar motivation for procuring high fat food using this paradigm. BC increased operant responding for high-fat pellets but decreased chow intake in both strains, suggesting that D2R stimulation may have enhanced the motivational drive to procure the fatty food while correspondingly decreasing the intake of regular food. These findings suggest that susceptibility to dietary obesity (prior to the onset of obesity) may not affect operant motivation for a palatable high fat food and that differential susceptibility to obesity may be related to differential sensitivity to D2R stimulation.

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1. Introduction

The dopamine (DA) reward system is implicated in the rewarding properties of natural and drug reinforcers and its decreased function has been implicated in the vulnerability for drug addiction and obesity [1–3]. Specifically, it has been hypothesized that lower striatal D2R levels may lead to behaviors that seek to reestablish D2R activation (i.e. substance abuse or hyperphagia) [3–4].

We recently showed that obese Zucker rats (leptin-receptor deficient) had significantly lower striatal D2R levels compared to lean rats, as assessed with autoradiography [5]. Moreover, rats that were food restricted had significantly greater D2R levels compared to those that were unrestricted [5].

The relevance of DA in food consummatory behaviors is highlighted by the findings from Szczypka et al. who showed that mice that could not synthesize DA were hypophagic and died within three weeks of birth unless L-DOPA, a DA precursor, was administered [6]. Also, D2R antagonism modifies feeding behaviors and in rats has been shown to increase meal sizes and to decrease feeding rate within a meal [7]. On the other hand, administration of DA agonists normalizes body weight in genetically obese mice [8]. Bromocriptine (BC) is a D2R agonist shown to reduce BMI in individuals with prolactinomas [9]; and is approved by the FDA as treatment for type 2 diabetes [10].

The present study examined the effects of BC on operant responding for high-fat food and on regular food consumption in two different rat strains, the Osborne–Mendel (OM) and S5B\PI (S5B) rats. When exposed to a high-fat diet, the OM rats become

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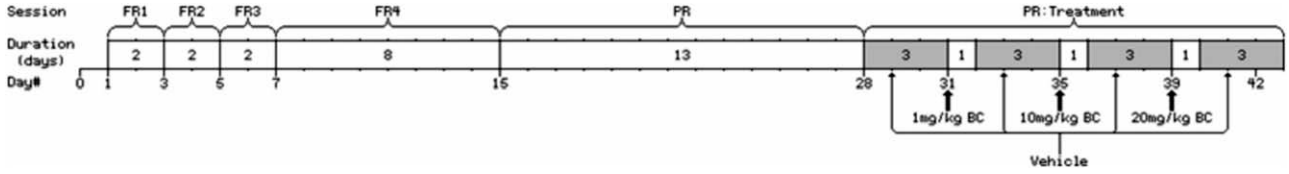

Fig. 1. Experimental timeline.

susceptible to diet-induced obesity (DIO) while the S5B rats are obesity resistant [11]. The two rat strains were examined in an operant self-administration (SA) paradigm where they could lever press for high fat food pellets, using a progressive ratio (PR) schedule. Here we examined the effects of BC on FSA behavior using a PR task and examined the effects of BC on food intake of regular chow as well as high fat pellets. We hypothesized that the OM rats would show enhanced responding for high-fat food self-administration (FSA) compared to the S5B rats in a PR task and that BC would decrease FSA in both strains.

2. Materials and methods

2.1. Animals

Male 3-month-old high fat DIO susceptible Osborne–Mendel (OM) and DIO resistant S5B/PI (S5B) rats were obtained from the laboratory of Dr. Bray at Pennington Biomedical Research Center (Baton Rouge, LA). All rats ($n = 6$/group) were individually housed with ad-libitum access to rat chow and water and kept in a 12 h/12 h light-dark reverse cycle, with the lights off at 0700 h and on at 1900 h. Experiments were performed between 1100 and 1500 h to minimize variations due to the circadian rhythm. The study was conducted in agreement with the National Academy of Sciences Guide for the Care and Use of Laboratory Animals (NAS and NRC, 1996) and Brookhaven National Laboratory Institutional Animal Care and Use Committee protocols.

2.2. Apparatus

The experiments utilized the 45 mg Dustless Precision Pellets® (Prod#: F0021 for Food Training Sessions and the 45% high fat pellets (#F05989 for the experimental sessions (Bio-Serv Inc.; Frenchtown, NJ) throughout the operant conditioning task. Clear acrylic operant test chambers measuring 32 cm × 25 cm × 33 cm were used (Coulbourn Instruments, Allentown, PA). Each test chamber was enclosed in an environment isolation chamber to minimize outside environmental stimuli. Cage floors were constructed of stainless steel horizontal bars spaced 2 cm apart. The test cages were equipped with two response levers; a reinforced and a non-reinforced lever, with cue lights located above each. Reinforced lever presses coincided with the illumination of the cue light (for 30 s; time out period) and resulted in the immediate release of a food pellet when pressed. Non-reinforced lever presses had no consequence (cue light, pellet delivery) when pressed. Locomotor activity data (total beam breaks) was collected during the operant sessions using an infrared activity monitor (Coulbourn Instruments, Allentown, PA) affixed to the back of the operant chamber. All data from the test chamber were recorded using Graphic State software version 3.5.

2.3. Procedures

Prior to each 30 min self-administration session, the body mass and food intake were measured and recorded. At the start of the SA sessions, rats were lever trained in the operant chambers with regular food pellets for six consecutive days. During the training period, rats were fasted overnight and then ran in a SA session with regular food pellets. After each session, the rats were given approximately 15 g of rat chow for the remainder of the day. By the sixth training session, rats had learned to discriminate and respond only to the active lever for food on a fixed-ratio 1 (FR1) schedule. During the remaining sessions, rats had ad-libitum access to regular rat chow in their home cages and the regular food pellets in the operant chamber were replaced with the high-fat pellets. The schedule was progressively increased from FR1 to FR4 with rats generally exposed to FR1, FR2 and FR3 scheduling for two days each, followed by FR4 for eight days (see Fig. 1 for study timeline).

Next rats were placed in a progressive ratio (PR) schedule for thirty-two days with each daily session again for 30 min in duration. The ratio series for the PR schedule was set as 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 179, 219, 268, 328 and 402 lever presses. The series was derived from the following equation:

$$\text{Response ratio (rounded to nearest integer)} = 5e^{[(\text{release number}+2)\times 0.2]} - 5$$

This series and equation is similar to others used in studies studying cocaine self-administration behavior [12], with the exception that we begin with a ratio of 4 (hence "*release number* + 2"). This change was made so that the PR ratio would begin at the last ratio the rats were trained on (i.e.: FR4).

During the 17th to the 32nd day of the PR schedule, the rats were administered vehicle intraperitoneal (IP) injections 15 min before each session with the exceptions of days 20, 24 and 28. During these days, BC (1, 10 or 20 mg/kg, respectively), was administered (see Fig. 1). Like the vehicle, BC was also administered IP 15 min before the session.

2.4. Drugs

The vehicle solutions were prepared by mixing distilled water, ethanol and peanut oil in a 1:1:8 ratio. BC (Sigma Chemical Co., St. Louis, Missouri) was similarly prepared. The 1, 10 and 20 mg/kg dose solutions were prepared by dissolving 1, 10 and 20 mg of BC, respectively, per 1 mL of vehicle solution.

2.5. Data analysis

Only the PR sessions were analyzed since the purpose of this study is to determine the effects of BC which was only administered during the PR schedule. Data from the prior training and during the FR phase was found not to be significantly different across groups or time. The PR data (active lever presses, inactive lever presses, food intake, body mass and locomotor activity) were analyzed using two way analysis of variance (ANOVA) with strain and treatment set as the factors. All pair-wise statistical comparisons were made versus the vehicle sessions preceding the days when BC was administered, using the Holm–Sidak method. All statistical tests were carried out using the SigmaPlot 11.0 software package.

3. Results

A summary of the behavior measures in this study is shown in Table 1.

3.1. Active lever presses

A two-way ANOVA of the active lever presses showed that there was no significant difference for strain [$F(1, 335) = 0.004$; $P > 0.05$] but there was for BC treatment [$F(13, 335) = 4.29$; $P < 0.001$]. A strain × treatment analysis showed no significant interaction [$F(13, 355) = 0.26$; $P > 0.05$]. Post hoc multiple pairwise comparisons (Holm–Sidak, $P > 0.05$), showed that 10 and 20 mg/kg BC treatment significantly increased lever responses (compared to vehicle; see Table 1). The increases occurred on the days following BC administration.

In OM rats, 10 mg/kg BC significantly increased active lever responses on the first (vs. vehicle: $t = 3.55$; $P < 0.001$) and second day (vs. vehicle: $t = 2.09$; $P < 0.05$) and 20 mg/kg BC significantly increased active lever presses on the first (vs. vehicle: $t = 2.63$; $P < 0.01$) and third day (vs. vehicle: $t = 2.15$; $P < 0.05$) following BC treatment.

In S5B rats, 10 mg/kg BC significantly increased active lever responses on the first (vs. vehicle: $t = 3.44$; $P < 0.005$), second (vs. vehicle: $t = 2.73$; $P < 0.001$) and third day (vs. vehicle: $t = 2.17$; $P < 0.05$) and 20 mg/kg BC significantly increased active lever presses on the first day (vs. vehicle $t = 2.93$; $P < 0.005$) following BC treatment.

3.2. Inactive lever presses

A two-way ANOVA showed no significant differences across strain in inactive lever presses [$F(1, 335) = 0.02$; $P > 0.05$], a significant treatment effect [$F(13, 335) = 2.07$; $P < 0.05$] and no strain