



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 D₂ 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 Szczytko 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/P (S5B) rats. When exposed to a high-fat diet, the OM rats become

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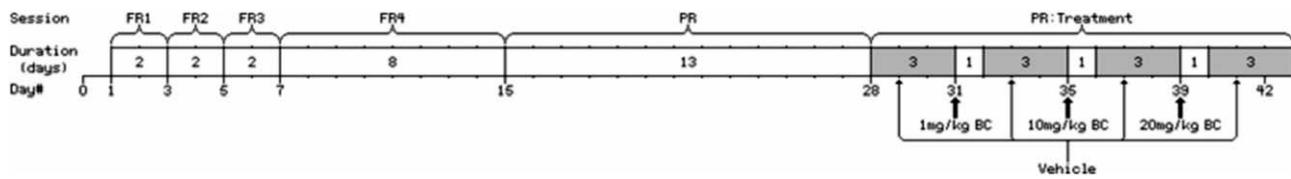


Fig. 1. Experimental timeline.

susceptible to diet-induced obesity (DIO) while the S5B rats were 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

Table 1
Summary of results.

Treatment														
Baseline	Vehicle	1 mg/kg BC schedule				10 mg/kg BC schedule				20 mg/kg BC schedule				
		BC	Vehicle 1	Vehicle 2	Vehicle 3	BC	Vehicle 1	Vehicle 2	Vehicle 3	BC	Vehicle 1	Vehicle 2	Vehicle 3	
Days 15–27	Days 28–30	Day 31	Day 32	Day 33	Day 34	Day 35	Day 36	Day 37	Day 38	Day 39	Day 40	Day 41	Day 42	
<i>Active lever presses</i>														
OM	105.0 ± 6.0	83.1 ± 15.0	106.8 ± 16.0	108.5 ± 25.0	63.5 ± 13.0	93.2 ± 27.0	135.3 ± 44.0	199.2 ± 52.0*	151.3 ± 29.0*	140.3 ± 30.0	83.5 ± 27.0	169.0 ± 59.0*	123.5 ± 21.0	153.2 ± 38.0*
S5B	91.9 ± 7.0	71.5 ± 11.0	116.7 ± 22.0	127.5 ± 26.0	108.5 ± 25.0	94.3 ± 30.0	127.7 ± 26.0	183.8 ± 31.0*	160.8 ± 20.0*	142.5 ± 25.0*	66.2 ± 21.0	167.3 ± 21.0*	117.2 ± 15.0	132.8 ± 16.0
<i>Non-reinforced active lever presses</i>														
OM	2.6 ± 0.3	3.7 ± 1.6	8.7 ± 5.1	2.2 ± 1.3	1.2 ± 0.5	4.8 ± 2.3	16.8 ± 6*	7.0 ± 2.7*	8.5 ± 3.4*	7.8 ± 3.2*	3.0 ± 1.5	10.8 ± 6.2*	8.8 ± 2.8*	10.2 ± 7.6*
S5B	3.9 ± 0.6	4.4 ± 2.0	7.7 ± 3.2	3.3 ± 1.7	5.0 ± 1.9	10.0 ± 2.7	9.8 ± 4.4	8.3 ± 3.5	6.7 ± 1.6	4.2 ± 3.0	3.0 ± 1.7	14.2 ± 7.3*	9.0 ± 1.9*	9.8 ± 1.9*
<i>Inactive lever presses</i>														
OM	5.7 ± 0.7	2.5 ± 0.7	1.2 ± 1.2	0.5 ± 0.3	0.7 ± 0.2	4.3 ± 2	2.3 ± 1.2	1.2 ± 0.8	2.7 ± 1.4	5.8 ± 4.7	4.2 ± 3.2	2.5 ± 1.3	5.0 ± 3.5	1.7 ± 0.8
S5B	6.2 ± 0.8	3.0 ± 0.9	1.7 ± 0.6	2.2 ± 1.0	2.5 ± 1.1	5.0 ± 2.1	3.2 ± 1.1	2.8 ± 0.9	3.2 ± 1.2	2.8 ± 1.6	0.8 ± 0.4*	2.2 ± 0.9	1.7 ± 0.8	4.5 ± 1.6
<i>Break point</i>														
OM	23.9 ± 1.3	20.1 ± 2.9	24.5 ± 1.8	27.3 ± 5.5	17.3 ± 2.5	21.2 ± 4.2	28.2 ± 7.9	40.7 ± 11.0*	30.8 ± 4.7*	31.7 ± 5.6*	18.7 ± 5.5	34.2 ± 9.6*	28.5 ± 3.8*	30.7 ± 6.8*
S5B	20.9 ± 1.6	17.3 ± 2.0	24.5 ± 4.1	29.5 ± 5.0*	24.0 ± 4.3	21.2 ± 6.2	28.5 ± 4.8	38.7 ± 5.2*	32.8 ± 3.6*	33.2 ± 4.4*	16.5 ± 4.4	33.7 ± 3.0*	26.8 ± 2.7*	29.5 ± 3.8*
<i>Released pellets</i>														
OM	6.4 ± 0.2	5.6 ± 0.5	6.8 ± 0.3	7.0 ± 0.8	5.3 ± 0.6	6.0 ± 0.7	6.8 ± 1.1	8.0 ± 1.8*	7.7 ± 0.6*	7.7 ± 0.8*	5.2 ± 1.2	8.2 ± 1.5	7.3 ± 0.6	7.3 ± 1
S5B	5.7 ± 0.2	5.1 ± 0.4	6.7 ± 0.7	7.3 ± 0.8*	6.5 ± 0.8	5.5 ± 1.2	7.2 ± 0.9*	8.7 ± 0.6*	8.0 ± 0.5*	8.0 ± 0.6*	4.7 ± 1.1	7.3 ± 0.4*	7.2 ± 0.5*	7.5 ± 0.6*
<i>Food intake (g)</i>														
OM	25.0 ± 0.5†	24.8 ± 1.7†	18.7 ± 0.9*	22.9 ± 1.6	23.8 ± 3.4	24.9 ± 1.9	7.6 ± 2.3*	22.8 ± 5.1	21.4 ± 4.6	21.1 ± 2.8	8.4 ± 2.4*	15.5 ± 3.9*	22.1 ± 2.9	21.0 ± 3.8
S5B	22.5 ± 0.4	19.9 ± 1.0	18.5 ± 1.0	20.8 ± 1.8	20.0 ± 1.8	23.2 ± 1.0	10.1 ± 1.5†	22.8 ± 1.0	16.2 ± 0.9	22.2 ± 1.3	9.3 ± 2.0*	16.8 ± 2.2	18.4 ± 2.1	23.4 ± 1.9
<i>Body mass (g)</i>														
OM	492.1 ± 3.3	491.4 ± 8.0	486.5 ± 12.4	483.3 ± 11.5	488.3 ± 12.4	491.3 ± 12.2	487.6 ± 12.2	476.4 ± 11.4	475.3 ± 14.8	479.9 ± 13.9	492.3 ± 16.4	479.4 ± 11.2	473.9 ± 11.5	477.9 ± 11.7
S5B	385.6 ± 3.1	384.6 ± 6.7	389.4 ± 13.1	389.5 ± 13.4	386.8 ± 13.3	389.3 ± 14.4	388.0 ± 14.0	380.4 ± 13.6	382.9 ± 13.3	386.5 ± 12.9	390.1 ± 13.9	378.8 ± 13.7	378.3 ± 13.8	381.2 ± 12.9
<i>Locomotor activity</i>														
OM	1257.6 ± 58.0	1263.4 ± 131.0	1388.3 ± 304.0	970.2 ± 172.0	814.5 ± 209.0	938.5 ± 109.0	725.2 ± 82.0	1359.3 ± 316.0	1347.0 ± 242.0	1075.3 ± 252.0	1118.5 ± 340	1164.0 ± 439.0	1327.0 ± 278.0	1443.8 ± 233.0
S5B	1684.9 ± 75.0	1643.2 ± 143.0	1259.7 ± 233.0	1605.2 ± 240.0	1179.3 ± 225.8	1396.8 ± 183.2	1131.0 ± 185.0	1438.3 ± 232.0	1448.0 ± 234.0	1560.7 ± 222.0	781.0 ± 162.0†	1484.2 ± 306.0	1044.7 ± 143†	1648.5 ± 244.0

* Significant differences ($P < 0.05$) compared to vehicle (days 28–30) for each strain.† Significant differences ($P < 0.05$) compared to S5B rats on respective days.

x treatment interaction effect [$F(13, 335)=0.33$; $P>0.05$]. Multiple pair-wise comparisons showed a significant decrease for the 20 mg/kg BC dose only in the S5B rats ($t=2.04$; $P<0.05$; Table 1).

3.3. Non-reinforced active lever presses

BC effects on non-reinforced active lever presses (lever responses on the active lever during the time out stage) are shown in Table 1. A two-way ANOVA showed no significant differences in strain [$F(1, 335)=0.03$ $P>0.05$], a significant treatment effect [$F(13, 335)=5.05$; $P<0.001$] and no significant strain \times treatment interaction effect [$F(13, 335)=0.59$; $P>0.05$]. Multiple pair-wise comparisons revealed a significant increase in non-reinforced active lever responses following BC treatment (at all three doses). Some of the increases occurred on the day of BC treatment as well as the following days. OM rats showed a significant increase in non reinforced active lever presses both for the 10 and the 20 mg/kg BC doses ($t=4.0$; $P<0.001$ and $t=2.17$; $P<0.05$; Table 1) respectively and S5B rats showed a significant increase only when treated with the 20 mg/kg BC ($t=2.96$; $P<0.005$; Table 1).

3.4. PR break point

A two-way ANOVA showed that BC had a significant effect on the break point during the progressive ratio (PR) phase (determined as the last completed ratio achieved of active responses to the acquisition of food pellets) [$F(13, 335)=4.21$; $P<0.001$; Table 1]; but no significant differences across strains [$F(1, 335)=0.001$; $P>0.05$] or the strain \times treatment interaction [$F(13, 335)=0.21$; $P>0.05$].

Pair-wise comparisons revealed that the 10 and 20 mg/kg BC doses significantly increased break point for both strains, whereas the 1 mg/kg BC dose increased the break point only in the S5B rats. The increases occurred on the days following the administration. Specifically in OM rats, 10 or 20 mg/kg BC doses significantly increased break points on the day following treatment ($t=3.43$; $P<0.001$ and $t=2.34$; $P<0.05$) respectively and in S5B rats 1, 10 or 20 mg/kg BC doses significantly increase break points on the day following treatment [($t=2.03$; $P<0.05$); ($t=3.56$; $P<0.001$) and ($t=2.72$; $P<0.01$) respectively (Table 1)]. The effects on break point following treatment with 10 mg/kg BC remained significant compared to vehicle on the second ($t=2.58$; $P<0.05$) and third day ($t=2.64$; $P<0.01$) and following 20 mg/kg BC they remained significant on the third day ($t=2.03$; $P<0.05$) following treatment.

3.5. High fat food self-administration

High fat pellet consumption did not differ significantly between the two strains [$F(1, 335)=0.11$; $P=0.739$] during the PR schedule when BC was administered. However, pair-wise comparisons revealed that significantly more fat pellets were consumed by the OM rats compared to S5B rats throughout the FR and PR phases (Table 1) and this was significant up to day 27 before any treatment ($t=2.17$; $P<0.05$).

There was a significant effect of treatment [$F(13, 335)=4.02$; $P<0.001$] and BC increased fat-food consumption. OM rats consumed significantly more high-fat pellets when treated with 10 mg/kg BC on the first ($t=2.38$; $P<0.05$), second ($t=2.05$; $P<0.05$) and third day ($t=2.05$; $P<0.05$) post-treatment when compared to days when the vehicle was administered. S5B rats consumed more fat pellets, following treatment with 1, 10 or 20 mg/kg BC doses ($t=2.16$; $P<0.05$) on the day following the administration (vs. vehicle: $t=2.16$; $P<0.05$). In S5B rats 10 mg/kg BC led to significant increases on administration day ($t=2.01$; $P<0.05$) and then one ($t=3.46$; $P<0.005$), two ($t=2.81$; $P<0.01$) and three days post treatment ($t=2.81$; $P<0.01$) and 20 mg/kg BC increased fat-

food consumption on the first ($t=2.97$; $P<0.005$), second ($t=2.01$; $P<0.05$) and third day ($t=2.33$; $P<0.05$) post treatment.

3.6. Locomotor activity

There were significant differences in locomotor activity between strains [$F(1, 335)=5.85$; $P<0.05$] (OM rats showed lower activity than the S5B rats) and treatment [$F(13, 335)=2.16$; $P>0.05$]. However, the strain \times treatment interaction was not significant [$F(13, 335)=0.84$; $P>0.05$]. Pair-wise comparisons showed that the locomotor activity of OM rats treated with BC was not significantly different from vehicle (Table 1). For the S5B rats, only the 20 mg/kg BC (compared to vehicle) significantly decreased locomotor activity ($t=2.87$; $P<0.005$) on the day of treatment ($t=1.99$; $P<0.05$).

3.7. Body weight

A two-way ANOVA on body weight showed significant differences between strains [$F(1, 334)=471.59$; $P<0.001$], no treatment effect [$F(13, 334)=0.46$; $P>0.05$] and no strain \times treatment interaction effect [$F(13, 334)=0.15$; $P>0.05$]. The pair-wise comparisons showed no significant changes for either strain in response to BC treatment (Table 1).

3.8. Home cage food intake

Home cage food intake did not differ between strains [$F(1, 334)=2.55$; $P>0.05$]; showed a significant treatment effect [$F(13, 334)=16.92$; $P<0.001$; Table 1] and no strain \times treatment interaction effect [$F(13, 335)=1.16$; $P>0.05$]. Despite the lack of significance for the strain effect on the ANOVA the pair-wise comparisons showed that the OM rats had significantly greater food intake compared to the S5B rats during baseline ($t=3.51$; $P<0.001$) and vehicle treatment ($t=2.92$; $P<0.005$). Also, 10 and 20 mg/kg BC treatments significantly decreased home cage food intake for both strains (Table 1).

In OM rats, 1, 10 mg/kg and 20 mg/kg BC significantly decreased home cage food intake on the day of administration compared to vehicle ($t=2.37$; $P<0.05$, $t=7.29$; $P<0.001$ and $t=6.95$; $P<0.001$) the 20 mg/kg BC dose also decreased it the day post administration ($t=3.91$; $P<0.001$). In S5B rats 10 mg/kg and 20 mg/kg BC significantly decreased home cage food intake on administration day ($t=4.14$; $P<0.001$ and $t=4.48$; $P<0.001$ respectively) (Table 1).

4. Discussion

4.1. Comparison of the OM and S5B strains

The OM and S5B rats did not differ significantly from one another with respect to overall reinforced and non-reinforced lever responses, inactive lever presses and break points when responding to high fat food pellets. Furthermore, the two strains did not differ in the amount of (high fat) food pellets consumed during BC treatment. This may be explained by the fact that the high fat food (pellets) in this study were presented in a progressive ratio operant task and not ad-libitum home cage consumption, as was the case for the original study by Schemmel et al. [11]. Nevertheless, OM rats had significantly great body weight and lower locomotor activity compared to S5B rats.

4.2. The effects of bromocriptine

BC had a similar effect for both rat strains with respect to the active and inactive operant lever responses, home cage food intake

and body mass. However, when break points, fatty pellet consumption and locomotor activity were considered; the S5B rats treated with BC tended to show a greater effect on behavior as evidenced by their sensitivity to the 1 mg BC dose, which had no effect on the OM rats. This may suggest that the S5B strain may be more susceptible to changes in the consumption and reward value (i.e.: break point) of fatty food pellets and in locomotor activity induced by DA stimulation of D2R by BC. The OM strain also appeared to have responded more to the BC treatment with respect to non-reinforced active lever presses (with the OM showing significant increases with 10 and 20 mg/kg BC while the S5B had a significant increase only with 20 mg/kg BC; Table 1). The greater effect that BC had on non-reinforced lever presses in the OM rats may suggest that the OM obesity prone rats may be more susceptible to compulsive/impulsive behaviors induced by changes in D2R activity. Previous studies have shown an association between impulsivity and obesity/eating disorders [13–15] and D2R [16].

BC (10 and 20 mg/kg doses), reduced home cage food intake on the day it was administered in both strains. This suggests that D2R agonism by BC may be responsible for the reduction in food intake. This may reflect direct hypothalamic effects that result in decreased appetite and/or be the consequence of increased sensitivity towards rewards induced by D2R agonism, thereby reducing the need for food intake. Indeed, we recently found that 10 mg/kg BC administration led to an increase in D2R binding in the lateral hypothalamus (LH) in obese leptin-receptor deficient Zucker rats [17]. This increase in D2R binding after BC treatment was also observed in other regions such as the striatum, nucleus accumbens shell/core and ventral tegmental area (albeit to a lesser extent) and was paralleled by decreases in food intake and adiposity. The reduction in food intake induced by D2R agonism is also supported by a previous study done by using N-0437, a selective D2R agonist [18]. In that particular study, N-0437 had a biphasic dose effect where a low dose led to increased food intake while higher doses led to decreased food intake. The increased intake induced by low doses of N-0437 was proposed to be attributed to activation of D2 autoreceptors.

BC significantly increased operant responses for the fatty food pellets. Although this was contrary to what was expected, it should be noted that the increases in reinforced operant activity were observed on days that followed the day of BC treatment. It is possible that the decreases in home cage food intake observed on the day of treatment played a role in the subsequent increases in operant response and fatty pellet consumption. It may be assumed that the reduced caloric consumption in rat's home cage may have been compensated by rats showing increased consumption of the energy dense fatty pellets. However, the problem with this assumption is that if the need to satisfy caloric intake is primarily responsible for the increased reinforced operant response, home cage food intake should return to baseline levels. This was not the case, as significant decreases in food intake persisted for days following the BC treatment. Another possibility could be that BC treatment leads to decreases in home cage or "regular" food intake, which may increase the preference for more palatable foods, such as the fatty pellets. Indeed, prenatal nutrient restriction positively influences later preference for high-fat food in young rats [19] and food restriction has also been suggested as positively influencing taste for ethanol in rats [20].

BC also significantly increased active lever presses during the time-out (non-reinforced) period. It is possible that this increase may be due dopaminergic effects, which has been shown to promote compulsivity and preservative behaviors in part by orbitofrontal–striatal activation [1,21,22].

BC treatment decreased locomotor activity in the operant chambers, although the effects were not as robust (less days with significant changes from baseline) as that observed with food intake

and operant response. The decreases in activity were observed during an operant task and not during an open field locomotor assessment as measured by previous reports that showed a positive correlation between DA activity and locomotor activity [23,24], especially with D2R [25].

BC treatment did not lead to significant changes in body weight. This is likely to reflect the fact that while BC treatment induced significant decreases in consumption of "regular" home cage food it increased consumption of fatty pellets under a progressive ratio condition. It is very likely that a loss of weight may have been seen had we not used a progressive ratio paradigm reinforced with high calorie food.

4.3. Drug and dose response

BC effects in this study appeared to be delayed (i.e.: effects did not always manifest on the day of administration) and relatively long lasting. However, it is unlikely that the observed effects were attributed to slow pharmacokinetics. In a study using ¹⁴C labeled BC, peak plasma concentrations of BC were obtained from rats 1–2 h after oral administration, thereby deeming unlikely the possibility that slow absorption of BC is responsible for its delayed effects [26]. Similarly, the DA action of BC peaked after 2–3 h and was eliminated 6–8 h after IP administration in the rat [27], which raises the question as to why there is a delayed and prolonged drug response. Thus we cannot exclude the possibility that the delayed effect from BC may reflect withdrawal effects that follow BC administration and resulting in an enhanced motivational drive for the high palatability food.

5. Conclusions

BC treatment led to decreased consumption of regular (home cage) food, but increased consumption of high-fat food similarly in OM and S5B rats. Thus, long-term BC treatment needs to be further examined given the possibility of a potential enhancement of the motivational drive for highly palatable foods. This is especially important, given that BC was recently approved to manage type 2 diabetes [10]. In addition, to better understand these results, future studies will examine the D2R availability in response to BC treatment as well as D2R levels between these two strains of rats.

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