BENEFICIAL EFFECT OF BROMOCRIPTINE ON HIGH FAT DIET-INDUCED BODY WEIGHT GAIN, ADIPOSITY AND BIOCHEMICAL ANOMALIES IN WISTAR RATS

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Received: 16 February 2017, Revised and Accepted: 01 April 2017

ABSTRACT

Objectives: Dopamine plays a critical role in various vital functions, including hormonal regulation, reward, emotions, and food intake. It affects on the multiple aspects of food intake that include food selection, satiety, and energy expenditure. Dopamine D2 receptors (D2R) were found to be lower in several brain regions in both obese experimental animals and humans, and it has been observed that dopamine D2 agonist bromocriptine (BC) can exert favorable metabolic changes in seasonal obesity. The aim of this study was to investigate the beneficial effect of chronic administration of BC a central dopamine receptor agonist on body weight gain, adiposity, and biochemical anomalies in rats.

Methods: In this study, chronic administration of BC (2.5 and 5 mg/kg/day, ip) a dopamine agonist for 8 weeks along with high-fat diet (HFD) to the obese rats which were pretreated with HFD feeding for 8 weeks on the various parameters of obesity were analyzed. The effects of these treatments on body weight, feed intake (kcal), weight and size of fat pads, levels of serum glucose, triglycerides (TG), total cholesterol (TC), high-density lipoproteins (HDL), and low-density lipoprotein were analyzed.

Results: Treatment with BC (2.5 and 5 mg/kg/day, ip) produced significant dose-dependent decrease (p<0.05) in body weight gain, feed intake (kcal), weight and size of fat pads, levels of serum glucose, TG, TC, and low-density lipoproteins as compared to HFD group. Moreover, the level of serum HDL was increased as compared to HFD group. BC, a dopamine receptor agonist positively modulate the parameters of obesity, and the effect was comparable to orlistat, a well-reported drug for obesity.

Conclusion: In conclusion, the study demonstrates that BC ameliorated established obesity and associated biochemical consequences.

Keywords: Obesity, Bromocriptine, High-fat diet, Dopamine.

INTRODUCTION

Obesity has become a serious and rising public health problem worldwide, affecting people across all ages, sex, ethnicities and races and its prevalence has been increasing at an alarming rate [1]. It is no more viewed as a cosmetic issue, but it becomes a potential risk factor of various comorbidities, such as type 2 diabetes, cardiovascular morbidity, and cancer [2,3]. Excessive fat accumulation in the body not only adversely affect on health but also impaired the quality of life, and it presents a significant challenge to future health-care budgets [4,5]. The psychological consequences are also severe and include body image disarrangement and among the severely obese, depression [6-8]. Obesity is an imbalance between energy intake and expenditure [9], i.e., more food is consumed than utilized, leading to excess fat stores being laid down. Freely available high-calorie food, sedentary lifestyle and many environmental factors predispose individuals to gain weight. Genetic factors also contribute to this imbalance [10]. In the severely obese, surgical intervention may be necessary. An alternative approach is to develop therapeutic agents that can either reduce food consumption or increase energy utilization. Despite intensive research on obesity pathogenesis, an effective therapeutic strategy to treat and cure obesity is still lacking. At present, only a few FDA-approved anti-obesity drugs such as orlistat, lorcaserin, phentermine-topiramate, and naltrexone-bupropion are available in the market, but they have considerable side effects [11]. Exciting studies in past decades have established the importance of neural pathway in the hypothalamus in the regulation of body weight homeostasis. Recent research significantly expanded the list of neurotransmitters involved in body weight regulating neural pathways [12]. Understanding the function of neurotransmitters released from key neurons for energy balance regulation is essential for delineating neural pathways and eventually for designing effective therapeutic drugs against the obesity epidemic. Considerable efforts have been devoted to the development of weight control medications that target neurotransmitters in the brain that regulate food intake [13]. Several neurotransmitters (dopamine, GABA, norepinephrine, and serotonin), as well as peptides and amino acids, are involved in the regulation of food intake [14]. The cerebral mechanisms underlying the behaviors that lead to pathological overeating and obesity are poorly understood [15]. Dopamine, a neurotransmitter in the mammalian brain plays, a critical role in various vital functions, including hormonal regulation, reward, emotions, and food intake. It affects on the multiple aspects of food intake that include food selection, satiety, and energy expenditure [16,17]. Several lines of research indicate that abnormal dopaminergic neurotransmission could be involved in pathophysiological processes leading to obesity. Most of these studies are focused on the hypothalamic dopaminergic transmission that is believed to play a pivotal role in the guidance of fuel flux and energy homeostasis [18]. In general, these investigations have indicated a decreased dopaminergic signaling in obese subjects. For example, dopamine D2 receptors (D2R) were found to be lower in several brain regions in both obese experimental animals and humans, and it has been observed that dopamine D2 agonist bromocriptine (BC) can exert favorable metabolic changes in seasonal obesity [19]. The aim of this study was to investigate the beneficial effect of chronic administration of BC a central dopamine receptor agonist on body weight gain, adiposity, and biochemical anomalies in rats.
METHODS

Drugs and chemicals
Casein (Modern Diary, New Karnal, India) and cholesterol (Thomas Baker, Mumbai, India) were used to prepare high-fat diet (HFD). BC was purchased from local market. Orlistat (Sigma-Aldrich) is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanylmethyl]dodecyl ester. All the drugs were dissolved in dimethyl sulfoxide (DMSO; 10%, v/v). The estimation kits for serum glucose, cholesterol, triglycerides (TG), and high-density lipoproteins (HDL) were obtained from (Reckon Diagnostics [P] Ltd. Vadodara, India). All other chemicals used in this study were of analytical grade. All drug solutions were freshly prepared before use.

HFD-induced obesity
Experimental obesity was induced by feeding HFD (containing; powdered normal chow [NC], 365 g; lard, 310 g; casein, 250 g; cholesterol, 10 g; vitamin mix and mineral mix, 60 g; dl-methionine, 03 g; yeast powder, 01 g; NaCl, 01 g were added to make 1.0 kg of diet) to rats [20]. The HFD contained 5.33 Kcal/g while the NC contains 3.80 Kcal/g. This diet provides 68% energy as carbohydrate, 20% as protein and 12% as fat to produce obesity in rats while as NC provides 65% of energy as carbohydrate, 20% as protein, and 4% as fat [21].

Animal treatment
Male Wistar rats of 7-8 weeks of age were procured from the animal facility of the Institute. The animals were housed in polypropylene cages (two rats/cage) and maintained under controlled room temperature (25±2°C) with 12:12 hrs light and dark cycle. The guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India were followed, and prior permission was sought from the Institutional Animal Ethics Committee for conducting the study. Animals were fed with NC or HFD for 8 weeks. Animals were divided into different groups and each group contained 6 animals. Animals fed on NC were continued on the same diet for further 8 weeks and were assigned as Group 1. HFD fed animals randomized on the basis of their body weight and divided into different 5 groups (Group 2-6), and these groups were continued on HFD for another 8 weeks. Group 2 was not given any treatment and assigned as HFD control. Group 3 was given DMSO 1 ml/kg day⁻¹, i.p [22] and assigned as vehicle control. Group 4 was given orlistat 30 mg/kg day⁻¹, p.o. [21] and assigned as a standard control. Groups 5 and 6 were given BC 2.5 and 5 mg/kg day⁻¹, i.p, respectively [23]. All the animals had free access to water, and the animals were inspected daily. Food intake and body weight were measured twice weekly. At the end of the stipulated period, blood for various biochemical parameters was obtained by retro-orbital puncture under light ether anesthesia, and the animals were sacrificed by cervical dislocation. The blood was collected into tubes, serum separated, and analyzed on the same day. The epididymal, mesenteric, and retroperitoneal white adipose tissue (WAT) were dissected, cleaned of, weighed and stored in 10% buffered formalin solution for histological analysis. Lee index was also significantly increased in obese rats as compared to normal rats (Fig. 1a). Lee index. Administration of DMSO (10% v/v DMSO, 1 ml/kg) from 9 to 16 weeks did not affect HFD induced increase in body weight, adipose pads weight, and Lee index. Administration of orlistat (30 mg/kg) a standard drug of obesity from 9 to 16 weeks produced a significant reduction in body weight gain, adipose pads weight, and Lee index in obese rats (Table 2).

Effect of various pharmacological interventions on biochemical parameters
Obese rats after 16 weeks of HFD feeding had significantly increased body weight and total fat content then the age-matched normal control rats (Fig. 1a and b). Blood parameters were measured using commercially available kits. All values are expressed as mean±SD. The significance of the differences between the means of various groups was established by one-way ANOVA followed by Tukey’s multiple range test. DMSO: Dimethyl sulfoxide. The p<0.05 was considered to be statistically significant.

RESULTS

Administration of HFD for 8 weeks significantly (p<0.05) increased body weight of animals then the age-matched normal control rats, and there was no significant difference of body weights of animals between the various treatment groups before initiation of treatment (Table 1).

Effect of various pharmacological interventions on body weight, adipose tissue weight, and Lee index
Obese rats after 16 weeks of HFD feeding had significantly increased body weight and total fat content then the age-matched normal control rats (Fig. 1a and b). Blood parameters were measured using commercially available kits. All values are expressed as mean±SD. The significance of the differences between the means of various groups was established by one-way ANOVA followed by Tukey’s multiple range test. DMSO: Dimethyl sulfoxide. The p<0.05 was considered to be statistically significant.

Effect of various pharmacological interventions on adipocyte size
Histological examination of epididymal WAT revealed that HFD fed rats had markedly increased adipocyte size than did NC fed rats. BC (2.5 and 5 mg/kg) or orlistat (30 mg/kg) markedly suppressed epididymal adipocyte size compared to HFD fed rats. While DMSO (10% v/v DMSO, 1 ml/kg) did not suppress these adipose tissue size as compared to HFD rats (Fig. 2).

Table 1: Body weight of animals at 0 week, at the end of 8th week and at the end of 16th week

<table>
<thead>
<tr>
<th>Groups</th>
<th>Initial body weight</th>
<th>Body weight at the end of 8th week</th>
<th>Body weight at the end of 16th week</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>22±1.9</td>
<td>24±1.3</td>
<td>26±1.7</td>
</tr>
<tr>
<td>HFD-C</td>
<td>233±11.9</td>
<td>321±11.5</td>
<td>399±16.2</td>
</tr>
<tr>
<td>Vehicle control (10% v/v DMSO, 1 ml/kg)</td>
<td>234±11.9</td>
<td>316±11.5</td>
<td>397±13</td>
</tr>
<tr>
<td>Orlistat (30 mg/kg)</td>
<td>236±11.9</td>
<td>309±13.6</td>
<td>29±14.6</td>
</tr>
<tr>
<td>Bromocriptine (2.5 mg/kg)</td>
<td>229±12.8</td>
<td>318±13.7</td>
<td>324±11.6</td>
</tr>
<tr>
<td>Bromocriptine (5 mg/kg)</td>
<td>282±110.8</td>
<td>311±13.7</td>
<td>305±13.29</td>
</tr>
</tbody>
</table>

All values are expressed as mean±SD, n=6, one-way ANOVA followed by Tukey’s multiple range test. DMSO: Dimethyl sulfoxide. *p<0.05 versus NC. Normal control, 1p<0.05 versus HFD-C. Obese high-fat diet control, SD: Standard deviation
Effect of various pharmacological interventions on daily feed intake (Kcal)

In HFD model, a significant increase (p<0.05) in feed consumption (Kcal) was observed as compared to NC-fed rats (Fig. 1g). Orlistat (30 mg/kg) which was standard control in this study significantly decreases the feed consumption as compared to HFD fed rats. Administration of DMSO (10% v/v DMSO, 1 ml/kg) from 9 to 16 weeks did not affect feed consumption of animals as compared to HFD fed rats. The food intake was significantly decreased by the administration of BC (2.5 and 5 mg/kg) from 9 to 16 weeks (Table 2).

DISCUSSION

In this study, experimental obesity was developed by long-term HFD treatment. HFD have been previously reported to increase energy intake and cause obesity in humans as well as animals [25,26]. The body weight gain observed in this study is consistent with studies in
In this investigation, it has been observed that administration of BC in the low and high dose for 8 weeks to the obese rats which were continued on high-fat diet for further 8 weeks.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NC</th>
<th>OIHF-C</th>
<th>Vehicle control (10% v/v DMSO)</th>
<th>Orlistat (30 mg/kg)</th>
<th>Bromocriptine (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial body weight (g)</td>
<td>222±9.3</td>
<td>233±8.1</td>
<td>234±7.9</td>
<td>236±1.9</td>
<td>229±2.8</td>
</tr>
<tr>
<td>Final body weight (g)</td>
<td>282±7.8</td>
<td>399±16.2</td>
<td>397±13.3</td>
<td>299±14.6</td>
<td>324.5±11.6</td>
</tr>
<tr>
<td>Lee index</td>
<td>348±9.2</td>
<td>389±16.7</td>
<td>394.1±14</td>
<td>361±2.14</td>
<td>379.3±16.9</td>
</tr>
<tr>
<td>Feed intake kcal day⁻¹</td>
<td>92±7.1</td>
<td>1171±8.8</td>
<td>110.15±10.4</td>
<td>85±12.8</td>
<td>104.4±9.9</td>
</tr>
<tr>
<td>Epidydimal fat</td>
<td>1.75±0.23</td>
<td>5.25±0.94</td>
<td>5.26±0.9</td>
<td>1.90±0.32</td>
<td>2.1±0.15</td>
</tr>
<tr>
<td>Retipertimental fat</td>
<td>1.56±0.29</td>
<td>5.8±0.87</td>
<td>5.78±0.89</td>
<td>1.96±0.29</td>
<td>2.4±0.52</td>
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<tr>
<td>Mesentric fat</td>
<td>2.1±0.19</td>
<td>6.5±0.95</td>
<td>5.71±0.74</td>
<td>2.6±0.38</td>
<td>2.9±0.67</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>94±5.5</td>
<td>150.5±6.47</td>
<td>149.6±5.8</td>
<td>96.7±4.9</td>
<td>101.1±5.9</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>67.7±4.4</td>
<td>146.5±10.65</td>
<td>145.5±10.4</td>
<td>71±5.17</td>
<td>80.4±2.2</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>95.9±4.1</td>
<td>163±12.64</td>
<td>162.6±12.8</td>
<td>95.8±15.9</td>
<td>100.8±4.8</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>49.8±5.7</td>
<td>110.3±12.54</td>
<td>110.9±11.5</td>
<td>49.4±7.06</td>
<td>54.6±4.4</td>
</tr>
<tr>
<td>VLDL (mg/dL)</td>
<td>13.5±0.89</td>
<td>29.3±2.13</td>
<td>29.1±2</td>
<td>14.2±1.03</td>
<td>16±4.2</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>32.5±2.19</td>
<td>23.3±2.94</td>
<td>22.6±1.75</td>
<td>32.1±2.85</td>
<td>30.1±1.9</td>
</tr>
</tbody>
</table>

All values are expressed as mean±SD, n=6, one-way ANOVA followed by Tukey’s multiple range test. DMSO: Dimethyl sulfoxide, TG: Triglycerides, TC: Total cholesterol, LDL: Low-density lipoproteins, VLDL: Very low-density lipoproteins, HDL: High-density lipoproteins. *p<0.05 versus NC. Normal control, *p<0.05 versus OIHF-C: Obese high-fat diet control. SD: Standard deviation

The results from this study have implications for the treatment of obesity since they would suggest that strategies aimed at improving dopamine function might be beneficial in the treatment of obese individuals. In animal models, exercise has been found to increase dopamine release, [37] and to raise D2R [38]. Further research to identify treatment approaches that enhance the function of the dopamine system as a means to promote long-term maintenance of weight control is warranted. This data demonstrate that D2R agonist has the potential to work by reduce food intake in obese rats. Hence, it has been observed that BC plays major beneficial role in obesity; also, this study has provided a rational pharmacological basis for the use of BC in obesity.

**CONCLUSION**

In conclusion, this data provide the first evidence that BC positively alters the various parameters of obesity. BC shows these effects by acting on dopaminergic receptor in the brain, it may decreases food intake in obese rats. These findings suggest that dopamine agonist BC could be new therapeutic reagents for obesity.

**ACKNOWLEDGMENT**

We are very thankful to Chandigarh College of Pharmacy, Landran and IKGPTU Jalandhar, for their support.

**REFERENCES**


