Bromocriptine Effect in Spontaneous Motor Activity Using Albino Mice

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ABSTRACT

Bromocriptine is a potent agonist at the D2 receptor. The aim of this study is to investigate the bromocriptine effect in spontaneous motor activity, using variable doses with acute and subacute administration and variable onset of measurement using albino mice. Acute intraperitoneal administration of bromocriptine using doses of 0.625, 2.5, 5, and 10mg/kg and the control group administration of 1% tween 80 (n=7) were used. Spontaneous motor activity was scored after 30 and 60min of administration. Subacute administration is as follows: group 1 was administered 1% tween 80 as a control and group 2 was administered 10mg/kg bromocriptine. Spontaneous motor activity was scored using an open field test. Acute administration of bromocriptine after 30min (0.625 and 2.5mg/kg) did not show any significant changes in spontaneous motor activity while 5 and 10mg/kg produced a significant decrease. Acute administration of bromocriptine after 60min produced a significant decrease in spontaneous motor activity, with 0.625, 2.5, 5, and 10mg/kg doses. Subacute administration of bromocriptine significantly increased spontaneous motor activity, compared to control. It is concluded that acute administration of bromocriptine at 30min decreased spontaneous motor activity, only with higher doses while its acute administration after 60min decreased spontaneous motor activity, with all doses (0.625, 2.5, 5, and 10mg/kg). As subacute administration increased spontaneous motor activity, these findings conclude that bromocriptine which produced its effect in spontaneous motor activity is time and dose dependence.

Keywords: Bromocriptine, spontaneous motor activity, open field.

INTRODUCTION

Bromocriptine is an ergoline derivative; it is a potent agonist at dopamine D2 receptors and various serotonin receptors. It inhibits the release of glutamate, by reversing the glutamate (GLT1) transporter. Bromocriptine has been used for the treatment of Parkinson’s disease and has also been found valuable in the treatment of a number of endocrinologic and gynaecologic disorders. As amenorrhea, female infertility, galactorrhea, hypogonadism, and acromegaly may be caused by pituitary problems such as hyperprolactinaemia, bromocriptine is believed to exert its antidiuretic actions from its influence on hypothalamic circadian neuronal activities thus resetting an abnormally elevated hypothalamic drive for an increase in plasma glucose, free fatty acids, and triglycerides in patients with type 2 diabetes.

Bromocriptine use has been associated with causing or worsening psychotic symptoms (its mechanism is in opposition to most antipsychotics, whose mechanisms generally block dopamine). In 2009, bromocriptine mesylate was approved by the FDA for treatment of type 2 diabetes. It is currently unknown how this drug improves glycemic control, but it has been shown to reduce HbA1c by ~0.5 percentage points.

MATERIALS AND METHODS

Drugs and Chemicals

Bromocriptine was purchased from MedaPharma
S.P.A. Milano and Tween 80 was obtained from Riedel-De Haen AG Seelze, Hannover, Germany.

**Test Animals**

Male albino mice (25±5grams) were bred in the animal house of the Faculty of Pharmacy, University of Tripoli. Each group was housed separately in a cage. Food and water were available ad lib. The animals were kept at constant room temperature (25±2°C) and a twelve hour dark/light cycle and fasted overnight before each experiment. The experimental protocol has been approved by the Institutional Animal Ethical Committee of the Tripoli College of Pharmacy(TCP/IAEC; 2011).

**Experimental Procedure**

**Open-field (Photocell)**

The open field test or the photocell is a square area (45x45 cm) with a glass floor and outer square area (height 20 cm) to prevent the mice from escaping. There were vertical and horizontal photocell detectors on the two sides of the box, which received infrared light from the opposed side of the box. Each time the animal moves in the cage it will interrupt the light beam, which will activate a counter recorder and detect the number of movements of the mouse during the experiment time.9 The test was performed in a closed room under a low level of illumination,10 under constant conditions of temperature and humidity. Experimental time was fixed between (9am-1pm). Each animal was placed at the centre of the apparatus and observed for four minutes.11 The ambulatory activity (movements from one place to another without purpose), and non-ambulatory activity (movements of the animal at the same place) were recorded automatically. The animal was tested only once and did not have any prior exposure to the open field test.

**Procedure**

Bromocriptine was administered by the intraperitoneal (i.p.) route. A volume of 0.5ml/100g of the body weight was adopted for all experiments.8 One percent Tween 80 (1% T80) in water was used as a suspending agent. Bromocriptine was freshly prepared.

Three experimental methods were carried out. The first experiment involved six groups. The first group which was considered as a control group received a single dose of 1% T80 while the second group to the sixth group received a single dose of 0.625, 1.25, 2.5, 5, and 10mg/kg bromocriptine, respectively. The ambulatory and non-ambulatory movements were scored after 30 minutes using an open field test (photocell). The second experiment was carried out as the first, but the ambulatory and non-ambulatory movements were scored after 60 minutes. The third experiment involved two groups, the first group received subacute administration (12, 5, and 1hr before scoring the SMA) of 1%T80 while the second group received 10mg/kg bromocriptine.

**Statistical Analysis**

Statistical analyses were conducted using SPSS (software packing version 13) for an IBM compatible computer. Descriptive statistical analysis was applied; the non-parametric Kolmogorov-Smirnov maximum deviation test for goodness of fit was applied to find out whether the observed samples were normally distributed or not. If the parameters were normally distributed, treatments were compared by applying one-way ANOVA. Post hoc tests (LSD) were performed. If the parameters were non-parametric, treatments were compared by applying the Mann-Whitney two samples (non-matched) test. The difference was considered significant at ($P \leq 0.05$).

**RESULTS AND DISCUSSION**

Spontaneous motor activity (SMA) after acute and subacute (i.p.) administration of bromocriptine, using male albino mice, was studied. Measurement of SMA was evaluated at different times with different doses of bromocriptine using the open field test.

Acute administration of bromocriptine decreased the SMA; although the small doses (0.625, 1.25, and 2.5mg/kg) needed 60 minutes to produce a significant decrease, higher doses (5and 10mg/kg) showed a significant decrease in SMA after 30 and 60 minutes when compared with the control group ($P \leq 0.05$). The acute administration of bromocriptine (10 mg/kg) showed a significant decrease in SMA after 30 minutes as compared with 0.625, 1.25, and 2.5 mg/kg bromocriptine but not with 5 mg/kg. A bromocriptine dose of 2.5 mg/kg produced a significant decrease in SMA compared to...
0.625, 1.25, and 10mg/kg bromocriptine after 60 minutes but not with the dose of 5 mg/kg (P ≤ 0.05), see tables 1 and 2.

### Table 1: Effect of acute administration of bromocriptine on ambulatory movement using photocell

<table>
<thead>
<tr>
<th>Treatment (n=7)</th>
<th>Ambulatory movements Onset (mean ± S.E)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Scoring after 30 min</td>
<td>Scoring after 60 min</td>
<td></td>
</tr>
<tr>
<td>1% Tween 80</td>
<td>80.43 ± 7.35</td>
<td>96.57 ± 8.94</td>
<td></td>
</tr>
<tr>
<td>Bromocriptine 0.625 mg/Kg</td>
<td>64.43 ± 9.23</td>
<td>69.71 ± 6.67</td>
<td>#</td>
</tr>
<tr>
<td>Bromocriptine 1.25 mg/Kg</td>
<td>68.00 ± 7.77</td>
<td>57.86 ± 12.00</td>
<td>#</td>
</tr>
<tr>
<td>Bromocriptine 2.5 mg/Kg</td>
<td>61.86 ± 12.22</td>
<td>32.86 ± 5.55</td>
<td>#</td>
</tr>
<tr>
<td>Bromocriptine 5 mg/Kg</td>
<td>46.71 ± 4.46</td>
<td>51.29 ± 9.27</td>
<td></td>
</tr>
<tr>
<td>Bromocriptine 10 mg/Kg</td>
<td>25.57 ± 2.97</td>
<td>59.00 ± 5.48</td>
<td></td>
</tr>
</tbody>
</table>

The values are the means (counts) ± S.E.; # significantly different from the control group at p ≤ 0.05; * Significantly different from bromocriptine 10mg/kg treated group after 30 minutes at p ≤ 0.05; µ Significantly different from bromocriptine 2.5 mg/kg treated group after 60 minutes at p ≤ 0.05.

### Table 2: Effect of acute administration of bromocriptine on non-ambulatory movements using photocell

<table>
<thead>
<tr>
<th>Treatments (n=7)</th>
<th>Non-ambulatory movements Onset of measurements</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Scoring after 30 min</td>
<td>Scoring after 60 min</td>
<td></td>
</tr>
<tr>
<td>1% Tween 80</td>
<td>82.57 ± 6.40</td>
<td>105.71 ± 8.17</td>
<td></td>
</tr>
<tr>
<td>Bromocriptine 0.625 mg/Kg</td>
<td>79.00 ± 10.23</td>
<td>80.57 ± 7.61</td>
<td>#</td>
</tr>
<tr>
<td>Bromocriptine 1.25 mg/Kg</td>
<td>78.71 ± 9.56</td>
<td>70.14 ± 13.14</td>
<td>#</td>
</tr>
<tr>
<td>Bromocriptine 2.5 mg/Kg</td>
<td>64.86 ± 8.35</td>
<td>42.29 ± 8.05</td>
<td>#</td>
</tr>
<tr>
<td>Bromocriptine 5 mg/Kg</td>
<td>53.14 ± 6.53</td>
<td>60.29 ± 10.06</td>
<td></td>
</tr>
<tr>
<td>Bromocriptine 10 mg/Kg</td>
<td>31.71 ± 3.05</td>
<td>69.00 ± 4.78</td>
<td>#</td>
</tr>
</tbody>
</table>

The values are the means (counts) ± S.E.; * significantly different from the control group at p ≤ 0.05; # Significantly different from bromocriptine 10 mg/kg treated group after 30 minutes at p ≤ 0.05; µ Significant different from bromocriptine 2.5 mg/kg treated group after 60 minutes at p ≤ 0.05.
Subacute administration of bromocriptine (10mg/kg) produces a significant increase in SMA when compared with the control group (P ≤ 0.05, table 3). These results corroborate with the findings from other studies which concluded that bromocriptine (5–20 mg/kg) produced dose-dependent and long lasting locomotor stimulation in mice.15 Bromocriptine increased motor activity that followed an initial period of hypomotility.13, 14, 15 Another study showed that very low doses of D2 agonist inhibited spontaneous locomotion, while higher doses modestly induced locomotion.16 Autoreceptor-activating doses of dopamine (DA) agonists reduced spontaneous activity in a novel environment.17 D2 agonist had a biphasic effect: the lowest dose decreased and the high doses increased the amount of locomotion of movement.18 The reduction in locomotion provoked by a "low" dose of D2 receptor agonist may be mediated by D2 autoreceptors, but the role of postsynaptic D3 receptors cannot be excluded.19 Other studies showed that bromocriptine tended to suppress the activity at low doses (1 and 2 mg/kg), but increased the activity at high doses (8 and 16 mg/kg). The biphasic effects depended on the doses administered, and the selective stimulation of D2 receptors stimulated locomotor activity while D2 receptors reduced locomotor activity.20, 21 Ambulation-increasing effects of bromocriptine were enhanced when the drug was repeatedly administered.20, 22, 23

Table 3: Effect of sub-acute administration of Bromocriptine on ambulatory and non-ambulatory movements using photo-cell

<table>
<thead>
<tr>
<th>Treatments (n=7)</th>
<th>Ambulatory movements</th>
<th>Non-ambulatory movements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% tween 80</td>
<td>73.57 ± 5.48</td>
<td>82.28 ± 4.62</td>
</tr>
<tr>
<td>Bromocriptine 10 mg/Kg</td>
<td>97.57 ± 6.21</td>
<td>108.28 ± 5.00</td>
</tr>
</tbody>
</table>

The values are the means (counts) ± S.E.; ★Significantly different from the control group at p ≤ 0.05.

A study indicated that the initial behavioural depression and later locomotor stimulation induced by bromocriptine are accompanied by a sharp mono-phasic fall in striatal extracellular DA levels as indicated by dialysis studies. It was suggested that the reduced DA turnover is influencing the amount of DA available to stimulate postsynaptic D1 receptors.24 Bromocriptine enhanced locomotor activity by complex involvement of both noradrenaline and dopamine pre- and postsynaptic neurons, possibly due to its partial agonist action or as a result of its active metabolite; these conclusions were deduced from an observation that the increased locomotor activity induced by bromocriptine was suppressed by drugs inhibiting both dopaminergic and noradrenergic pre- and postsynaptic actions.23

It was concluded that the stimulant phase of bromocriptine in mice occurred despite continued occupation of the DA autoreceptors by bromocriptine, because adequate endogenous DA was available to provide the required D1 receptor stimulation.14 Amlodipine, nicardipine, diltiazem, and verapamil, which by itself did not affect locomotor activity, inhibited the stimulant phase of bromocriptine without altering the depressant phase. This indicated that L-type voltage-dependent Ca²⁺ channels were involved in the motor stimulant effect of bromocriptine-induced locomotor stimulation although bromocriptine-induced locomotor stimulation was decreased by haloperidol. The effects of Ca²⁺ channel blockers on the dopaminergic system appeared not to be directly related to dopamine receptor blockade.21

In vitro binding studies showed that bromocriptine exhibited high affinities for D2A, D2B, D3, alpha 1, and
alpha 2 adrenergic receptors together with unexpectedly high affinity for 5HT1A receptors. A biochemical study indicated that bromocriptine affected the turnover of 5HT in the brain. Thus, the behavioural effects of bromocriptine may depend not only on the effects on the DA system but also on 5HT systems.\textsuperscript{25} Bromocriptine stimulated 5-HT1A receptors displayed potent agonist properties at 5-HT2A and 5-HT1B receptors and was an efficacious agonist at 5-HT2C receptors.\textsuperscript{26} 5-HT1A and 5-HT2A receptors mediated stimulatory behaviour in mice.\textsuperscript{27}

5-HT1A receptors have been enriched in regions controlling motor function, such as the striatum, nucleus accumbens, and frontal cortex.\textsuperscript{28, 29} 5-HT2C agonists exerted an inhibitory influence upon striatal, mesolimbic, and frontocortical DA release\textsuperscript{29, 30, 31} and, correspondingly, suppressed motor behavior.\textsuperscript{32} Bromocriptine interacted with native 5-HT1B sites, and notwithstanding species’ differences, they exerted agonist actions at 5-HT1B receptors.\textsuperscript{28, 33}

The interaction between glucocorticosteroids and the dopaminergic system has attracted considerable attention, since this link could be involved in certain psychopathological conditions including depression. The study has shown the presence of glucocorticoid receptors in neurons of the limbic system, a structure involved in mood control and regulation of hypothalamic-pituitary-adrenal (HPA) axis. Structures of the limbic system were also rich in dopaminergic innervations. Therefore, the effect of dexamethasone on hyperactivity induced by dopamine agonists (bromocriptine) in mice was investigated. The results showed that dexamethasone might decrease the locomotor activity and reduce the hyperactivity induced by dopamine agonists in mice. It was suggested that dexamethasone weakened the activity of dopamine agonists in the mesolimbic system.\textsuperscript{34}

In 2005, a study showed that GABAA receptors, together with D1 and D2 receptors, played a major role in modulating the control of motor function by the nucleus accumbens of rats;\textsuperscript{35} more research is needed to investigate this interaction.

Repeated administration of bromocriptine to rodents have shown increase, decrease, or no change in brain dopaminergic activity.\textsuperscript{36} Others have suggested that there is a cumulative effect of bromocriptine on the behaviours studied with more changes being seen after repeated administration rather than after a single dose; the cumulative bromocriptine enhanced locomotor activity where the single dose decreased.\textsuperscript{37}

In a Y-maze, locomotor activities was significantly increased at 2.5 and 5.0 mg/kg of repeated administration of bromocriptine, and this was in accordance with bromocriptine’s ability to enhance locomotor activity.\textsuperscript{38}

**Conclusion**

Acute administration of bromocriptine produced a dose-related decrease in spontaneous motor activity. Low doses of bromocriptine did not show any changes in SMA after 30 minutes, while higher doses produced significant decrease in ambulatory movements. All doses of bromocriptine produced significant decreases in SMA after 60 minutes. Subacute administration of bromocriptine (10 mg/kg) increased SMA significantly. These findings conclude that bromocriptine produced its effect in spontaneous motor activity time and dose dependence.

**REFERENCES**


(4) SherwalV, Malik S and Bhatia V. Effect of bromocriptine on the severity of ovarian hyper-stimulation syndrome and outcome in high responders undergoing assisted
(24) Jackson D.M., Mohell N., Georgiev J., Bengtsson A., Larsson L.G., Magnusson O. and Ross S.B. Time course of bromocriptine induced excitation in rat: behavioural and
(37) Omaolapo O.J. and Omaolapo A.Y. Sub-chronic Oral Bromocriptine Methanesulfonate Enhances Open Field Novelty-Induced Behavior and Spatial Memory in Male Swiss Albino Mice; Neuroscience Journal, Volume 2013, Article ID 948241, 5 pages.
The study assessed the effect of anterior fowling on mink movements and its impact on the reproductive cycle. The study was conducted at the Faculty of Pharmacy, University of Jordan.

The study sample included 80 male mink, divided into two groups: a control group of 40 mink and an experimental group of 40 mink. The study divided the first 30 days by time and the remaining 60 days by focal time. The study aimed to assess the reproductive cycle during the experimental period.

The results indicated that the number of days of focal time significantly increased with the decrease of the focal time, which was accompanied by the decrease of the focal time. This finding was consistent with previous studies that showed a significant decrease in mink movements during the experimental period.

The study concluded that the anterior fowling significantly affected the reproductive cycle of mink, which was reflected in the significant increase in the number of days of focal time. Therefore, it is recommended to reduce the focal time to reduce the effect of anterior fowling on mink movements.