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Behavioral Response to Apomorphine in Diet-Restriction-Induced Hyperactivity in Rats

Darakhshan M Saleem[1], Moona Khan[2], Khalid Aftab[3*], Shafaque Mehboob[4], Shafia Tabassum[1], Darakhshan J Haleem[5]

[1]Biomedical Engineering Department, Sir Syed University of Engineering & Technology, Karachi, Karachi, Pakistan

[2]Department of Pharmacy, Dow University of Health Sciences, Karachi, Pakistan

[3]Department of Pharmacology & Therapeutics, Islam Medical & Dental College, Sialkot, Pakistan

[4]Jinnah Sindh Medical University, Faculty of Pharmacy, Karachi, Pakistan

[5]Dr.Panjwani Center for Molecular Medicine and Drug Research International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Pakistan

[*]**Corresponding author:** Khalid Aftab, Department of Pharmacology & Therapeutics, Islam Medical & Dental College, Sialkot, Pakistan. Tel: +923335632975; Email: khalidaftabkhan@hotmail.com

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Abstract

Background: Repeated administration to Apo morphine (1.0 mg/kg) induced hyperactivity is mediated by the stimulation of dopamine auto-receptors. Evidences suggest that the greater hyperactivity in Diet Restricted (DR) rats may be due to increased activity of Somatodendritic 5-HTIA receptors, results in decreased 5-HT contents in DR rats. The present study is designed to monitor the behavioural response to Apomorphine on locomotor activity in DR in rats.

Methods: Animals of diet-restricted group given access to food 2 h daily for five weeks. After four weeks' animals were subdivided into two groups i.e. saline and Apo morphine treated groups at a dose of 1mg/kg for seven days in week five.

Results: Animals of DR group exhibited decreased in body weight (16.4%) in Apo morphine and (18.8 %) in saline injected DR group when compared to respective controls. Animals exposed in activity box showed progressively increased in hyperactivity for seven days. The sensitization effect of Apo morphine was greater in diet-restricted rats.

Conclusions: The results of this study highlight that greater increase in the locomotor activity in Apomorphine-induced behavioural sensitization could be due to increased Somatodendritic 5-HT1Areceptors activity in diet-restricted rats. Furthermore, the pharmacological agents which tend to desensitize 5-HT1A receptors might be helpful in reducing the hyperactivity in diet-restriction.

Keywords: Anorexia Nervosa; ApoMorphine Sensitization; Diet-Restriction; Serotonin

Introduction

Apomorphine is a dopaminergic D1/D2 receptors agonist [1] with slightly higher affinity for D2-like dopamine receptors [2]. Sensitization to Apomorphine (1.0 mg/kg) develops upon repeated administration, as assessed in an open field [3]. This hyperactivity induced by Apomorphine is suggested to be mediated by the stimulation of dopamine auto-receptors [4,5]. Apomorphine (2.0mg/kg) induced locomotor sensitization varies with peak concentration of drug as well as the habituation. Repeated Apomorphine (1.0 mg/kg) administration increases behavioral sensitivity, which could be attenuated upon repeated co-administration with 7-hydroxy 7-hydroxy-N, N-dipropyl-2-aminotetralin (7-OH-DPAT; dopamine receptor agonist) [4]. This Apomorphine-induced sensitization could be monitored after single injection of the drug as well [6].

Researchers have reported that serotonin and dopamine modulate the neurotransmission of each other [7-10]. Serotonin has an inhibitory effect dopaminergic neurotransmission while an increase in dopaminergic activity may also modulate serotonergic functions [11]. Evidences suggest that DR-induced hyperactivity in

rat's results in an increased in the inhibitory influence of 5-HT on the activity of dopaminergic neurons possibly due to increase super sensitivity of 5-HT1Areceptors [12,13]. The present experiment is designed to monitor the effects of Apomorphine on locomotor activity in diet-restricted rats.

Materials and Methods

Animals and Treatment

Locally bred female Sprague-Dawley rats weighing 165.4±15.2g were housed individually under 12-hour light dark cycle and controlled room temperature (22±2ºC) with the access of cubes of standard rodent diet and water, a week. Animals were cared according to a protocol approved locally which is consistent with the NIH guidelines for the care and use of laboratory animals.

Experimental Protocol

One week after arrival 24 female Sprague-Dawley rats were randomly divided into Freely Feeding (FF) and Diet Restriction (DR) group of 12 each. Food was available for 24 h to FF group while animals of DR group were given access to food daily for 2 h. Food intake and body weights of the two groups were monitored weekly. After 4 weeks of treatment FF group and DR group animals were divided into 4 groups containing six animals each:

- FF-saline (1.0ml/kg),
- FF-Apomorphine (1.0mg/kg)
- DR-saline (1.0ml/kg) and
- DR-Apomorphine (1.0mg/kg).

Animals were placed in the activity box (one in each box) 15 min before injection. Animals were then injected with the respective dose of Apomorphine or saline for seven days in week 5. Activity in familiar environment was monitored for a period of 15 minutes' post injection every day.

Drugs and Doses

Apomorphine-HCl (Sigma, St. Louis, USA) was dissolved in saline and injected intraperitoneally. Drug solutions were freshly prepared before each experiment. Control animals were injected with saline (0.9% NaCl) at a dose of 1.0 ml/kg.

Behavioral Assessment

Activity Monitoring Activity Cage

To monitor the behavioral response of Apomorphine on locomotor activity an animal was transferred to transparent, Perspex activity cages (26× 26× 26 cm) with a saw-dust covered floor were used to monitor activity. Experiment was conducted in a separate quite room. Locomotor activity was observed in activity boxes for 15 minutes in terms of numbers of cage crossings in all groups in a balanced design as described earlier [14-16].

Statistical Analysis

Results are represented as means±S.D. Data were analyzed by two-way ANOVA (Repeated Measure Design). Post hoc comparisons done by Tukey's test. p values <0.05 were taken significant.

Results

Effect of Apomorphine administration on food intake of rats fed on DR schedule of 2 h/day is shown in (Figure 1)Two -way ANOVA (d.f. 1, 20) showed significant effect of DR ($F = 21.5$; $p < 0.01$) interaction (d.f.1, 20; $F=126.8$, $p<0.01$) significant; Apomorphine (d.f.1,20; $F=1.8$, $p>.0.05$) was insignificant. Post hoc test showed that food intakes were significantly ($p < 0.01$) decreased in saline injected and Apomorphine injected DR groups than respective FF group.

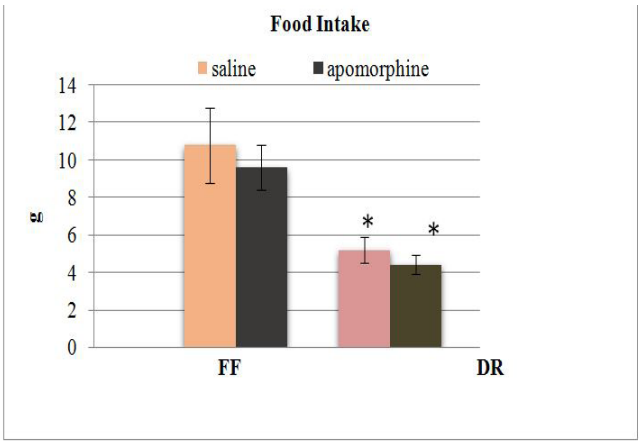


Figure 1: Values are means±S.D (n=6). Significant differences by Tukey's test*p<0.01 from respective FF group following two-way ANOVA.

Body weight changes in FF and DR groups are shown in (Figure2)Two -way ANOVA (d.f. 1, 20) showed significant effect of DR ($F = 31.68$; $p < 0.01$), interaction (d.f.1, 20; $F=131.5$, $p<0.01$) significant; Apomorphine (d.f.1, 20; $F=2.86$, $p>.0.05$) was insignificant. Post hoc test showed that body weights were significantly ($p < 0.01$) decreased (16.4%) in Apomorphine and 18.8 % in saline injected DR group when compared to respective controls.

(Figure 3)shows effects of administration of Apomorphine on motor activity in a familiar environment. Repeated measure two-way ANOVA revealed significant effects of Apomorphine on days ($df = 6, 20$; $F = 259.32$; $p<0.01$), repeated monitoring days ×Apo morphine ($df = 12, 20$; $F = 154.915$; $p<0.01$),interaction ($df = 1, 20$; $F = 544.6$; $p<0.01$) and Apo morphine($df = 1, 20$; $F = 113.1$; $p<0.01$) were significant. Post hoc test showed that activ-

ity scores (number of cage crossings) were greater in DR than FF group. Administration of Apomorphine elicited hyperactivity ($p < 0.01$) in FF as well as DR groups and the scores were greater ($p < 0.01$) in DR than FF group. Post hoc analysis by Tukey's showed that Apomorphine significantly ($p<0.01$) increased motor activity from day 3 to day 7 in FF as well as in DR groups. The increases were insignificant on day 1 and day 2 both in FF and DR group with respective saline injected group.

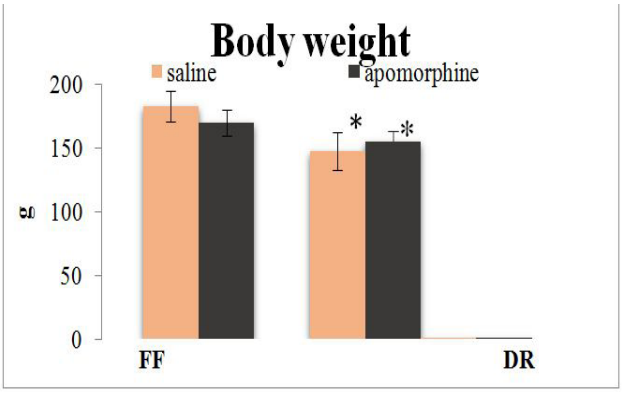
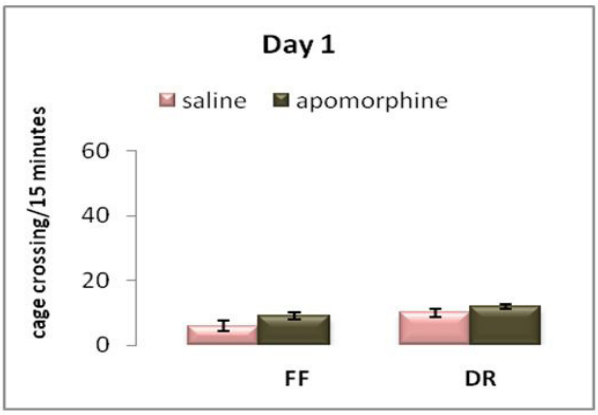
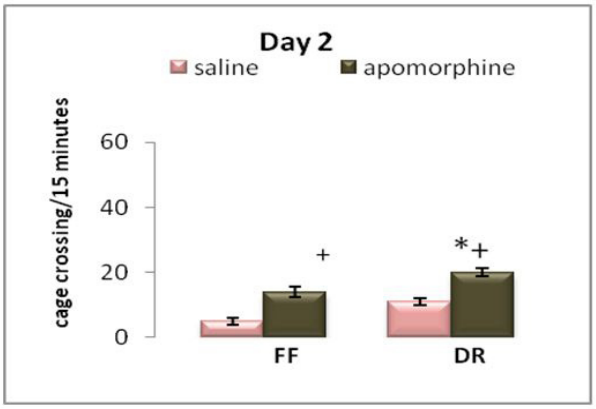
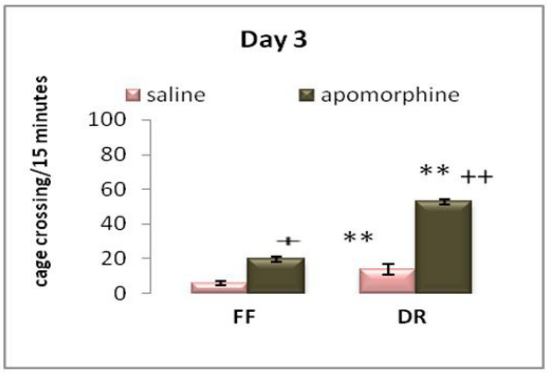
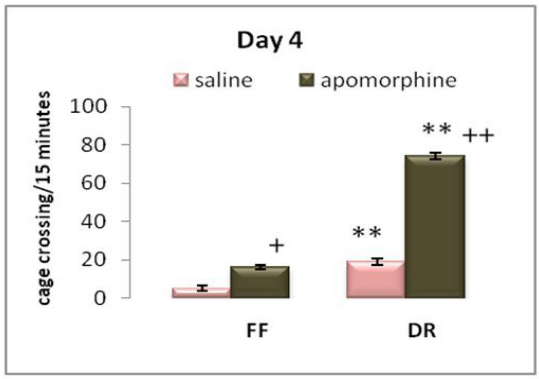


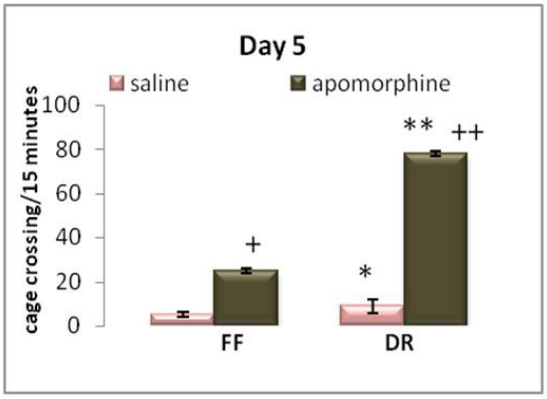
Figure 2: Body weight of Freely Feeding (FF) and Diet Restriction (DR) group of rats.Values are means±S.D (n=6). Significant differences by Tukey's test. *p<0.01 from

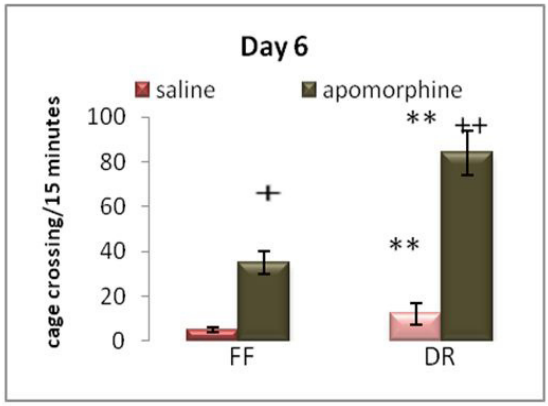












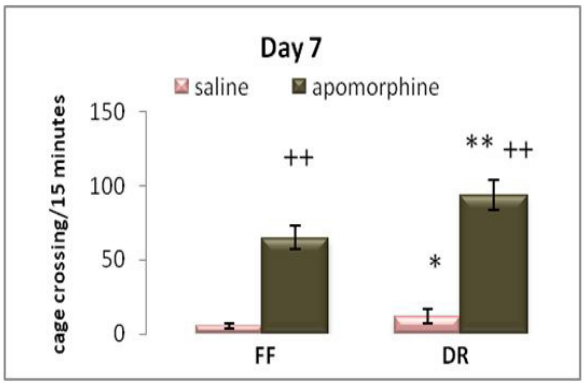


Figure 3: Activity in activity box in Freely Feeding (FF) and Diet Restriction (DR) group of rats. Values are means±S.D (n=6). Significant differences by Tukey's test*p<0.05, **p<0.01 from respective FF saline injected; +p<0.05, ++p<0.01 from respective FF Apomorphine injected animals following two-way ANOVA (repeated measure design).

Discussion

In the present study rats fed on DR schedule of 2 h/day for five weeks exhibited decreased in body weight (16.4%) in Apomorphine and (18.8 %) in saline injected DR group when compared to respective controls, decreased in food intake and increased motor activity in activity box. Similar (15-25%) reduction in body weight and behavioral deficits have also been reported in diet restriction induced AN [13,17,18].

The aim of the present study was to observe the behavioral response to Apomorphine in DR rats. Results showed that Apomorphine induced increases of motor activity were greater in DR groups compared to FF group in activity box. Number of cage crossing in activity box was greater in DR-Apomorphine treated rats than respective DR-saline treated group. Many studies have reported that there is a considerable amount of interaction between the dopaminergic and serotonergic neurotransmitter systems [19]. Some authors reported evidence for a facilitator role for 5-HT over DA. There is an abundance of evidence demonstrating that dopaminergic neurotransmission is functionally regulated by serotonin, which has important implications for 5-HT in controlling the behavior commonly exhibited in AN. Pretreatment with 5-hydroxytryptophan or TRP decreased Apomorphine-induced hyperactivity [20]. Disruption of the 5-HT system will disrupt the DA system and affect DA mediated behaviors.5-HT neurons send projections to DA cell bodies located in the midbrain regions including the Substantialnigra and ventral tegmental area. In addition, they project to DA terminals present in the striatum, nucleus accumbens, and prefrontal cortex. The 5-HT innervations of dopaminergic cell bodies and terminals allows for the functional regulation by 5-HT of both DA neuronal firing and DA release. Results from electrophysiological and neurochemical studies on rodents have generally shown that 5-HT exerts an inhibitory influence on midbrain dopamine cell bodies. 5-HT influence over DA release in terminal regions, however, is less clear as both inhibitory and excitatory effects have been observed [19]. It has been reported that by repeated administration of Apomorphine induced sensitization increased Somatodendritic 5-HT_{1A} receptors activity [17] which was attenuated by Buspirone.

In the present study, our results showed that daily administration of Spomorphine (1.0 mg/kg) for seven days progressively increased locomotor activity. Greater activity of DR than FF rats in the activity box in Apomorphine-induced hyperactivity in the present study might be due to an increased sensitivity of Somatodendritic 5-HT_{1A} receptors. This results in release of dopamine because of the inhibitory influence of 5-HT.

Conclusion

The present study concluded that greater increase in the hyperactivity in Apomorphine treated DR rats could be due to increased Somatodendritic 5-HT_{1A} receptors activity.The study also suggests that the pharmacological agents who tend to desensitize 5-HT_{1A} receptors might be helpful in reducing the hyperactivity associated with diet-restriction.

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