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Attenuation of apomorphine-induced sensitization by buspirone

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ABSTRACT

Apomorphine, a dopamine D_1/D_2 agonist is effective in the treatment of parkinson's disease; but its long term use is often associated with the dependence and addiction. The development of locomotor sensitization to psychostimulants including apomorphine is considered to be an important contributor to psychostimulant drug abuse. Previous studies have shown that long term administration of drugs of abuse increases the effectiveness of somatodendritic 5-hydroxytryptamine (5-HT)-1A receptors. Repeated administration of buspirone attenuates the effectiveness of somatodendritic 5-HT_{1A} receptors. The present study was designed to test the hypothesis that coadministration of buspirone may attenuate apomorphine induced sensitization. Administration of apomorphine at a dose of 1.0, 2.0 & 4.0 mg/kg increased motor activity in an activity box in a dose dependent manner. Locomotor enhancing effects of a low dose of apomorphine were augmented upon repeated administration suggesting drug-induced sensitization. The sensitization effects were significant in an activity box as well as in an open field. Coadministration of buspirone at a dose of 1.0 mg/kg reversed apomorphine-induced sensitization. Repeated administration of buspirone at a dose of 2.0 mg/kg but not 1.0 mg/kg also elicited sensitization in motor behavior. It is suggested that buspirone may oppose the development of sensitization to apomorphine by decreasing the sensitivity of somatodendritic 5-HT_{1A} receptors. Findings may help in extending therapeutics in parkinson's disease.

1. Introduction

Apomorphine, a mixed D_1/D_2 agonist having slightly higher affinity for D_2-like dopamine receptors, is effective in the treatment of parkinson's disease (Deleu et al., 2004; Pahwa et al., 2007). However, addiction associated with the repeated use of the drug is the major limitation of the therapy (Rowlett et al., 1991). The development of locomotor sensitization to psychostimulant drugs including apomorphine is considered to be an important contributor of psychostimulant drug abuse (Robinson and Berridge, 1993). Although a decrease in the dopamine D_2 autoreceptor sensitivity (Bevan, 1983) is often linked with the expression of behavioral sensitization to psychostimulants (Pierce and Kalivas, 1997, Marin et al., 2008), the exact mechanism underlying the pathophysiology of sensitization is not clear.

The central dopamine (DA) system plays a crucial role in the psychostimulant-induced increase in motor activity as well as addiction (Robinson and Berridge, 2000). The central serotonergic system can modulate both activity enhancing as well as rewarding effects of drugs of abuse (Przegaliski et al., 2000; Muller et al., 2003; Hall et al., 2004). A role of 5-HT_{1A} receptors in the reinforcing effects of drugs of abuse was suggested because stimulation of 5-HT_{1A} receptors is capable of modulating the hyperactivity evoked by cocaine (De La Garza and Cunningham, 2000).

5-HT_{1A} receptors are present both pre- and postsynaptically (Riad et al., 2000). Studies have suggested an important role of 5-HT_{1A} receptors in the pathophysiology of addiction. *WAY100635*, a 5-HT_{1A} antagonist, attenuates cocaine primed reinstatement (Schenk, 2000). It attenuates cocaine induced locomotor activity and increases extracellular 5-HT, but not DA in NAcc and hippocampus (Muller et al., 2003). However, this is unclear that whether effects of *WAY100635* are due to the blockade of post synaptic 5-HT_{1A} receptors or due to an increase in extracellular 5-HT levels via blockade of somatodendritic 5-HT_{1A} receptors (Burmeister et al., 2004). The partial HT_{1A} receptor agonist buspirone (1 and 3 mg/ml/kg, s.c.) induced conditioned place preference (CPP) in rats (Neisewander et al., 1990). Other researchers have also reported that there is an important role of 5-HT_{1A} receptors in drug-induced reinforcement and locomotor sensitization (Ali and Kelly, 1996, 1997; Muller et al., 2007).

Buspirone is an azaspirodecanedione derivative that has partial affinity for 5-HT_{1A} receptors as agonist and dopamine D_2 receptors as an antagonist (Peroutka, 1985; Gobert et al., 1999). A decrease in the 5-HT turnover occurred when the animals were injected with low (1.0 mg/kg) dose of buspirone suggesting that at low dose the drug could preferentially stimulate somatodendritic 5-HT_{1A} receptors.

Previously it has been shown that repeated administration of buspirone at a dose of 1 mg/kg decreased the responsiveness of somatodendritic 5-HT_{1A} receptor responsiveness as buspirone-induced

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decreases of 5-HT metabolism were smaller in repeated buspirone treated animals (Haleem et al., 2007). The purpose of the present study was to evaluate the role of somatodendritic 5-HT_{1A} receptors in behavioral sensitization produced following repeated administration of apomorphine (Bloise et al., 2007; Haleem and Khan, 2003). It was hypothesized that desensitization of somatodendritic 5-HT_{1A} receptors by coadministration of buspirone will increase the inhibitory influence of serotonin on the activity of dopaminergic neurons (Khan and Haleem, 2006) to attenuate the expression of locomotor sensitization to apomorphine. In the present study, we have investigated the effects of buspirone on the establishment of locomotor sensitization as induced by repeated administration of apomorphine.

2. Materials and methods

2.1. Animals

Locally bred male Albino Wistar rats (weighing 180–200 g) purchased from HEJ Research Institute of Chemistry, Karachi were housed individually under 12 hr light and dark cycles (lights on at 06:00 hr) and controlled room temperature (24±2 °C) with free access to tap water and cubes of standard rodent diet at least 7 days before the start of experiment so that they could become familiar to the environment. Animals were tested in light phase. Before starting the experiment, rats were accustomed to various handling procedures in order to nullify the psychological affliction of environment. All protocols for experimentation were approved and performed in strict accordance with National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85–23, revised 1985) and the Institutional Animal Ethics Committee (IAEC).

2.2. Behavioral assessment

2.2.1. Activity in a familiar environment (activity box)

Transparent Perspex cages (26×26×26 cm) with sawdust covered floor were used to monitor activity in familiar environment. Rats were placed individually in these cages to get familiar with the environment. 15 min later the animals were injected with drug or vehicle. Numbers of cage crossings were counted 5 min post-injection for 10 min (Batool et al., 2000).

2.2.2. Activity in a novel environment (open field)

A square area (76×76 cm) with walls 42 cm high was used to monitor activity in a novel environment. The floor of apparatus was divided by lines into 25 squares of equal size. Animals were injected with drug or vehicle and placed in the central square of the open field immediately after the injection. Numbers of squares crossed with all four paws were counted for 5 min (Ikram et al., 2007).

2.3. Drugs

Apomorphine–HCl (Sigma, St. Louis, USA) and buspirone (Research Biochemicals Incorporated, USA) were dissolved in saline and injected intra-peritoneally. 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.

2.4. Experimental protocol

2.4.1. Experiment No. 1

Twenty-four male Albino Wistar rats (weighing 180–220 g) were randomly assigned to four groups each containing six animals each: (i) saline (1.0 ml/kg), (ii) apomorphine (1.0 mg/kg), (iii) apomorphine (2.0 mg/kg) and (iv) apomorphine (4.0 mg/kg) injected groups. Animals were placed in the activity box, 15 min before injection. Animals were then injected with the respective dose of apomorphine or saline. Activity in familiar environment was monitored 30 min post injection for a period of 10 min.

2.4.2. Experiment No. 2

Twelve male Albino Wistar rats (weighing 180–220 g) were randomly assigned to two groups each containing six animals: (i) saline and apomorphine injected groups. Injections of apomorphine (1.0 mg/kg) or saline (1.0 ml/kg) were made on alternate days. Animals were injected with apomorphine on days 2, 4, 6, 10 and 12. Activities in the familiar environment were monitored 15 min post injection for a period of 10 min (Fig. 2a). Activities in a novel environment were monitored 30 min post apomorphine or saline injection after 1st and 6th injections only, to maintain the novelty of environment.

2.4.3. Experiment no. 3

Thirty-six male Albino Wistar rats (weighing 180–220 g) were randomly assigned to six groups, each containing six animals: (i) saline–saline, (ii) saline–$buspirone_1$, (iii) saline–$buspirone_2$, (iv) apomorphine–saline, (v) apomorphine–$buspirone_1$ and (vi) apomorphine–$buspirone_2$ injected rats (where $buspirone_1$ = 1.0 mg/kg and $buspirone_2$ = 2.0 mg/kg). The drugs were injected on alternate days (day 2, 4, 6, 8, 10, and 12) for a period of 12 days. Activities in familiar environment were monitored 15 min post injection for a period of 10 min while activities in a novel environment were monitored 30 min post injection for a period of 5 min.

2.5. Statistical analysis

Results are represented as means ± SD. Statistical analyses were performed by one-way, two-way- or three-way analysis of variance (ANOVA). Post hoc individual comparisons of groups were performed by Newman–Keuls test. Values of $p<0.05$ and $p<0.01$ were considered as significant.

3. Results

3.1. Dose–response curve of apomorphine

Fig. 1 shows effects of different doses (1.0, 2.0 and 4.0 mg/kg) of apomorphine on the activity of rats in familiar environment of activity box. Data analyzed by one-way ANOVA showed significant effect of drug ($df = 3,20$; $F = 28.29$; $p<0.01$). Post hoc analysis by Newman–Keuls test showed that the administration of apomorphine increased activity in the familiar environment in a dose dependant manner. A

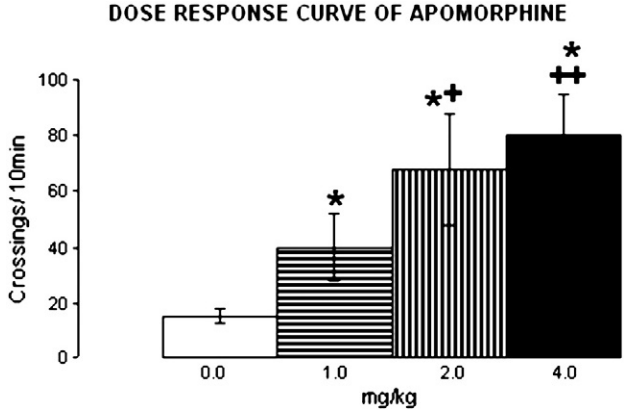

Fig. 1. Effects of different doses (1.0, 2.0 and 4.0 mg/kg) of apomorphine on locomotor activity in a familiar environment. Values are means ± SD (n = 6) 30 min after injections. Significant differences by Newman–Keuls test: *$p<0.01$ from saline injected controls; +$p<0.05$, ++$p<0.01$ from apomorphine (1.0 mg/kg) injected rats following one-way ANOVA.

significant ($p<0.01$) increase in motor activity occurred following administration of apomorphine at all three doses (i.e., 1.0, 2.0 and 4.0 mg/kg) as compared to saline injected controls. This drug-induced increased activity at doses of 2.0 mg/kg and 4.0 mg/kg were significantly greater ($p<0.05$ and $p<0.01$ respectively) than animals injected with 1.0 mg/kg dose.

3.2. Effect of repeated apomorphine administration on motor activity in novel and familiar environments

Fig. 2a shows effects of repeated administration of apomorphine on motor activity in a familiar environment. Repeated measure two-way ANOVA revealed significant effects of apomorphine ($df=1,10$; $F=523.26$; $p<0.01$) repeated monitoring ($df=1,10$; $F=526.83$; $p<0.01$) and interactions between the two ($df=4,10$; $F=59.81$; $p<0.01$) at a dose of 1.0 mg/kg. Post hoc analysis by Newman–Keuls test showed that apomorphine increased motor activity after first till sixth injection ($p<0.01$) as compared to saline injected controls. Fourth injection of apomorphine on day 8 augmented locomotor activity ($p<0.01$) as compared to apomorphine-induced enhancement of motor activity in apomorphine-induced animals after first injection. The sensitization effects following 5th and 6th administration were also significantly increased than first injection of apomorphine in apomorphine-injected animals.

Fig. 2b shows effects of repeated apomorphine administration on activity in a novel environment of open field, after first and sixth administration on day 1 and 12 respectively. Data analysis by repeated measure two-way ANOVA showed significant effects of apomorphine ($df=1,20$; $F=230.46$; $p<0.01$), repeated monitoring ($df=1,20$; $F=32.30$; $p<0.01$), as well as interaction ($df=1,20$; $F=17.35$; $p<0.01$) between the two factors. Post hoc analysis by Newman–Keuls test showed that apomorphine increased ($p<0.01$) activity in a novel environment after sixth injection, as compared to respective saline injected controls. The effects following sixth administration were greater ($p<0.01$) than the first administration of apomorphine.

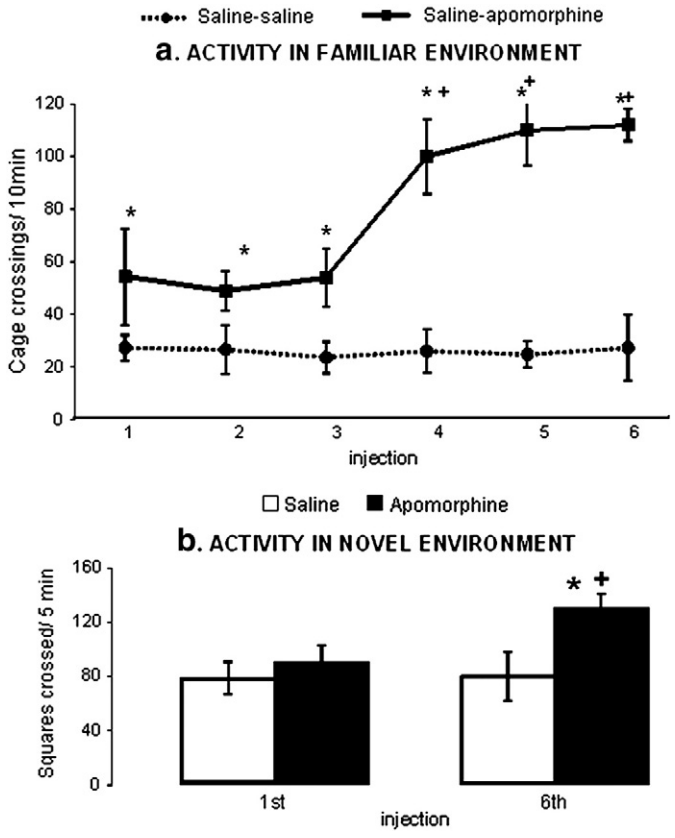

Fig. 2. Effects of repeated saline (1.0 ml/kg) and repeated apomorphine (1.0 mg/kg) administrations on activities in familiar and novel environments. Values are means ± SD ($n=6$) 15 min after injections. Significant differences by Newman–Keuls test: *$p<0.01$ from respective saline injected controls; +$p<0.01$ from similarly treated rats, following two-way ANOVA.

3.3. Comparison of activities in novel and familiar environments after apomorphine administration

Fig. 3a shows effects of 1st injection of apomorphine on activities in novel and familiar environments. Data analysis by student's *t*-test showed that apomorphine significantly ($p<0.05$) increased locomotor activity in familiar environment as compared to saline injected controls, whereas, single apomorphine injection did not alter activity in novel environment.

Fig. 3b shows effects of 6th injection of apomorphine on activities in novel and familiar environments. Data analysis by student's *t*-test showed that repeated administration of apomorphine significantly ($p<0.01$) increased locomotor activity in familiar environment as compared to respective saline injected controls. Activity in novel environment was also increased ($p<0.05$) as compared to respective saline injected controls.

3.4. Effect of co-administration of buspirone on apomorphine-induced hyperactivity and sensitization

Fig. 4a shows effects of repeated administration of apomorphine, buspirone (at the dose of 1.0 mg/kg and 2.0 mg/kg) and their coadministration on motor activity in an activity box (on alternate days). Data analyzed by repeated measure three-way ANOVA revealed significant effects of apomorphine ($df=1,150$, $F=10.10$, $p<0.01$), buspirone ($df=2,150$, $F=103.92$, $p<0.01$) and repeated monitoring ($df=1,150$, $F=4.5$, $p<0.05$). Interactions between

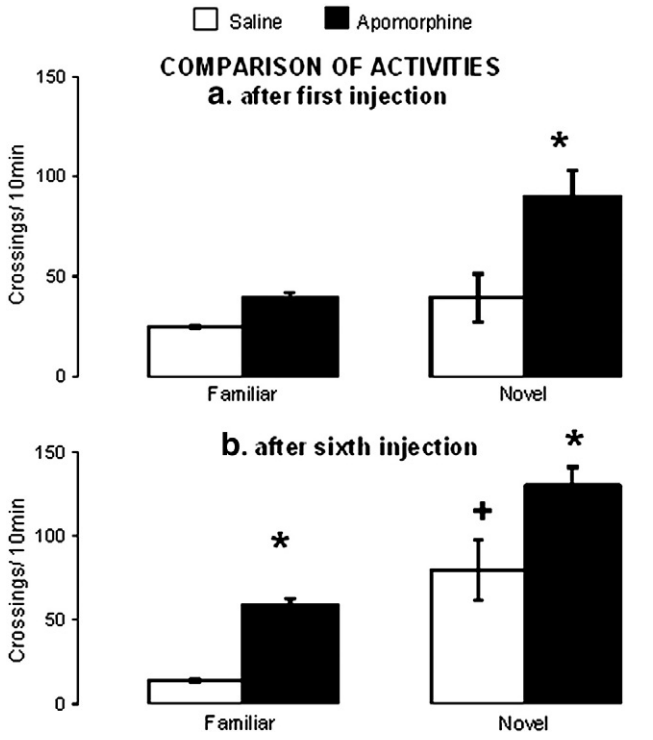

Fig. 3. Activities of repeated saline (1.0 ml/kg) and repeated apomorphine (1.0 mg/kg) injected rats as monitored in novel and familiar environments respectively. Values are means ± SD ($n=6$) as monitored 5 and 30 min after first (a) and sixth (b) injection respectively. *$p<0.05$ following student's *t*-test.

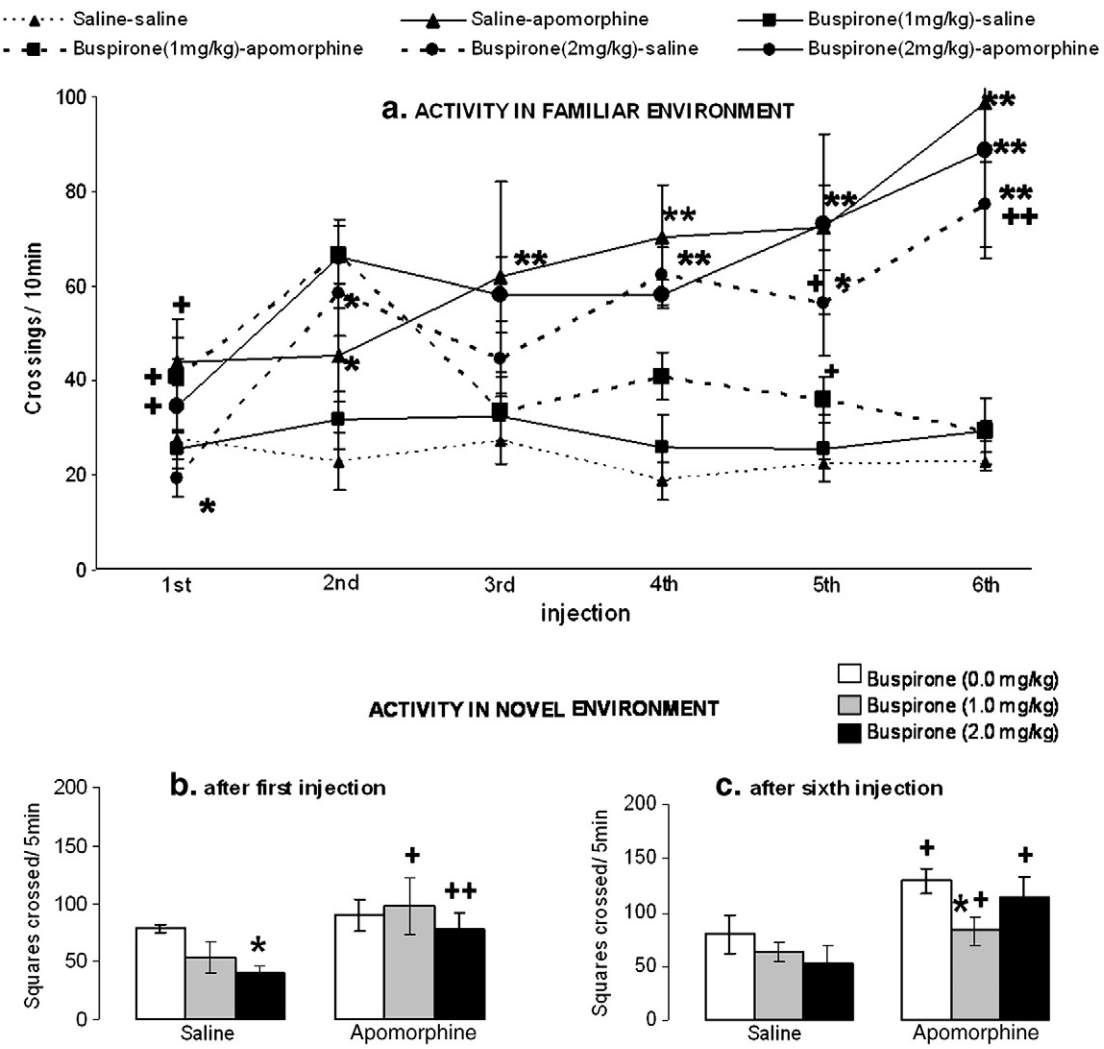

Fig. 4. Effects of apomorphine (1.0 mg/kg), buspirone (at the dose of 1.0 mg/kg & 2.0 mg/kg) and their coadministration on home cage activity (from first to sixth injection). Values are means + SD (n = 6) 10 min after apomorphine and buspirone administration (on alternate days). Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from respective saline (first injection) injected animals; + p<0.05, ++ p<0.01 from respective apomorphine (first injection) injected animals following three-way ANOVA.

buspirone*apomorphine (df = 2,150, F = 198.25, p<0.01), day*buspirone (df = 2,150, F = 22.37, p<0.01), day*buspirone*apomorphine (df = 2,150, F = 15.78, p<0.01) and day*apomorphine (df = 2,150, F = 17.0, p<0.01) were found to be significant. Post hoc analysis by Newman–Keuls test demonstrated that apomorphine increased activity in a familiar environment following first and second injection (p<0.05) as compared to saline injected controls. This increase in activity was more pronounced upon repeated administration of apomorphine from third till sixth injection (p<0.01). Buspirone at the dose of 1.0 mg/kg, did not alter activity in familiar environment as compared to saline injected controls, but at the dose of 2.0 mg/kg, it increased activity after second injection (p<0.05) as compared to saline injected controls. A consistent increase in activity was then monitored after fourth till sixth injection (p<0.01). At the dose of 1.0 mg/kg, buspirone did not alter apomorphine-induced increase in activity following first and second injection. After the third injection (p<0.05) it attenuated apomorphine-induced increase in activity as compared to apomorphine injected rats. These effects were more pronounced after the sixth injection (p<0.01). However, high dose of buspirone at the dose of 2.0 mg/kg, did not alter apomorphine-induced increases in activity upon repeated administration as compared to apomorphine injected animals.

Fig. 4b shows effects of apomorphine, buspirone (at the dose of 1.0 mg/kg and 2.0 mg/kg) and their coadministration on activity in novel environment of an open field 30 min after the first apomorphine injection. Data analyzed by two-way ANOVA showed that the effects of apomorphine (df = 1,30, F = 156.86, p<0.01), buspirone (df = 2,30, F = 28.64, p<0.01) as well as their coadministration (df = 2,30, F = 10.93, p<0.01) were all significant. Post hoc analysis by Newman–Keuls test showed that apomorphine-induced increase in the activity was not significant as compared to saline injected controls. However buspirone at the dose of 1.0 mg/kg (p<0.05) as well as at the dose of 2.0 mg/kg (p<0.01) potentiated the effects of apomorphine as compared to buspirone (1.0 mg/kg)–saline and buspirone (2.0 mg/kg)–saline injected controls respectively.

Fig. 4c demonstrates effects of apomorphine, buspirone (at the dose of 1.0 mg/kg and 2.0 mg/kg) and their coadministration on activity in novel environment of an open field 30 min after the sixth apomorphine injection. Data analyzed by two-way ANOVA showed that the effects of apomorphine (df = 1,30, F = 352.07, p<0.01), buspirone (df = 2,30, F = 45.05, p<0.01) as well as their coadministration (df = 2,30, F = 23.45, p<0.01) were all significant. Post hoc analysis by Newman–Keuls test demonstrated significantly increased (p<0.01) activity by the apomorphine injected animals as compared to saline injected controls. Activities of buspirone (1.0 mg/kg)–apomorphine and buspirone (2.0 mg/kg)–apomorphine injected were also greater (p<0.01) than the buspirone (1.0 mg/kg)–saline and buspirone (2.0 mg/kg)–saline injected animals

respectively. Buspirone at the dose of 1.0 mg/kg attenuated ($p<0.01$) the apomorphine-induced activity as compared to apomorphine–saline injected animals.

4. Discussion

In first phase of the present study, we monitored locomotor effects of apomorphine in the familiar environment of an activity box at different doses (i.e., 1.0, 2.0 and 4.0 mg/kg). Because somewhat maximum increase in activity occurred at a dose of 2.0 mg/kg (Fig. 1), smaller dose (1.0 mg/kg) of drug was used to further study development of locomotor sensitization to apomorphine (experiment no. 2) and attenuation of apomorphine-induced sensitization by buspirone coadministration (experiment no. 3). Results from second experiment show that apomorphine-induced sensitization was developed in both familiar (Fig. 2a) as well as novel (Fig. 2b) environment. In the familiar environment, the animals were tested 15 min after administration and in the novel environment the animals were tested 30 min after administration of treatments. It is known that the apomorphine plasma peak occurs between 15 and 20 min after drug administration. However, the remarkable fact of these results is that in the novel environment (Fig. 2b), the apomorphine group showed higher activity than the saline group. This could be due to an expansion of the temporal effects of apomorphine produced by sensitization. Although expression of locomotor sensitization to apomorphine is dependent on time interval between injection and testing (Braga et al., 2009a) these sensitization effects can persist for a substantial period of time. In the present study, we monitored the activities in novel environments 30 min after injections to observe the temporal effects of apomorphine as Braga et al. (2009b) have reported that after 20 min the sensitization effects of apomorphine decrease in a novel environment. However they did not monitor the development of sensitization in familiar environment. We therefore, monitored development of sensitization in familiar environment 10 min after injection, while that in novel environment after 30 min.

Activities in the open field were monitored after 1st and 6th injections of apomorphine (day 12) to maintain the novel effect of environment as daily monitoring in the open field could result in familiarization to environment. Comparison of the results obtained upon monitoring activity of animals in novel and familiar environments (experiment no. 2) shows that upon first injection apomorphine did increase activity in a familiar environment whereas in novel environment hyperlocomotive effects were monitored after 1st injection (Fig. 3a and b). Several studies have reported development of sensitization to the locomotor effects of psychostimulants (Crombag et al., 2000; Bell et al., 2000; Anagnostaras et al., 2002). Bloise et al. (2007) have reported that sensitization processes can be initiated with single apomorphine injection and could be amplified with exposure to higher drug dosage levels. It has been reported that medium and high post-synaptic doses of apomorphine (0.5 and 2.0 mg/kg respectively) produce sensitized locomotor stimulation after single injection as well as following a latent (3rd injection) period, as monitored in the novel environment of an open field (Braga et al., 2009a, 2009b). In the present study we have monitored the development of sensitization in familiar environment. Novel environment was used to monitor the expression of sensitization. It is therefore suggested that sensitization developed in familiar environment may also be expressed in novel environment. Sensitization was not observed after 1st injection of apomorphine in novel environment (Fig. 3a). This could be due to the reason that activity in novel environment was monitored 30 min post injection. Development of sensitization depends on time interval between testing and injection (Braga et al., 2009b). In the present study we paired drug administration with placement in familiar environment rather than novel one as repeated exposure of animals to the novel environment would have led to the development of familiarization to novel environment as well.

In the second phase of our study, development of apomorphine-induced sensitization was monitored in familiar environment. Whereas activities of animals were also monitored in novel environment, results show that the sensitization developed in familiar environment was also expressed in novel environment. Since we were interested in the time-course required to for the development of sensitization we monitored the activities in familiar environment after each apomorphine injection. Since daily exposure of animals might have resulted in familiarization to novel environment, therefore we monitored only “expression” but not “development” of sensitization in the novel environment. Familiar environment was therefore used in the third experiment to observe the effects of buspirone on apomorphine-induced sensitization.

In the present study administration of apomorphine at the dose of 1.0 mg/kg on alternate days produced locomotor sensitization following 4th administration as assessed in the familiar environment of an activity box (Fig. 2a). Locomotor sensitization in the effects of apomorphine at the dose of 1.0 mg/kg occurred following 3rd administration (Haleem et al., 2005). We also monitored locomotor effects of apomorphine in the novel environment (open field). Activities were monitored after first and sixth injections of apomorphine, to maintain novelty of environment. It was found that apomorphine increased activity in novel environment after first as well as sixth injection (Fig. 2b). The hyperlocomotory effects of apomorphine were greater ($p<0.01$) after 6th than 1st injection, suggesting development of sensitization effects in novel environment as well. Same hyperlocomotive effects of apomorphine were observed in a novel environment in experiment 3 (Fig. 4b and c). Results show that the low (1.0 mg/kg) but not high (2.0 mg/kg) dose of buspirone could attenuate apomorphine-induced hyperlocomotion. In the second experiment of present study repeated administration of low dose of apomorphine (1.0 mg/kg) increased motor activity in familiar but not in novel environment. As activity in novel environment was monitored 30 min after apomorphine administration, drug administration was not paired with the placement in environment. However, in the third experiment activity in novel environment was monitored 30 min after apomorphine injections and as a result, increased activity was observed after first as well as sixth injection of apomorphine. Since exposure to novel environment on alternate days could lead to the familiarization, we monitored activity in novel environment after first as well as last injection of apomorphine.

Carey et al. (2004) have reported that for both spontaneous and cocaine induced locomotor behavior, low dose 8-OH-DPAT and apomorphine treatments suppress locomotor activity by decreasing 5-HT and dopamine metabolism respectively. It is therefore suggested that mixed 5-HT/DA drugs could serve as effective drug therapy for the treatment of akinetic disorders such as parkinson's disease. Results therefore suggest that pairing of the drug administration with the familiar environment will result in a delay in expression of motor sensitivity (after 4th injection). However, apomorphine and other psychostimulants could express locomotor sensitization upon acute administration if the drug administration is paired with a novel environment. Apart from locomotor sensitization, development of tolerance to drugs of abuse had also been reported to be associated with the environmental context (Westbrook and Greeley, 1992) suggesting that the effects of psychostimulants are related to environmental cues.

A number of investigations have shown that the behavioral sensitization induced by CNS stimulants such as cocaine and amphetamine could be attenuated by the administration of 5-HT_{1A} receptor agonists. Ago et al. (2008) have reported that the administration of osemozotan (5-HT_{1A} receptor agonist) to methamphetamine-sensitized mice inhibited the maintenance of behavioral sensitization. Coadministration of 8-OH-DPAT (a selective 5-HT_{1A} agonist) to amphetamine (2.5 mg/kg) injected rats has also been shown to attenuate the expression of sensitization to a challenge dose of (2.5 mg/kg) amphetamine (Przegaliski et al., 2000). Acute administration of 8-OH-DPAT produced

specific changes in locomotor activity patterns induced by cocaine (De La Garza and Cunningham, 2000).

We report that the development of sensitization to apomorphine can be reversed by coadministration of buspirone at a dose of 1.0 mg/kg. A higher dose (2.0 mg/kg) of buspirone did not reverse or attenuate apomorphine-induced sensitization in the present study. Single administration of buspirone at high (2.0 mg/kg) but not at low (1.0 mg/kg) dose was found to decrease motor activity in an open field (Haleem et al., 2007). A decrease in the 5-HT turnover has also been reported to occur following administration of buspirone at a dose of 1.0 mg/kg (Shireen and Haleem, 2005) suggesting that at low doses the drug could preferentially stimulate somatodendritic 5-HT_{1A} receptors. Since other studies have reported that buspirone administration could have reinforcing effects (Troisi et al., 1993), therefore, we injected buspirone at the doses of 1.0 and 2.0 mg/kg to monitor the effects on apomorphine sensitization.

Buspirone is 5-HT_{1A} presynaptic receptor agonist (Peroutka, 1985) also having mixed dopaminergic D_2 antagonistic activity (Holroyd-Leduc et al., 2005). Since our main focus was to desensitize somatodendritic 5-HT_{1A} receptors to inhibit apomorphine-induced sensitization effects. We coadministered buspirone at a dose of 1.0 mg/kg. A decrease in 5-HT turnover has been reported to occur following administration of low but not high dose of buspirone (Shireen and Haleem, 2005) suggesting that at low doses the drug could preferentially stimulate somatodendritic 5-HT_{1A} receptors. Buspirone injected at a dose of 1.0 mg/kg was found to decrease 5-HT turnover in the striatum without producing a significant decrease in motor activity (Haleem et al., 2004; Shireen and Haleem, 2005).

In the present study, buspirone at a dose of 1.0 mg/kg did not alter motor activity in saline injected animals as monitored in a familiar environment of activity box, whereas high dose (2.0 mg/kg) of the drug produced hypolocomotion in the same environment (Fig. 4a). Buspirone at a dose of 1.0 mg/kg, potentiated apomorphine-induced hyperlocomotion upon single administration. As single injection of buspirone at a dose of 1.0 mg/kg decreases 5-HT turnover due to the affinity of drug for 5-HT_{1A} receptors at this dose (Trulson & Trulson, 1986). Decreased availability of 5-HT at somatodendritic 5-HT_{1A} receptors results in a decrease in inhibitory influence of 5-HT on dopamine neurotransmission (Haleem et al., 2004) which may potentiate the hyperlocomotion induced by apomorphine. However repeated administration of buspirone at this dose (i.e., 1.0 mg/kg), attenuated apomorphine-induced sensitization (Fig. 4a). As repeated administration of buspirone desensitizes somatodendritic 5-HT_{1A} receptors (Sato et al., 2008), more 5-HT would be available at 5-HT_{2C} receptors resulting in an increased inhibitory influence over dopaminergic neurotransmission.

Results from the present study on attenuation of apomorphine-induced sensitization may be explained in terms of the reversal of supersensitivity at somatodendritic receptors. Since buspirone is partial agonist of somatodendritic 5-HT_{1A} receptors with affinity for D2 receptors, it would be interesting to investigate the role of somatodendritic and/or post synaptic 5-HT_{1A} receptors in the attenuation of apomorphine-induced sensitization by full 5-HT_{1A} agonist 8-OH-DPAT (Naidu and Kulkarni, 2001) or 5-HT_{1A} agonist/dopamine-D_3/D_4 ligand sarizotan (Rosengarten et al., 2006).

5. Conclusion

In conclusion, the present study shows that coadministration of buspirone at low but not high doses could attenuate apomorphine-induced motor sensitization. It supports the hypothesis that an increase in the inhibitory serotonergic influence on the activity of dopaminergic neurons may be the mechanisms by which 5-HT_{1A} receptor agonists could attenuate apomorphine-induced motor sensitization. As repeated administration of apomorphine increases the responsiveness of somatodendritic 5-HT_{1A} receptors and repeated administration of buspirone decreases it, the present results suggest that an increase n the sensitivity of somatodendritic 5-HT_{1A} receptors may have an important role in apomorphine-induced sensitization. The findings may have important consequences in the use of apomorphine for the treatment of Parkinson's disease.

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References

Ago Y, Nakamura S, Baba A, Matsuda T. Neuropsychotoxicity of abused drugs: effects of serotonin receptor ligands on methamphetamine- and cocaine-induced behavioral sensitization in mice. J Pharmacol Sci 2008;106(1):15–21.
Ali I, Kelly ME. 8-OH-DPAT enhances the expression of cocaine-induced place preference. Br J Pharmacol Suppl 1996;119:207P.
Ali I, Kelly ME. Buspirone fails to affect cocaine-induced conditioned place preference in the mouse. Pharmacol Biochem Behav 1997;58:311–5.
Anagnostaras SG, Schallert T, Robinson TE. Memory processes governing amphetamine-induced psychomotor sensitization. Neuropsychopharmacology 2002;26:703–15.
Batool F, Siddiqui S, Haleem DJ. Neurochemical and behavioral profiles of 1-(1-naphthyl)piperazine in rats. J Coll Physicians Surg Pak 2000;11(1):50–6.
Bell K, Duffy P, Kalivas PW. Context-specific enhancement of glutamate transmission by cocaine. Neuropsychopharmacology 2000;23:335–44.
Bevan P. Repeated apomorphine treatment causes behavioural supersensitivity and dopamine D2 receptor hyposensitivity. Neurosci Lett 1983;35(2):185–9.
Bloise E, Carey RJ, Carrera MP. Behavioral sensitization produced by a single administration of apomorphine: implications for the role of Pavlovian conditioning in the mediation of context-specific sensitization. Pharmacol Biochem Behav 2007;86:449–57.
Braga PQ, Dias FRC, Carey RJ, Carrera MP. Low dose apomorphine induces context-specific sensitization of hypolocomotion without conditioning: Support for a new state dependent retrieval hypothesis of drug conditioning and sensitization. Pharmacol Biochem Behav 2009a;93(2):128–33.
Braga PQ, Galvanho JP, Bloise E, Carey RJ, Carrera MP. The Expression of locomotor sensitization to apomorphine is dependent o time interval between injection and testing. Pharmacology, Biochemistry & Behav 2009b;91(3):278–82.
Burmeister JJ, Lungren EM, Kirschner KF, Neisewander JL. Differential roles of 5-HT receptor subtypes in cue and cocaine reinstatement of cocaine-seeking behavior in rats. Neuropsychopharmacology 2004;29:660–8.
Carey RJ, DePalma G, Damianopoulos EN, Hopkins A, Muller CP, Huston JP. Dopaminergic and serotonergic autoreceptor stimulation effects are equivalent and additive in the suppression of spontaneous and cocaine induced locomotor activity. Brain Res 2004;1019:134–43.
Crombag HS, Badiani A, Maren S, Robinson TE. The role of contextual versus discrete drug-associated cues in promoting the induction of psychomotor sensitization to intravenous amphetamine. Behav Brain Res 2000;116(1):1-22.
De La Garza R, Cunningham KA. The effects of the 5-hydroxytryptamine1A agonist 8-hydroxy-2-(di-n-propylamino)tetralin on spontaneous activity, cocaine-induced hyperactivity and behavioral sensitization: a microanalysis of locomotor activity. J Pharmacol Exp Ther 2000;292(2):610–7.
Deleu D, Hanssens Y, Northway MG. Subcutaneous apomorphine. An evidence-based review of its use in Parkinson's disease. Drugs Aging 2004;21:687–709.
Gobert A, Rivet JM, Cisterilli L, Melon C, Millan MJ. Buspirone modulates basal and fluoxetine-stimulated dialysate levels of dopamine, noradrenaline and serotonin in the frontal cortex of freely moving rats: activation of serotonin1A receptors and blockade of alpha2-adrenergic receptors underlie its actions. Neuroscience 1999;93:1251–62.
Haleem DJ, Hasnat A, Shireen E, Khan A, Haleem MA. Dopamine and serotonin neurotransmission in the reinforcing effects of alcohol and apomorphine. J Coll Physicians Surg Pak 2005;15(8):458–62.
Haleem DJ, Khan NH. Enhancement of serotonin-1A receptor dependent responses following withdrawal of haloperidol in rats. Prog. Neuro-Psychopharmacol. Biol. Psychiatr 2003;27(4):645–51.
Haleem DJ, Samad N, Haleem MA. Reversal of haloperidol-induced tardive vacuous chewing movements and supersensitive somatodendritic serotonergic receptors by buspirone in rats. Pharmacol Biol Behav 2007;87:115–21.
Haleem DJ, Shireen E, Haleem MA. Somatodendritic and postsynaptic 5-HT-1A receptors in the attenuation of haloperidol-induced catalepsy. Prog Neuropsychopharmacol Biol Psychiatry 2004;28:1323–9.
Hall FS, Sora I, Drgonova J, Li XF, Goeb M, Uhl GR. Molecular mechanisms underlying the rewarding effects of cocaine. Ann NY Acad Sci 2004;1025:47–56.
Holroyd-Leduc JM, Liu BA, Maki BE, Zecevic A, Herrmann N, Black SE. The role of buspirone for the treatment of cerebellar ataxia in an older individual. Can J Clin Pharmacol 2005;12(3):e218–21.
Ikram H, Samad N, Haleem DJ. Neurochemical and behavioral effects of m-CPP in a rat model of tardive dyskinesia. Pak J Pharm Sci 2007;20(3):188–95.
Khan A, Haleem DJ. 5-HT-1A receptor responsiveness following subchronic administration of buspirone. Pak J Pharm Sci 2006;19(4):333–7.
Marin MT, Cruz FC, Planeta CS. Cocaine-induced behavioral sensitization in adolescent rats endures until adulthood: lack of association with GluR1 and NR1 glutamate

receptor subunits and tyrosine hydroxylase. Pharmacol Biochem Behav 2008;91 (1):109–14.
Muller CP, Carey RJ, Huston JP. Serotonin as an important mediator of cocaine's behavioral effects. Drugs Today 2003;39:497–511.
Muller CP, Carey RJ, Huston JP, De Souza Silva MA. Serotonin and psychostimulant addiction: focus on 5-HT1A-receptors. Prog Neurobiol 2007;81:133–78.
Naidu PS, Kulkarni SK. Effect of 5-HT-1A and 5-HT-2A/2 C receptor modulation on neuroleptic-induced vacuous chewing movements. Eur J Pharmacol 2001;428:81–6.
Neisewander JL, Pierce RC, Bardo MT. Naloxone enhances the expression of morphine-induced conditioned place preference. Psychopharmacology 1990;100:201–5.
Pahwa R, Koller WC, Trosch RM, Sherry JH. Subcutaneous apomorphine in patients with advanced Parkinson's disease: a dose-escalation study with randomized, double-blind, placebo-controlled crossover evaluation of a single dose. J Neurol Sci 2007;258(1–2):137–43.
Peroutka SJ. Selective interaction of novel anxiolytics with 5-hydroxytryptamine1A receptors. Biol Psychiatry 1985;20:971–9.
Pierce RC, Kalivas PW. A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. Brain Res Reviews 1997;25(2):192–216.
Przegaliski E, Siwanowicz J, Baran L, Filip M. Activation of serotonin (5-HT)1A receptors inhibits amphetamine sensitization in mice. Life Sci 2000;66(1):1011–9.
Riad M, Garcia S, Watkins KC, Jodoin N, Doucet E, Langlois X, El Mestikawy S, Hamon M, Descarries L. Somatodendritic localization of 5-HT1A and preterminal axonal localization of 5-HT1B serotonin receptors in adult rat brain. J Comp Neurol 2000;417:181–94.
Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev 1993;18(3):247–91.
Robinson TE, Berridge KC. The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction 2000;95(2):S91-S117.
Rosengarten H, Bartoszyk GD, Quartermain D, Lin Y. The effect of chronic administration of sarizotan, 5-HT-1A agonist/D3/D4 ligand on the previous termhaloperidolnext term-induced repetitive jaw movements in rat model of tardive dyskinesia. Prog Neuropsychopharmacol Biol Psychiat 2006;30:273–9.
Rowlett JK, Mattingly BA, Bardo MT. Neurochemical and behavioral effects of acute and chronic treatment with apomorphine in rats. Neuropharmacology 1991;30(2): 191–7.
Sato H, Skelin I, Debonnel G, Diksic M. Chronic buspirone treatment normalizes open field behavior in olfactory bulbectomized rats: assessment with a quantitative autoradiographic evaluation of the 5-HT1A binding sites. Brain Res Bull 2008;75(5):545–55.
Schenk S. Effects of the serotonin 5-HT(2) antagonist, ritanserin, and the serotonin 5-HT(1A) antagonist, WAY 100635, on cocaine-seeking in rats. Pharmacol Biochem Behav 2000;67:363–9.
Shireen E, Haleem DJ. Motor effects of buspirone: relationship with dopamine and serotonin in the striatum. J Coll Physicians Surg Pak 2005;15(12):753–6.
Troisi JR, Critchfield TS, Griffiths RR. Buspirone and lorazepam abuse liability in humans: behavioral effects, subjective effects and choice. Behav Pharmacol 1993;4 (3):217–30.
Trulson ME, Trulson TJ. Buspirone decreases the activity of serotonin-containing neurons in the dorsal raphe in freely-moving cats. Neuropharmacology 1986;25 (11):1263–6.
Westbrook RF, Greeley JD. Conditioned tolerance to morphine hypoalgesia: compensatory hyperalgesia in the experimental group or conditioned hypoalgesia in the control group? Q J Exp Psychol 1992;45B:161–87.