# Attenuation of methylphenidate-induced sensitization by co-administration of buspirone

**Nausheen Alam[2]*, Rahila Najam[1] and Sadaf Naeem[1]**
[1]Department of Pharmacology, Faculty of Pharmacy & Pharmaceutical Sciences, University of Karachi, Karachi, Pakistan
[2]Department of Pharmacology, Federal Urdu University of Arts, Sciences and Technology, Gulshan-e-Iqbal, Karachi, Pakistan

**Abstract**: Methylphenidate, which inhibit dopamine transporter is effective in the treatment of ADHD (attention deficit hyperactivity disorder), but long term use of this drug is often associated with addiction and dependence. Locomotor sensitization development to psychostimulants like methylphenidate is an important contributor to drug abuse induced by psychostimulants. Different studies have shown that long term administration of drugs of abuse increases the effectiveness of 5-hydroxytryptamine (5-HT)-$_{1A}$ somatodendritic receptors. Repeated buspirone administration reduces the effectiveness of 5-HT$_{1A}$ somatodendritic receptors. This study was designed to determine that buspirone co-administration may reduce methylphenidate-induced sensitization. The motor activity was compared by using familiar and novel environments after long-term administration of methylphenidate, buspirone and their co-administration. Long term oral administration of methylphenidate at a dose of 2.0mg/kg/day enhanced motor activity in home cage i.e activity of familiar environment monitored at alternate day. Locomotor enhancing effects of methylphenidate were augmented on 13$^{th}$ day of drug administration suggesting sensitization induced by the drug. The sensitization effects were significant in home cage monitored on alternate day and also in an open field monitored weekly. Buspirone co-administration at a dose of 10mg/kg/day prevented methylphenidate-induced sensitization. It is suggested that the sensitization development to methylphenidate may oppose by buspirone co-administration due to the reduction in the sensitivity of 5-HT$_{1A}$ somatodendritic receptors. These findings may help extend future therapeutics in ADHD.

**Keywords**: Methylphenidate, buspirone, open field, home cage and sensitization.

## INTRODUCTION

Psycho-stimulants like methylphenidate have long been utilized in young children with ADHD (attention-deficit hyperactivity disorder) (Pliszka., 2007, Greenhill *et al*., 2002).ADHD is identified as hyperactivity, inattention and impulsivity disorder. Patients identified with ADHD display noradrenergic and dopaminergic dysfunction within caudate nucleus (CN) and prefrontal cortex (PFC) (Arnsten and Dudley. 2005, Bush *et al*., 2005, Sergeant *et al*., 2002, Seidman *et al*., 2004). Investigations in children with ADHD have shown influences on self-esteem, academic attainment, employment stability, social and professional functioning (Barkley *et al*., 1990). The principle objectives of treatment are not simply to treat the symptoms but in addition to restore optimal functionality (Steele *et al*., 2006).

Despite of different beneficial effects, psychostimulants are also categorized as the drug of abuse because of their dependence and sensitization (Berridge and Devilbiss 2011., Solanto. 1998, Segal. 1975, Steketee, 2005). With repeated exposure to particular drug, the augmented motor-stimulant responseis characterized by behavioral sensitization (Steketee and Kalivas., 2011). Development of locomotor sensitization to psycho-stimulant drug is an important predictor of psycho-stimulant drug abuse in animal models (Robinson and Berridge., 1993).

**Corresponding author:* e-mail: nausheenasarosh@hotmail.com

Methylphenidate enhances levels of dopamine in the neocortex (Berridge *et al*., 2006). It blocks the dopamine transporter (Ferris and Tang., 1979, Ritz *et al*., 1987, Kollins *et al*., 2001, Barrett *et al*., 2005) thus enhances extra cellular concentration of dopamine and this action is thought to be the initiating molecular event that reinforces drug seeking behavior, eventually culminating in addiction (Teter, *et al*., 2006, Alizadeh and Ghabili. 2008). Acute intake of methylphenidate creates hyperactivity in rodents which is further enhanced with its repeated administration (Castellanos and Tannock. 2002, Rubia *et al*., 2010, Schecklmann *et al*., 2010).

Studies have shown that the dopamine system is very important for development and expression of behavioral sensitization (Kalivas *et al*., 1993a, 1993b). It has been shown that dopamine release was directly correlated with the consumption history of psycho stimulant, suggesting an increased response of dopamine with repeated use of drug (Cox *et al*., 2009). The stimulation of $D_2$ dopamine receptor is crucial for the diverse physiological functions regulation, like locomotor activity control (Picetti *et al*., 1997). Serotonin has inhibitory influence on dopamine neurotransmission in the mid brain as well as in the terminal region (Haleem, 2006).

Buspirone is agonist at 5-hydroxytryptamine (5-HT)-$_{1A}$ auto receptors and an antagonist at certain postsynaptic 5HT$_{1A}$ receptor site.5-HT$_{1A}$ somatodendritic inhibitory

receptors that control release of 5-HT are readily desensitized by chronic stimulation with a high-efficacy 5-$HT_{1A}$ agonist. 5-$HT_{1A}$ auto receptors desensitization leads to an increased 5-HT release which results in tonic activation of 5-$HT_{1A}$ postsynaptic receptors in the hippocampus and 5-$HT_{2c}$ in dopaminergic neuron (Haddjeri *et al*., 1998). Increased 5-$HT_{2C}$ expression decreases dopamine release and 5-$HT_{2C}$ receptor antagonism results in an increased extracellular dopaminergic response to many drugs (Bubar*et al*., 2006, Esposito *et al*., 2006).

Previously it is reported that repeated administration of oral therapeutic doses of methylphenidate produces locomotor sensitization whereas sensitization and cognitive improvement are more pronounced at smaller doses (Alam and Najam., 2013). The purpose of this study was to investigate the role of 5-$HT_{1A}$ somatodendritic receptors in behavioral sensitization produced after repeated administration of methylphenidate (Bloise *et al*., 2007, Haleem and Khan., 2003). It was hypothesized that 5-$HT_{1A}$ somatodendritic receptors desensitization by buspirone co-administration will increase the serotonin inhibitory influence on dopamine neurons to reduce the locomotor sensitization already reported for methylphenidate (Khan and Haleem., 2006).This study was designed to determine the effects of buspirone co-administration on motor sensitization as induced by repeated methylphenidate administration.

## MATERIALS AND METHOD

### *Animals*

Albino Wistar rats bred locally, weighing 180-200g, were individually housed under 12h dark and light cycles and controlled room temperature at 24±2°C. Animals were given access to free tap water and rodent diet cubes at least 7 days before starting the experiment to familiarize them with the environment. To eliminate the effects of stress, the rats were accustomed to different handling procedures. All the experiments were performed according to the approved protocols and were in accordance to the rules and regulation given by local animal care committee.

### *Behavioral parameters*

#### *Activity in a familiar environment of home cage.*

Home cages were used to monitor the activity of rats in familiar environment. Cages are (26x26x26cm) transparent perspex with sawdust cover floor. Rats were individually placed in these cages for 15min before monitoring the activity to get familiar with the environment (Batool *et al*., 2000). After 15minutes the numbers of cage-crossings were counted for 10 minutes.

### *Activity in a novel environment of open field*

Open field consists of square area (76x76cm) with 42cm high walls. The floor of open field is divided into 25 squares of equal size. Experiment was performed under white light in a quiet room. Animals were placed in the open field at the centre square. Numbers of square crossed by all four paws and latency to move were counted for 5 minutes (Ikram *et al*., 2007).

### *Drugs*

Methylphenidate HClwas obtained from local medical store and prepared in 0.9% NaCl (saline) and buspirone (Research Biochemicals Incorporated) prepared in distilled water. Drugs were administered in a volume of 1 ml/kg of body weight by per oral route twice a day individually and also co-administered to the 3rd group of treated animals. Control animals were treated with saline (0.9%) at the dose of 1 ml/kg PO twice a day.

### *Experimental protocol*

The protocol of experiment was designed to administer methylphenidate to 1st group of treated animals, buspirone and saline to 2nd group of treated animals, methylphenidate and buspirone to 3rd group of treated animals and saline to control animals orally two times daily (8.00 AM and 8.00 PM) for 6 weeks. Among the three groups of treated rats 1st group were given methylphenidate at the dose of 2mg/kg/day, 2nd group were given buspirone at the dose of 10mg/kg/day and 3rd group were given methylphenidate at the dose of 2mg/kg/day co-administered with buspirone at the dose of 10mg/kg/day according to the weight of the rats. Activity of drug treated and control rats in familiar environment were monitored on every alternate day during six weeks where as in novel environment were monitored on 1st day and weekly during the six weeks. To avoid order effect the experiment was performed in a balance design.

## STATISTICAL ANALYSIS

Results are represented as mean ±S.D. Statistical analysis was performed by using SPSS software (version 16.0). Data on the effect of methylphenidate, buspirone and co-administration of methylphenidate-buspirone on activity at alternate day in familiar environment and weekly in novel environment were statistically tested by three-way (ANOVA) analysis of variance repeated measure design to see the effects of various factors involved. Newman-Keuls test was performed for post hoc comparison and $P<0.01$ and $P<0.05$ were considered as significant values.

## RESULTS

### *Effect of repeated administration of methylphenidate, buspirone and their co administration on locomotor activity in home cage (familiar environment)*

Fig. 1 shows effects of repeated methylphenidate, buspirone and their co-administration on locomotor activity in home cage (activity box) on alternate days for 6 weeks. Analysis of data by 3-way ANOVA repeated

measure design showed significant effects of methylphenidate (df=1,19, F=19.48, p<0.01), buspirone (df=1,19, F=47.43, p<0.01) and repeated monitoring (df=2,40, F=18.71, p<0.01). Interactions between buspirone* methylphenidate (df=1,19, F=3.8, p<0.01), day*bus pirone (df=3,17, F=79.5, p<0.01), day* buspirone*methylphenidate (df=5,15, F=70.9, p<0.01) and day*methylphenidate (df=3,17, F=93.9, p<0.01) were significant.

***Effect of methylphenidate, buspirone and their co-administration on motor activity in familiar environment***

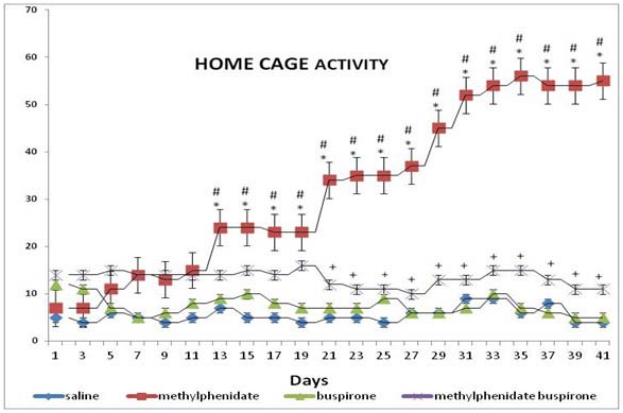


**Fig- 1**: Effect of methylphenidate, buspirone and their co-administration on motor activity in familiar environment of home cage (from day 1 to day 41 at alternate day). Values are means ± SD (n=8). Significant differences by Newman-Keuls test: *p<0.01 from similar week saline treated animals; +p<0.01 from similar week methylphenidate treated animals; #p<0.01 from similarly treated first day values following three-way ANOVA (repeated measure design).

Newman-Keul test showed that methylphenidate significantly increased activity in a home cage upon repeated administration from 13$^{th}$ day till 41$^{st}$ day (p<0.01) as compared to saline treated controls and from similarly treated first day values. Buspirone and co-administration (methylphenidate + buspirone) in familiar environment did not alter activity as compared to saline treated controls. Buspirone attenuated methylphenidate induced increase in activity was more pronounced (P<0.01) from 21$^{st}$ day till 41$^{st}$ day as compared to methylphenidate treated rats.

***Effect of repeated administration of methylphenidate, buspirone and their co administration on locomotor activity in open field (novel environment)***

Fig. 2 shows effects of repeated administration of methylphenidate, buspirone and their co administration on square crossed in open field (novel environment) monitored on first day and weekly for 6 weeks. Analysis of data by 3-way ANOVA repeated measure design showed significant effects of methylphenidate (df=1,30, F=14.2, p<0.01), buspirone (df=1,30, F=113.79, p<0.01) and repeated monitoring (df=5,90, F=79.6, p<0.01). Interactions between buspirone* methylphenidate (df=1,30, F=430.1, p<0.01), week*buspirone (df=5,30, F=100.7, p<0.01), week* buspirone*methylphenidate (df=5,30, F=40.88, p<0.01) and week*methylphenidate (df=5,30, F=14.3, p<0.01) were significant.

***Effect of methylphenidate, buspirone and their co-administration on motor activity in novel environment***

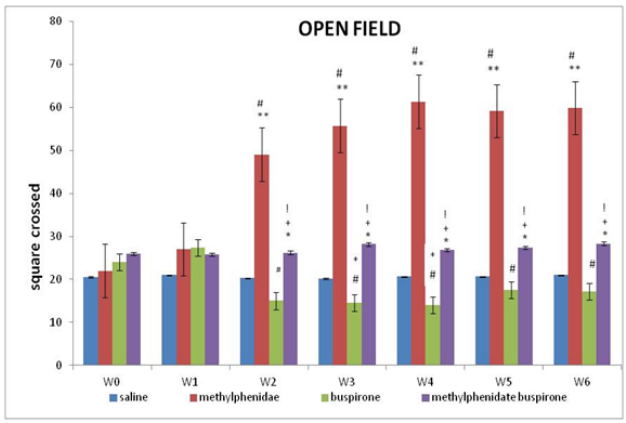


**Fig- 2**: Effect of methylphenidate, buspirone and their co-administration on square crossing in novel environment of open field (from day 1 to 6th week). Values are means ± SD (n=8). Significant differences by Newman-Keuls test:*p<0.05, **p<0.01 from similar week saline treated animals; #p<0.01 from similarly treated first day values; +p<0.01 from similar week methylphenidate treated animals; !p<0.01 from similar week buspirone treated animals following three-way ANOVA(repeated measure design).

Newman-Keul test showed that from 2$^{nd}$ till 6$^{th}$ week methylphenidate administration increased motor activity significantly (P<0.01) as compared to saline treated controls and from their first day values. Buspirone administration significantly (P<0.01) decreased activity from 2$^{nd}$ till 6$^{th}$ week as compare to the first day values and decreased significantly (P<0.05) in 3$^{rd}$ and 4$^{th}$ week as compared to saline treated controls. In co-administration treated rats motor activity significantly (P<0.01) decreased as compared to similar week methylphenidate treated rats from 2$^{nd}$ till 6$^{th}$ week whereas significantly increased as compare to similar week buspirone treated rats (P<0.01) and saline treated controls (P<0.05).

## DISCUSSION

The development of locomotor sensitization to psycho stimulants like methylphenidate is an important contributor to drug abuse induced by psycho stimulants (Robinson and Berridge., 1993). In the present study oral therapeutic dose (2.0mg/kg/day) of methylphenidate was administered to determine the locomotor sensitization

development and reduction of methylphenidate-induced sensitization by oral co-administration of buspirone (10mg/kg/day) via monitoring the rat's activity in the home cage i.e. familiar environment, and in the open field i.e. novel environment. Locomotor activity in home cage was monitored on every alternate day and in open field to maintain environment novelty, activity was monitored on day 1 and then weekly because monitoring frequent activity in open field could result in familiarization. Administration of methylphenidate produced locomotor sensitization in both familiar and novel environments i.e. on 13$^{th}$ day of drug administration in the home cage and in 2$^{nd}$ week in the open field i.e. novel environment where as buspirone administration decreased activity after 2 weeks in both environments and could attenuate methylphenidate -induced hyper locomotion in familiar and novel environments following co-administration. The activity of rats treated with both the drugs i.e. methylphenidate and buspirone have shown almost constantly same activity throughout 6 weeks of drug administration.

Methylphenidate used in children with ADHD (Pliszka. 2007, Greenhill *et al*., 2002) enhances extracellular concentrations of dopamine by blocking the dopamine transporter (Ferris and Tang, 1979, Ritz *et al*., 1987, Kollins *et al*., 2001, Barrett *et al*., 2005). This action is thought to be the initiating molecular event that reinforces drug-seeking behaviors, eventually culminating in addiction (Teter, *et al*., 2006,Alizadeh and Ghabili, 2008).

Role of dopamine is important in the psychostimulant-induced addiction as well as increase in motor activity (Robinson and Berridge, 2000). Subsensitization of dopamine $D_2$ auto receptor (Bevan, 1983) and super sensitization of DA postsynaptic receptors (Ackerman and White., 1992, Henry *et al*., 1989, Hopf *et al*., 2007) are directly related with behavioral sensitization induced by psychostimulants (Marin *et al*., 2008, Pierce and Kalivas, 1997). At the level of origin of dopamine system i.e. in the mid brain as well as in the terminal region serotonin has inhibitory influence on the activity of dopamine neurotransmission (Haleem, 2006).Therefore, activity enhancing effect of drugs of abuse could be modulated by serotonergic system (Hall *et al*., 2004, Przegaliski *et al*., 2000, Muller *et al*., 2003). The 5-$HT_{2C}$ receptor is one of the serotonergic receptor and this receptor activation by serotonin inhibits release of dopamine in different brain areas (Alex., 2005).

5-$HT_{1A}$ receptors role in the drug of abuse reinforcing effect was proposed because 5-$HT_{1A}$ receptors stimulation is capable of modulating cocaine-induced hyperactivity (De La Garza and Cunningham, 2000). CNS stimulants induced locomotor sensitization could be reduced by 5-$HT_{1A}$ receptor agonist administration. It has been reported that 5-$HT_{1A}$ receptor agonist osemozotan administration to mice sensitized by methamphetamine inhibited long-term behavioral sensitization (Ago *et al*., 2008). Co-administration of 8-OH-DPAT a 5-$HT_{1A}$ selective agonist to rats injected with amphetamine (2.5mg/kg) cause reduction in the sensitization to amphetamine challenge dose (2.5mg/kg) (Przegaliski *et al*., 2000). Acute 8-OH-DPAT administration causes certain changes in cocaine induced patterns of locomotor activity (De La Garza and Cunningham, 2000).

Buspirone is partial agonist at 5-$HT_{1A}$ receptors and antagonist at dopamine D2 receptors (Gobert *et al*., 1999, Peroutka, 1985). Turnover of 5-HT is reduced when the animals were injected with buspirone suggesting that the buspirone could preferentially stimulate 5-$HT_{1A}$somatodendritic receptors. Repeated buspirone administration decreased 5-$HT_{1A}$somatodendritic receptor responsiveness (Haleem*et al*., 2007, Haleem and Khan., 2003, Bloise *et al*., 2007, Khan and Haleem, 2006). 5-$HT_{1A}$somatodendritic receptors desensitization by buspirone co administration will increase release of 5-HT at 5-$HT_{2C}$ receptors. 5-HT would be available resulting in an increase serotonin inhibitory influence on the dopaminergic neurons activity to reduce locomotor sensitization expression to psycho stimulants (Khan and Haleem, 2006).

Results from the present study on reduction of sensitization induced by methylphenidate could be explained as reversal of super sensitivity of soma to dendritic receptors. Buspirone is 5-$HT_{1A}$somatodendritic receptors partial agonist with D2 receptors affinity, so it would be interesting to determine the role of post synaptic 5-$HT_{1A}$ and/or soma to dendritic receptors in the reduction of methylphenidate-induced sensitization by 8-OH-DPAT which is a full 5-$HT_{1A}$ agonist (Naidu and Kulkarni, 2001).

## CONCLUSION

It supports the hypothesis that serotonergic inhibitory influence enhancement on the dopaminergic neurons activity may be the mechanisms due to which methylphenidate-induced motor sensitization could be attenuated by 5-$HT_{1A}$ receptor agonists. As methylphenidate repeated administration increases 5-$HT_{1A}$somatodendritic receptors responsiveness and buspirone repeated co-administration decreases it, suggests that an increase in 5-$HT_{1A}$somatodendritic receptors sensitivity play a crucial role in sensitization induced by methylphenidate. The findings may play an important role in the use of methylphenidate for the treatment of ADHD**.**

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