Buspirone attenuates methylphenidate-induced growth inhibition

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Abstract: Methylphenidate is effective in the treatment of attention deficit hyperactivity disorder (ADHD) in children and adults, but its long term use can cause potential adverse effect on growth rate and variable effects on appetite. Previous studies have shown that long term administration of psychostimulant drugs 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 co-administration of buspirone may attenuate methylphenidate-induced effects on growth rate and food intake. Growth rate was calculated weekly in terms of change in body weight as percentage of preceding week's body weight and food intake was calculated weekly by subtracting the amount of food left in the hopper from the amount of food placed in the hopper as % in preceding week mg/gm of body weight after long-term administration of methylphenidate, buspirone and their co-administration. Long term oral administration of methylphenidate at a dose of 2.0 mg/kg/day decrease growth rate, but co-administration of buspirone at a dose of 10 mg/kg/day attenuates effect of methylphenidate on growth rate however food intake was significantly greater in all treated groups after 3 weeks of treatment. It is suggested that buspirone may oppose methylphenidate-induced growth inhibition by decreasing the sensitivity of somatodendritic 5-HT_{1A} receptors. These findings may help to extend future therapeutics in ADHD.

Keywords: Methylphenidate, buspirone, growth rate, food intake, dopamine, serotonin, $5HT_{1A}$ receptors.

INTRODUCTION

Methylphenidate is a medication of choice for persons, in specifically young children, who are suffering from attention-deficit/hyperactivity disorder (ADHD) (Sharma and Couture, 2014, Habibzadeh *et al*., 2011, Dopheide and Pliszka, 2009). The attention-improving aspect of methylphenidate has been attributed towards the amplification of dopamine release within the central nervous system. (Volkow *et al*., 2002). Methylphenidate enhances levels of norepinephrine and dopamine in the neocortex (Berridge *et al*., 2006). It blocks the dopamine transporter and the noradrenaline transporter (Ferris and Tang, 1979, Ritz *et al*., 1987, Kollins *et al*., 2001, Barrett *et al*., 2005) thus enhances extracellular concentrations of these catecholamines**.**

Stimulants have a favorable risk-benefit profile but they can cause potential adverse reactions in children using them, like weight loss (Vitiello, 2008) and anorexia (Goldfield *et al*., 2011, Davis *et al*., 2012). However previous studies have shown that long term administration of MPH can have variable effects on appetite (Işeri, 2007). Dopamine is one of the important neurotransmitters that affect feeding behavior, and its pharmacological manipulation produce marked effects on food intake (Bello and Hajnal., 2010). MPH by blocking dopamine transporters enhanced dopamine signals in dorsal striatum, amplification of weak dopamine signals in dorsal striatum increases the normal drive to eat. (Yolkow *et al*., 2002).

Prolonged treatment (more than 3 years) with stimulant medication was linked with attenuation of physical development during puberty (Poulton *et al*., 2013). Studies demonstrated that methylphenidate produce temporary reduction in height and weight gain (Aronsona, 2006). However, there is variance in the reported long-term ability of methylphenidate to sustain weight loss ranging from 3 months to the duration of administration of a clinically effective dose (Leddy *et al*., 2009, Spencer *et al*., 2005, Barkley *et al*., 1990). Studies have shown that it could link with the dopaminergic effect of stimulants. Dopamine can inhibit growth hormone secretion and directly affect height and growth in children (Faraone *et al*., 2008).

Buspirone is agonist at somatodendritic 5-HT_{1A} receptors and an antagonist at certain postsynaptic $5HT_{1A}$ receptor site (Zifa and Fillion1992). Buspirone also preferentially blocks the presynaptic rather than the postsynaptic (McMillen and Mc Donald 1983) D_2 dopamine receptors. Somatodendritic 5-HT_{1A} inhibitory receptors that control 5-HT release are readily desensitized by chronic stimulation with a high-efficacy 5-HT_{1A} agonist, the desensitization of 5-HT_{1A} autoreceptors, has been shown to lead to an increased release of 5-HT which results in tonic activation of postsynaptic 5-HT_{1A} receptors in the hippocampus and 5-HT_{2c} in dopaminergic neuron (Haddjeri *et al*., 1998).

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Feeding, social interaction and sexual activity all release dopamine subject to inhibition by 5-HT_{2C}. Increased 5-HT_{2C} expression decrease dopamine release in both the presence and absence of stimuli. Therefore it is hypothesize that buspirone co-administration with methylphenidate can reduce growth retardation produce after long-term administration of methylphenidate in therapeutic doses.

MATERIALS AND METHOD

Animals

Locally bred Albino Wister rats (weighing 180-200g) were housed individually under 12 h light and dark cycles (light on at 06:00h) and controlled room temperature (24±2 □c) with free access to rodent diet cubes and tap water at least 7 days before the start of experiment so that they could become familiar to the environment. They were accustomed to various handling procedures to nullify stress effects. All experiments were performed according to the approved protocols of local animal care committee.

Measurement of growth rate

Rats were weighted before starting the experiment. Gain in body weight was monitored weekly during the six-week treatment. The growth rate of each rat was calculated in terms of change in body weight as percentage of preceding week's body weight.

Measurement of food intake

Amount of food intake was monitored weekly by giving rats weighted amount of food and weighing the remaining food in the hopper of the cage. The amount of food consumed was calculated by subtracting the amount of food left in the hopper from the amount of food placed in the hopper. Intake was calculated for whole week as % in preceding week mg/gm of body weight.

Drugs

Methylphenidate HCl was obtained from local medical store and prepared in 0.9% NaCl (saline) and buspirone (Reserch Biochemicals Incorporated) prepared in distilled water. Drugs were administered by per oral route twice a day individually and also co-administered to the 3rd group of treated animals whereas control animals were treated with saline (0.9%) per oral twice a day.

Experimental protocol

The protocol of experiment was designed to administer methylphenidate and saline to 1st group of treated rats, buspirone and saline to 2nd group of treated rats, methylphenidate and buspirone to 3rd group of treated rats and saline and saline to control rats orally two times daily (8.00 AM and 8.00 PM) for six weeks. Among the three groups of treated rats 1st group was given methylphenidate in the dose of 2mg/kg/day (0.18-0.2ml of methylphenidate suspension 2 times daily), 2nd group was given buspirone at the dose of 10mg/kg/day (0.9-1ml of buspirone suspension 2 times daily) and 3rd group was given methylphenidate at the dose of 2mg/kg/day (0.18-0.2ml of methylphenidate suspension 2 times daily), and buspirone at the dose of 10mg/kg/day (0.9-1ml of buspirone suspension 2 times daily) according to the weight of the rats. The tablets were powdered and 10mg methylphenidate tablet was added in 10ml 0.9% NaCl and 5mg buspirone tablet was added in 5ml distilled water to make the suspension i.e. 1mg/ml, then calculated amount of suspension was administered to each rat with the feeding tubes. Control rats were given Saline 2.0 ml/kg/day i.e. 0.18-0.2ml 2 times daily according to the weight of the rats. Food intake and growth rate of rats were monitored weekly. The experiment was performed in a balanced design in such a way that food intake and growth rate of control and drug treated rats were measured alternately to avoid the order effect.

STATISTICAL ANALYSIS

Results are represented as mean ±S.D. Data on the effect of methylphenidate, buspirone and co-administration of methylphenidate-buspirone on weekly food intake and growth rate were statistically tested by three-way analysis of variance (ANOVA) repeated measure design to see the effects of various factors involved. Post hoc comparison was performed by Newman-Keuls test and $P<0.05$ and $P<0.01$ values were considered as significant.

RESULTS

Effect of repeated administration of methylphenidate, buspirone and their co administration on growth rate:

Fig. 1 shows effects of repeated administration of methylphenidate, buspirone and their co administration on growth rate monitored weekly for 6 weeks. Data analyzed by repeated measure three-way ANOVA revealed non-significant effects of methylphenidate ($df=1, 30$ $F=0.521$, $p>0.05$), buspirone ($df=1,30$, $F=0.761$, $p>0.05$) and significant effect of repeated monitoring ($df=5,90$, $F=6.598$, $p<0.01$). Interactions between buspirone* methylphenidate ($df=1,30$, $F=6.212$, $p<0.01$) and week*buspirone*methylphenidate ($df=5,30$, $F=3.73$, $p<0.05$) were found to be significant whereas interactions between week*methylphenidate ($df=5,30$, $F=1.269$, $p>0.05$) and week*buspirone ($df=5,30$, $F=0.560$, $p>0.05$) were non-significant.

Post hoc analysis by Newman–Keuls test demonstrated that co-administration of methylphenidate buspirone significantly ($p<0.01$) increased growth rate in 6th week from similar week saline, methylphenidate and buspirone treated rats but the increase growth rate in 1st till 5th week is not significant.

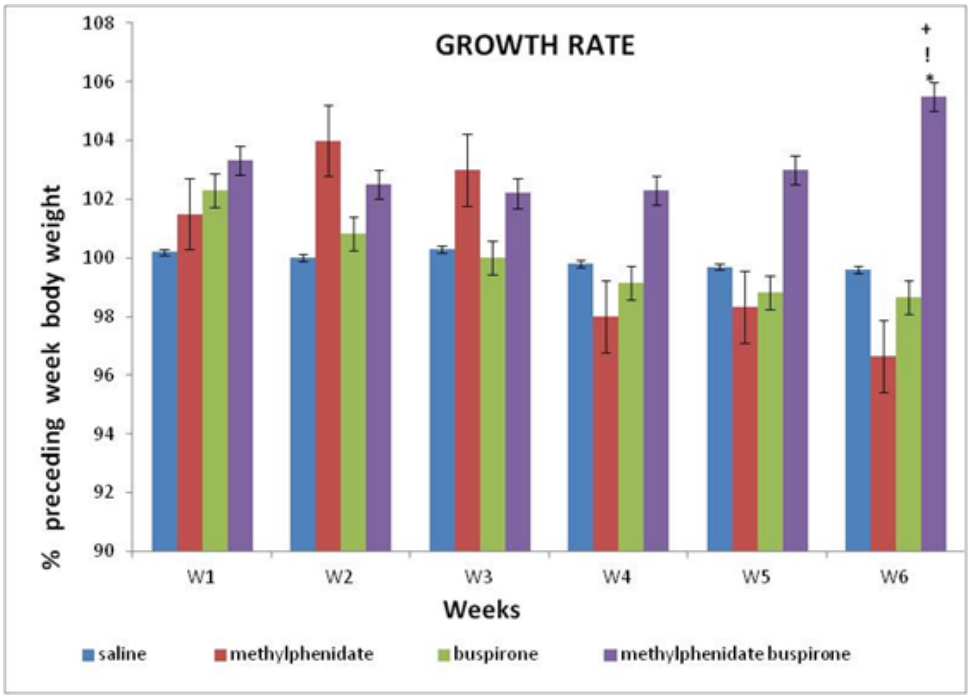

Fig. 1: Effect of methylphenidate, buspirone and their co-administration on growth rate monitored weekly for 6 weeks. Values are means ± SD (n=8). Significant differences by Newman-Keuls test: +p<0.01 from similar week methylphenidate treated animals; !p<0.05 from similar week buspirone treated animals; *p<0.05 from similar week saline treated animals following three-way ANOVA (repeated measure design).

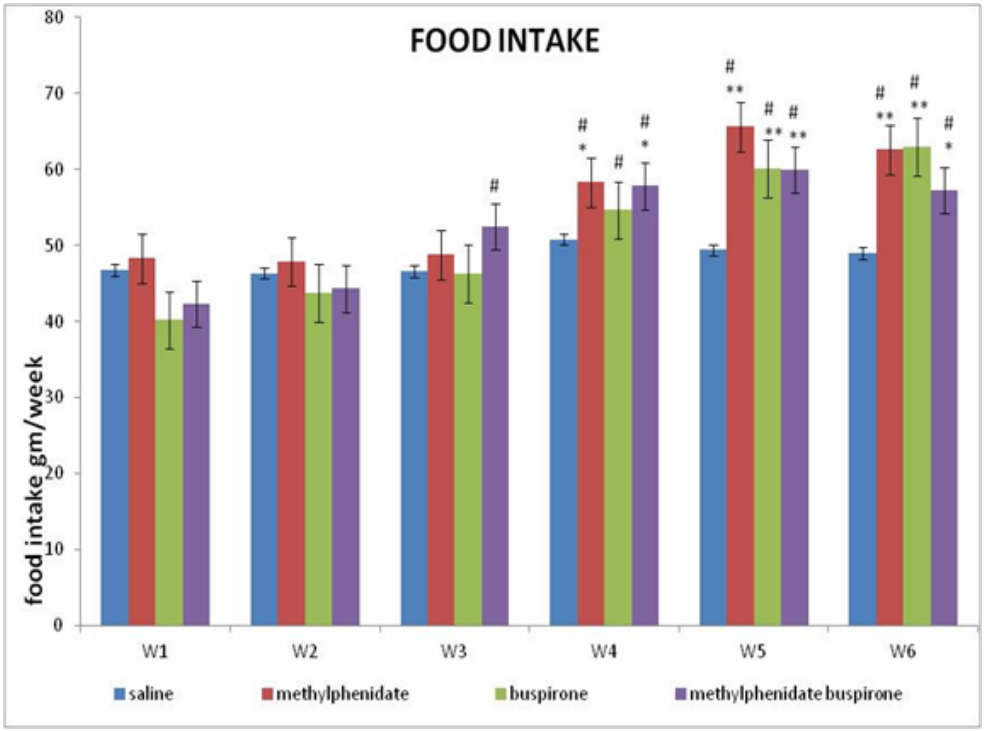

Fig. 2: Effect of methylphenidate, buspirone and their co-administration on food intake monitored weekly for 6 weeks. Values are means ± SD (n=8). Significant differences by Newman-Keuls test: #p<0.01 from similarly treated first day values, *p<0.05, **p<0.01 from similar week saline treated animals following three-way ANOVA (repeated measure design).

Effect of repeated administration of methylphenidate, buspirone and their co administration on food intake:
Fig.2 shows effects of repeated administration of methylphenidate, buspirone and their co administration on food intake monitored weekly for 6 weeks. Data analyzed by repeated measure three-way ANOVA revealed significant effects of methylphenidate ($df=1,30$, $F=39.39$, $p<0.01$), buspirone ($df=1,30$, $F=6.09$, $p<0.05$) and repeated monitoring ($df=5,90$, $F=12.5$, $p<0.01$). Interactions between buspirone* methylphenidate ($df=1,30$, $F=24.904$, $p<0.01$), week*buspirone ($df=5,30$, $F=17.884$, $p<0.01$), week*buspirone*methylphenidate ($df=5,30$, $F=18.834$, $p<0.01$) and week*methylphenidate ($df=5,30$, $F=15.87$, $p<0.01$) were found to be significant.

Post hoc analysis by Newman–Keuls showed that methylphenidate increased food intake non-significantly in 1st till 3rd week but significantly ($P<0.05$) in 4th and significantly ($P<0.01$) in 5th and 6th week as compare to similar week controls whereas methylphenidate significantly ($P<0.01$) increased caloric intake in 4th till 6th week from their first week values. Buspirone increased food intake significantly ($P<0.01$) in 5th and 6th week from similar week controls and from 4th till 6th week from their first day values. Co-administration of methylphenidate and buspirone significantly increased ($P<0.01$) caloric intake from 3rd to 6th week as compare to their first week values whereas increased significantly ($P<0.05$) in 4th and 6th week and significantly ($P<0.01$) in 5th week as compare to similar week controls.

DISCUSSION

Prolonged treatment with stimulant medication is known to associated with a slower rate of physical development (Poulton *et al*., 2013). Methylphenidate a medication prescribed for ADHD in children is known to produce temporary weight and height retardation. (Aronsona 2006, Leddy *et al*., 2009, Spencer *et al*., 1998, Barkley *et al*., 1990). This effect of methylphenidate observes after long-term administration but buspirone attenuate methylphenidate-induced growth retardation leads to increase growth rate in co-administration treated rats.

Mechanisms that can affect height and growth in children receiving stimulant medications are associated with the dopaminergic effect of stimulants. Dopamine might suppress growth hormone secretion and directly affect height development in children (Faraone *et al*., 2008, Lawton 1981). Other studies also shown that dopamine (DA) inhibit prolactin release and reduce lactotroph proliferation by activating D_2 receptors (Radl 2008).

Dopamine is one of the neurotransmitter involved with feeding behavior and its pharmacological manipulation has marked effects on food intake (Bello and Hajnal, 2010). In the present study caloric intake significantly increase in all drug treated groups following 3 weeks of treatment the dopamine release is significantly correlated with the increase in self-reports of hunger and desire for food. MPH blocks dopamine transporters, to enhance the detection of dopamine (Volkow *et al*., 2002) and buspirone interacts directly with dopaminergic systems to increase feeding. Buspirone increases striatal dopamine activity and increased dopaminergic neurotransmission in the striatum induces a general behavioral activation, which under certain conditions facilitates feeding (Fletcher and Davies 1990).

Serotonin has inhibitory effect on the dopaminergic neuron (Haleem 2006). Increase 5HT release by chronic buspirone co-administration stimulates 5-HT_{2C} receptors present on dopaminergic neurons (Millan *et al*., 1998). Activation of this receptor by serotonin inhibits dopamine release in certain areas of the brain (Alex 2005). 5-HT_{2C} receptors mediate the release and increase of extracellular dopamine in response to many drugs including caffeine, nicotine, amphetamine, morphine, cocaine, and others. 5-HT_{2C} antagonism increases dopamine release in response to reinforcing drugs, and many dopaminergic stimuli (Bubar *et al*.2006, Esposito *et al*., 2006).

Buspirone has partial affinity for 5-HT_{1A} receptors as agonist (Peroutka, 1985; Gobert *et al*., 1999). A decrease in the 5-HT turnover occurred when the animals were injected with buspirone suggesting that the drug could preferentially stimulate somatodendritic 5-HT_{1A} receptors. Repeated administration of buspirone decreased the responsiveness of somatodendritic 5-HT_{1A} receptor (Haleem *et al*., 2007, Bloise *et al*., 2007; Haleem and Khan, 2003 Khan and Haleem, 2006). Desensitization of somatodendritic 5-HT_{1A} receptors by co administration of buspirone will increase 5-HT release and 5-HT would be available at 5-HT_{2C} receptors resulting in an increase inhibitory influence of serotonin on the activity of dopaminergic neurons (Khan and Haleem, 2006). Feeding, social interaction, and sexual activity all release dopamine subject to inhibition by 5-HT_{2C}. Increased 5-HT_{2C} expression by buspirone and methylphenidate co-administration reduces dopamine release leads to growth enhancement.

Results from the present study on attenuation of methylphenidate-induced growth rate may be explained in terms of the reversal of supersensitivity at somatodendritic receptors. Since buspirone is partial agonist of somatodendritic 5-HT_{1A} receptors, it would be interesting to investigate the role of somatodendritic and/or post synaptic 5-HT_{1A} receptors in the attenuation of methylphenidate-induced growth rate by full 5-HT_{1A} agonist 8-OH-DPAT (Naidu and Kulkarni, 2001).

CONCLUSION

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 methylphenidate-induced inhibition of growth rate. As repeated administration of methylphenidate increases the responsiveness of somatodendritic 5-HT_{1A} receptors, the present results suggest that an increase in the sensitivity of somatodendritic 5-HT_{1A} receptors may have an important role in methylphenidate-induced growth inhibition. The findings may have important consequences in the use of methylphenidate for the treatment of ADHD.

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