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Reversal of haloperidol-induced tardive vacuous chewing movements and supersensitive somatodendritic serotonergic response by buspirone in rats

Darakhshan Jabeen Haleem [a,*], Noreen Samad [a], Muhammad Abdul Haleem [b]

[a] Department of Biochemistry, Neurochemistry and Biochemical Neuropharmacology Research laboratory, University of Karachi, Karachi 75270 Pakistan
[b] Department of Biomedical Engineering, Sir Syed University of Engineering and Technology, Karachi, Pakistan

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Abstract

Tardive dyskinesia (TD), a syndrome of involuntary hyperkinesias in the orofacial region that develops in patients chronically treated with neuroleptic agents is a major limitation of the therapy. Rats chronically treated with haloperidol exhibit vacuous chewing movements (VCMs) with the twitching of facial musculature and tongue protrusion. The syndrome is widely used as an animal model of TD. Evidence suggests a role of 5-hydroxytryptamine (5-HT; serotonin)-1A receptors in the pathogenesis and treatment of TD because repeated administration of haloperidol resulted in an increase in the effectiveness of 5-HT-1A receptors while drugs with agonist activity at 5-HT-1A receptors could attenuate haloperidol-induced VCMs. The present study was designed to test the hypothesis that a decrease in the responsiveness of somatodendritic 5-HT-1A receptors by the coadministration of buspirone could reverse the induction of VCMs and supersensitivity at 5-HT-1A receptors by haloperidol. Rats treated with haloperidol at a dose of 1 mg/kg twice a day for 2 weeks displayed VCMs with twitching of facial musculature that increased in a time dependent manner as the treatment continued to 5 weeks. Coadministration of buspirone attenuated haloperidol-induced VCMs after 2 weeks and completely prevented it after 5 weeks. The intensity of 8-hydroxy-2-di (*n*-propylamino) tetralin (8-OH-DPAT)-induced locomotion was greater in saline+haloperidol injected animals but not in buspirone+haloperidol injected animals. 8-OH-DPAT-induced decreases of 5-HT metabolism were greater in saline+haloperidol injected animals but not in buspirone+haloperidol injected animals. It is suggested that an impaired somatodendritic 5-HT-1A receptor dependent response is a major contributing factor in the pathophysiology of TD and a normalization of the somatodendritic response by drugs may help extending therapeutics in schizophrenia.

Keywords: Tardive dyskinesia; VCMs; Neuroleptics; Buspirone; Somatodendritic 5-HT-1A receptors

1. Introduction

Tardive dyskinesia (TD), a syndrome of involuntary hyperkinesias tic disorder in the orofacial region, which develops in patients chronically treated with neuroleptic agents such as haloperidol, is a major limitation of the neuroleptics therapy (Egan et al., 1997; Casey, 2000). In spite of its high frequency of occurrence the exact mechanism underlying the pathophysiology of TD is not known. Dopamine D2 receptor supersensitivity, gamma amino butyric acid (GABA) ergic hypofunction, excitotoxicity and oxidative stress have all been implicated in the pathophysiology of TD (Wright et al., 1998; Sachdev, 2000; Naidu et al., 2002, 2006).

Role of 5-hydroxytryptamine (5-HT; serotonin) and particularly 5-HT-1A receptors may be important in the etiology of schizophrenia and in the pathophysiology of tardive dyskinesia because postsynaptic 5-HT-1A receptors were upregulated in postmortem schizophrenic brains (Tauscher et al., 2002). 5-HT-1A receptor mediated endocrine responses were diminished in female schizophrenics compared to normal control subjects (Lee & Meltzer, 2001). Clozapine and other antipsychotics with

* Corresponding author.
E-mail addresses: djh@super.net.pk, darakhshan_haleem@yahoo.com (D.J. Haleem).

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substantial affinity for 5-HT-1A receptors (Newman-Tancredi et al., 1996; Jordan et al., 2002) produced negligible levels of extrapyramidal symptoms (EPS) while still controlling psychotic symptoms effectively (Haleem et al., 2002; Wilson, 1996).

Studies in animal models show that rats treated chronically with high doses of haloperidol develop orofacial movements described as vacuous chewing movements (VCMs) with the twitching of facial musculature (TFM). The dyskinetic orofacial parameters reported to occur after subchronic exposure to haloperidol (early onset VCMs) or only after chronic drug administration (tardive VCMs) are widely used for quantification in the animal model of TD (Ellison and See, 1989; Tamminga et al., 1990; Waddington, 1990, Egan et al., 1996; Kulkarni and Naidu, 2001).

A role of 5-HT-1A receptors in the treatment of TD is also shown in animal research. Thus reserpine-induced dyskinetic movements in a rat model of TD were reversed by the coadministration of buspirone (Queiroz and Frussa-Filho, 1999) a partial agonist at 5-HT-1A receptors (Peroutka, 1985; Gobert et al., 1999). 8-Hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT), a selective 5-HT-1A agonist, inhibited haloperidol-induced VCMs dose dependently (Naidu and Kulkarni, 2001).

In a previous study we have shown that administration of haloperidol at a dose of 5 mg/kg for only 2 weeks elicited an increase in the responsiveness of postsynaptic as well as presynaptic 5-HT-1A receptors (Haleem and Khan, 2003). It was suggested that a resultant decrease in the normal inhibitory serotonergic influence on motor activity may be involved in the precipitation of TD in patients on haloperidol therapy. Other authors have reported that repeated administration of buspirone, a partial 5-HT-1A agonist resulted in a decrease in the effectiveness of somatodendritic 5-HT-1A receptors (Tunnicliff et al., 1992; Okazawa et al., 1999). The present study was designed to test the hypothesis that coadministration of buspirone could reverse the induction of VCMs and supersensitivity at somatodendritic 5-HT-1A receptors by haloperidol in a rat model of TD.

In the first part of the study effects of various doses of buspirone were determined on motor activity and a selected dose of buspirone that did not decrease motor activity (Haleem et al., 2004, Shireen and Haleem, 2005) was used to monitor possible effects on the reversal of haloperidol-induced VCMs and supersensitive somatodendritic serotonergic response in the rat model.

2. Materials and methods

2.1. Animals & treatments

Locally bred male Wistar rats weighing 180–220 g purchased from HEJ Research Institute, Karachi, Pakistan were housed individually under a 12-hour light and dark cycle with free access to cubes of standard rodent diet and tap water 3 days before experimentation. All animal experiments were carried out according to a protocol approved by the Institutional Ethics Committee.

Forty eight animals were randomly divided to four equal groups (twelve animals in each group). (i) saline+saline (ii) saline+haloperidol (iii) buspirone+saline (iv) buspirone+haloperidol. The animals were injected accordingly with saline (1 ml/kg), haloperidol (1 mg/kg) and/or buspirone (1 mg/kg). The animals were injected twice a day at 9:00–9:30 and 17:00–17:30 h for 5 weeks as described by Marchese et al. (2002). Behavioral assessment of tardive VCMs was carried out weekly at 8:00–8:30 h i.e. 1 h before the drug injection. Behavioral and neurochemical effects of 8-OH-DPAT were monitored after a drug washout period of 2 days so that the presence of drug may not interfere with the effects of drug.

Animals of each of the above four groups divided in to saline or 8-OH-DPAT injected subgroups were injected accordingly with saline (1 ml/kg) or 8-OH-DPAT at a dose (0.5 mg/kg) selected on the basis of a previous study (Haleem and Khan, 2003). Hyperlocomotion and forepaw treading elicited by the drug were scored for 25 min starting 5 min post injection. Behavioral data were collected by a blind observer. Animals were killed 1 h after the drug or saline injection to collect the striatum as described before (Haleem and Khan, 2003). The samples were stored at a set temperature of −78°C for the estimation of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA).

2.2. Effects of buspirone on exploratory activity in an open field

Effects of different doses of buspirone on exploratory activity in an open field were monitored in a separate experiment. The experiment was conducted for selecting a dose of buspirone that is not effective in reducing motor activity. Twenty four animals divided in to four equal groups were injected with saline (1 ml/kg) or buspirone at doses of 1.0, 2.5 and 5.0 mg/kg. Activity in an open field was monitored for 5 min starting 1 h post injection.

2.3. Quantification of orofacial dyskinesia

Animals placed individually in a rectangular Perspex activity cage (26×26×26 cm) with saw dust covered floor were allowed to adapt to the observation cage for a period of 15 min. Orofacial dyskinesias were quantified as tardive VCMs during a 10 min observation period. A tardive VCM referred to the opening of mouth in the vertical plane with twitching of facial musculature and tongue protrusions, not directed towards physical materials.

2.4. Monitoring activity in an open field

The open field apparatus used in the present investigation consisted of a square area 76×76 cm with walls 42 cm high. The floor was divided in to 25 equal squares. To determine activity an animal was placed gently for the first time in the centre square of the open field. Number of square crossed were scored for a cut off time of 5 min.

2.5. 8-OH-DPAT-elicited 5-HT syndrome

Saline or haloperidol injected animals were placed individually in rectangular Perspex activity cages (26×26×26 cm)

with sawdust covered floor 15 min before injecting 8-OH-DPAT. The animals were observed for a total scoring period of 25 min starting 5 min post injection. During the observation period number of cage crossings and forepaw treading were scored. As described by Haleem and Khan (2003).

2.6. HPLC-EC determination of 5-HT and 5-HIAA

HPLC-EC determination was carried out as described before (Haleem et al., 2004). A 5 μ Shim-Pack ODS separation column of 4.0 mm internal diameter and 150 mm length was used. Separation was achieved by a mobile phase containing methanol (14%), octyl sodium sulfate (0.023%) and EDTA (0.0035%) in 0.1 M phosphate buffer of pH 2.9 at an operating pressure of 2000–3000 psi on Shimadzu HPLC pump. Electrochemical detection was achieved on Shimadzu LEC 6A detector at an operating potential of 0.8 volts. Calculations were done by an in line Shimadzu C-R6A Chromatopac.

2.7. Statistical analysis

Dose related effects of buspirone on exploratory activity in an open field were analyzed by one way ANOVA. Effects of buspirone on the time course of haloperidol-induced VCMs were analyzed by three factor ANOVA with buspirone and haloperidol as between subject factors and weeks as within subject factor. Effects of 8-OH-DPAT on 5-HT and 5-HIAA concentrations in the striatum were also analyzed by three way (8-OH-DPAT × buspirone × haloperidol) ANOVA. Data on 8-OH-DPAT-induced hyperactivity and forepaw treading, monitored only in 8-OH-DPAT injected animals were analyzed by two way (buspirone × haloperidol) ANOVA. Post-hoc comparisons were done by Newman–Keuls test. *P* values only of <0.05 were taken as significant.

3. Results

Fig. 1 shows the effects of buspirone at doses of 1.0, 2.5 and 5.0 mg/kg on the exploratory activity in an open field. One way ANOVA showed significant drug effect ($F=8.5$ *df* 3, 20 $p<0.01$). The post-hoc test showed that administration of buspirone at doses of 2.5 and 5.0 mg/kg decreased exploratory activity in the open field. The decreases at a dose of 1 mg/kg were not significant.

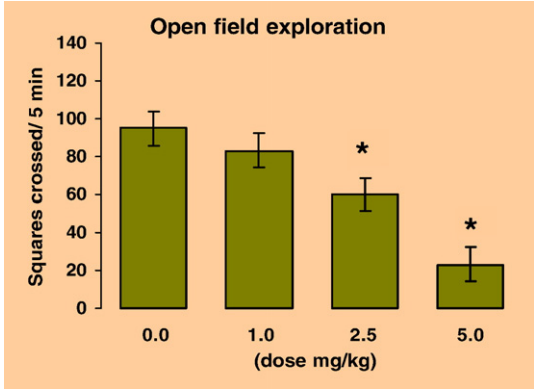

Fig. 1. Effects of various doses of buspirone on exploratory activity in an open field. Values are means ± S.E.M. ($n=6$) 1 h post injection. Significant differences by Newman–Keuls test *$P<0.01$ from saline injected animals following one way ANOVA.

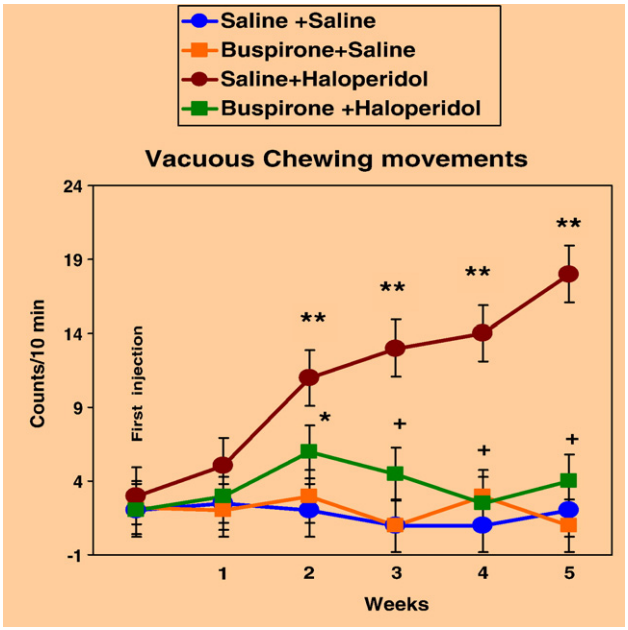

Fig. 2. Time course of the effects of buspirone on haloperidol-induced VCMs. Values are means ± S.E.M. ($n=12$) 22 h after the injection of drugs. Significant differences by Newman–Keuls test: *$p<0.05$, **$p<0.01$ from saline + saline injected rats. +$p<0.01$ from saline + haloperidol injected rats following three way ANOVA.

Fig. 2 shows the induction of tardive VCMs by haloperidol in saline and buspirone cotreated animals during 5 weeks of treatment. Three factor ANOVA revealed significant effects of haloperidol ($F=265$ *df* 1,44 $p<0.01$), buspirone ($F=105$ *df* 1,44 $p<0.01$) and week ($F=12.5$ *df* 5,220 $p<0.01$). Interaction between haloperidol × buspirone ($F=71$ *df* 1,44 $p<0.01$), week × buspirone ($F=23.7$ *df* 5,220 $p<0.01$), haloperidol × week ($F=15.2$ *df* 5,220 $p<0.01$) and buspirone × haloperidol × week ($F=14.5$ *df* 5,220 $p<0.01$) were all significant. Post-hoc analysis showed that haloperidol administration resulted in a significant induction of VCMs at 2 weeks and this increased in a time dependent manner during the subsequent weeks of drug administration. Animals cotreated with buspirone exhibited VCMs after 2 weeks but not after 3–5 weeks of drug administration. Buspirone + saline injected animals did not exhibit any increase in VCMs over control values. The results show a reversal of haloperidol-induced VCMs in rats cotreated with buspirone for only 3 weeks.

Fig. 3 shows 8-OH-DPAT-induced hyperactivity and forepaw treading in saline + saline, saline + haloperidol, buspirone + saline and buspirone + haloperidol treated animals. Data on number of cage crossings analyzed by two way ANOVA showed significant effect of haloperidol ($F=8.6$ *df* 1,20 $p<0.01$) and a significant interaction ($F=5.3$ *df* 1,20 $p<0.05$) between buspirone and haloperidol. Effects of buspirone ($F=2.2$ *df* 1,20 $p>0.05$) were not significant. Effects of haloperidol ($F=1.9$ *df* 1,20 $p>0.05$), buspirone ($F=0.8$ *df*

1,20 $p>0.05$) and interaction between haloperidol and buspirone ($F=2.8$ *df* 1,20 $p>0.05$) were not significant for forepaw treading. Post-hoc test showed that 8-OH-DPAT-induced cage crossings were greater in saline+haloperidol than saline+saline injected animals. Values were not significantly different in saline+saline, buspirone+saline and buspirone+haloperidol injected animals. Cage crossings were smaller in buspirone +haloperidol than saline+haloperidol injected animals. The results suggested an increase in 8-OH-DPAT-induced hyperactivity in haloperidol injected animals and reversal of this response in rats cotreated with buspirone.

Fig. 4 shows 8-OH-DPAT-induced decreases of 5-HT and 5-HIAA concentrations in rats treated with saline+saline, buspirone+saline, saline+haloperidol and buspirone+haloperidol. Data on 5-HT analyzed by three way ANOVA showed significant effect of 8-OH-DPAT ($F=7.9$ *df* 1,40 $p<0.01$), haloperidol ($F=5.3$ *df* 1,40 $p<0.05$) and significant haloperidol×buspirone ($F=4.8$ *df* 1,40 $p<0.05$), 8-OH-DPAT×haloperidol ($F=5.9$ *df* 1,40 $p<0.05$) interaction. Effects of buspirone ($F=1.2$ *df* 1,40 $p>0.5$), buspirone×8-OH-DPAT ($F=1.8$ *df* 1,40 $p>0.5$) and buspirone×aloperidol×8-OH-DPAT ($F=2.6$ *df* 1,40 $p>0.05$) were not significant. Data on 5-HIAA also showed significant effect of 8-OH-DPAT ($F=8.2$ *df* 1,40 $p<0.01$), haloperidol ($F=4.3$ *df* 1,40 $p<0.05$) and significant haloperidol×buspirone ($F=5.1$ *df* 1,40 $p<0.05$), 8-OH-DPAT×haloperidol ($F=4.8$ *df* 1,40 $p<0.05$) interaction. Effects of buspirone ($F=2.8$ *df* 1,40 $p>0.05$), buspirone×8-OH-DPAT ($F=2.8$ *df* 1,40 $p>0.5$) and buspirone×haloperidol×8-OH-DPAT ($F=1.6$ *df* 1,40 $p>0.05$) were not significant. Post-hoc test showed that

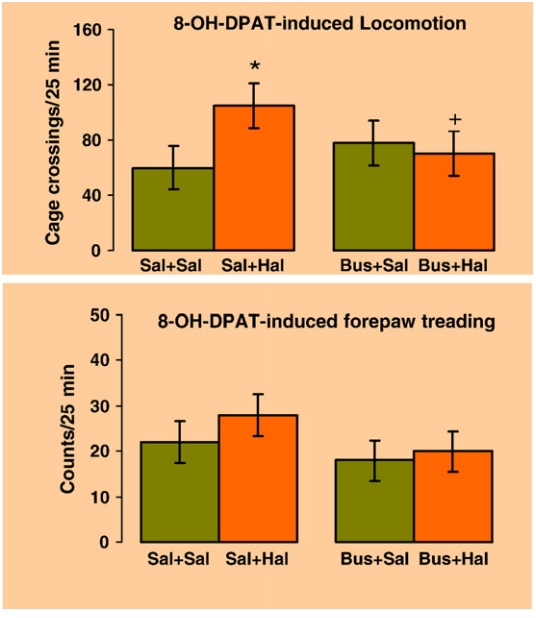

Fig. 3. 8-OH-DPAT-induced hyperactivity and forepaw treading in saline+saline, buspirone+saline, saline+haloperidol and buspirone+haloperidol injected animals. Values are means±S.E.M. ($n=6$) from 5–30 min post 8-OH-DPAT injection and 48 h after buspirone or haloperidol injection. Significant differences by Newman–Keuls test *$p<0.01$ from saline+saline injected animals. +$p<0.01$ from saline+haloperidol injected animals following two way ANOVA.

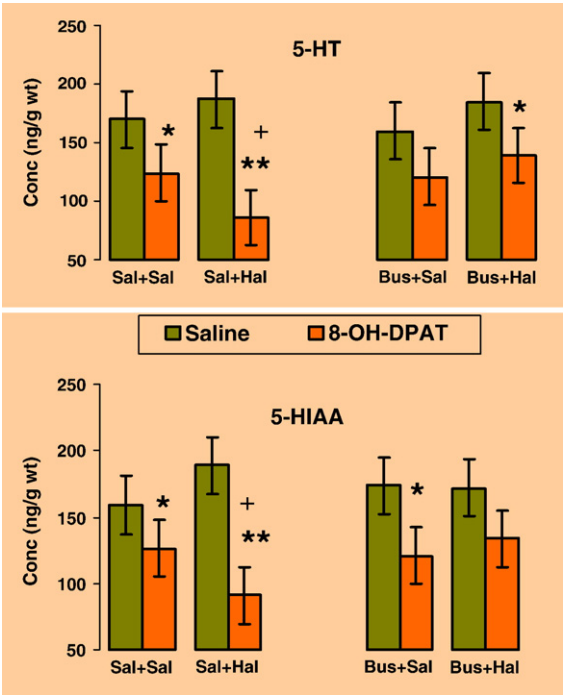

Fig. 4. 8-OH-DPAT-induced decreases of 5-HT and 5-HIAA concentrations in the striatum of saline+saline, buspirone+saline, saline+haloperidol and buspirone+haloperidol injected animals. Values are means±S.E.M. ($n=6$) 1 h after the injection of 8-OH-DPAT and 48 h after buspirone or haloperidol injection. Significant differences by Newman–Keuls test *$p<0.05$, **$p<0.01$ from respective saline injected animals; +$p<0.05$, ++$p<0.01$ from saline+saline injected animals following three way ANOVA.

administration of 8-OH-DPAT decreased 5-HT and 5-HIAA concentrations in saline+saline as well as saline+haloperidol treated animals. The decreases were greater in saline+haloperidol than saline+saline injected animals. Administration of 8-OH-DPAT decreased 5-HIAA but not 5-HT levels in buspirone+saline treated animals while 5-HT but not 5-HIAA levels decreased significantly in buspirone+haloperidol injected animals.

4. Discussion

Other authors have reported that induction of orofacial dyskinesias by haloperidol at a dose of 1.5 mg/kg/day for 3 weeks could be reversed by the coadministration of 5-HT-1A agonists such as 8-OH-DPAT (Naidu and Kulkarni, 2001) and sarizotan (Rosengarten et al., 2006). Reserpine-induced orofacial dyskinesias were also reversed by the coadministration of buspirone (Queiroz and Frussa-Filho, 1999), a partial agonist at 5-HT-1A receptors (Peroutka, 1985). In the present study treatment with haloperidol at a dose of 1 mg/kg twice a day induced tardive VCMs in 2 weeks that increased in a time dependent manner as the treatment continued for 5 weeks. Coadministration of buspirone at a dose of 1.0 mg/kg attenuated and completely reversed the induction in a time dependent manner (Fig. 2).

A role of somatodendritic 5-HT-1A receptors in the onset of VCMs was proposed (Haleem and Khan, 2003) because

administration of haloperidol for 2 weeks elicited VCMs (Egan et al., 1996; Ellison and See, 1989; Kulkarni and Naidu, 2001; Tamminga et al., 1990; Waddington, 1990) and increased the responsiveness of somatodendritic serotonin-1A receptors in rats (Haleem and Khan, 2003). An important finding of the present study is that the reversal of haloperidol-induced VCMs in rats cotreated with buspirone was associated with the reversal of haloperidol-induced increase in the responsiveness of somatodendritic 5-HT-1A receptors. The present results therefore suggest that somatodendritic 5-HT-1A receptors have an important role in the precipitation and alleviation of haloperidol-induced VCMs.

The dopamine system has traditionally been considered crucial to the control of motor activity (Clausing et al., 1995; Petry et al., 1993). With respect to the anatomical site of action a view has developed that striatum is involved in the control of motor behavior. The serotonergic system is known to play a role in the modulation of activity of dopaminergic neurons. The nature of modulation seems to be inhibitory and at the level of origin of dopamine system in the midbrain as well as in the terminal region (Balsara et al., 1979; Sandyk and Fisher, 1988). Serotonin antagonists with selectivity towards 5-HT-2C receptors could release dopamine neurotransmission from the inhibitory influence of 5-HT to alleviate parkinsonian like effects of neuroleptics (Kapur and Ramington, 1996; Pessia et al., 1994; Millan et al., 1998).

Stimulation of somatodendritic 5-HT-1A receptors by a selective 5-HT-1A agonist 8-OH-DPAT resulting in a decrease in the availability of serotonin at 5-HT-2C receptors could also release dopamine neurotransmission from the inhibitory influence of 5-HT to attenuate neuroleptic-induced catalepsy (Haleem et al., 2004). An increase in the effectiveness of somatodendritic 5-HT-1A receptors in rats treated with haloperidol for 5 weeks (Fig. 4) would be expected to decrease the inhibitory influence of serotonin on the activity of dopaminergic neurons. The results are therefore consistent with the notion that a decrease in the serotonergic influence on the activity of dopaminergic neurons is involved in the elicitation of VCMs while a normalization of serotonergic influence in rats cotreated with buspirone could reverse the induction of VCMs by haloperidol.

Buspirone is an azaspirodecanedione derivative that has affinity for 5-HT-1A receptors as partial agonist and dopamine D2 receptors as an antagonist (Peroutka, 1985; Gobert et al., 1999). The drug used to relieve clinical anxiety is also effective in the treatment of depression (Blier and Montigny, 1990; Blier and Ward, 2003; Haller et al., 2004; Khouzam and Emes, 2002). A decrease in 5-HT turnover has been reported to occur following the 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. In the present study buspirone was injected at a dose (1 mg/kg) that was found to decrease 5-HT turnover in the striatum (Haleem et al., 2004; Shireen and Haleem, 2005) without producing a significant decrease in motor activity (Fig. 1). The mechanism by which buspirone could reverse haloperidol-induced increase in the effectiveness of somatodendritic 5-HT-1A receptors (Fig. 4) may involve a desensitization of the receptors by repeated administration of the drug (Okazawa et al, 1999) at doses that stimulate preferentially somatodendritic 5-HT-1A receptors (Shireen and Haleem, 2005).

A reversal of reserpine-induced dyskinesia by higher (3 mg/kg) dose of buspirone (Queiroz and Frussa-Filho, 1999) may also involve desensitization of somatodendritic 5-HT-1A receptor. However, in the present investigation higher (>1.0 mg/kg) doses of buspirone as they tend to decrease motor activity (Fig. 1) due to dopamine D2 receptor blockade were not used. Thus long term administration of buspirone at this dose did not alter 8-OH-DPAT-induced hyperactivity in buspirone+saline injected animals (Fig. 3).

Although acute administration of buspirone decreased 5-HT synthesis and release in the terminal region but repeated administration at a dose of 10 mg/kg for 2 weeks (Blier and Ward, 2003) and at a dose of 3 mg/kg for 10 days (Tunnicliff et al., 1992) produced no effect on 5-HT synthesis suggesting a decrease in the responsiveness of receptors involved in the effect. This is also evident in the present study (Fig. 4) where the effects of 8-OH-DPAT in decreasing 5-HT concentration were smaller in buspirone+saline than saline+saline injected animals. The results suggest that a decrease in the responsiveness of 5-HT-1A receptors could reverse the induction of supersensitivity by haloperidol.

Administration of 8-OH-DPAT elicits a hyperactivity syndrome often described as serotonin syndrome. Increase in motor activity, forepaw treading and flat body posture are some of the distinct behavioral components of the syndrome (Haleem, 1992). Administration of haloperidol for 2 weeks elicited a significant increase in motor activity while the intensity of forepaw treading was not altered has been shown previously (Haleem and Khan, 2003). Similar effects were found after 5 weeks of haloperidol administration in the present study (Fig. 3). In addition the present study shows that long term administration of buspirone at a dose of 1 mg/kg twice daily for 5 weeks did not alter 8-OH-DPAT-induced motor activity or forepaw treading.

The mechanism by which 8-OH-DPAT elicits hyperactivity may involve a stimulation of somatodendritic 5-HT-1A receptors resulting in a decrease in the inhibitory influence of 5-HT on dopamine neurotransmission (Haleem et al., 2004). A decrease in the intensity of 8-OH-DPAT-induced hyperactivity syndrome by reserpine and haloperidol suggests that dopamine D2 receptors also contribute in the expression of the syndrome (Tricklebank et al., 1984; Yamada et al., 1988; Haleem and Khan, 2003). An increase in the sensitivity of dopamine D2 receptors has been shown to occur following long term administration of haloperidol (Halperin at al., 1988). The present study shows that an increase in the effectiveness of somatodendritic 5-HT-1A receptors in rats treated chronically with haloperidol (Fig. 4) resulting in an extra decrease in the inhibitory influence of 5-HT on motor activity may also contribute to the greater hyperactivity observed in these rats (Fig. 3). Thus reversal of somatodendritic serotonin-1A receptor dependent response in rats cotreated with buspirone (Fig. 4) resulted in the reversal of hyperactivity to 8-OH-DPAT (Fig. 3).

On the other hand, a marginal but significant decrease in the effectiveness of somatodendritic 5-HT-1A receptors in

buspirone+saline treated rats (Fig. 4) did not produce a significant decrease in 8-OH-DPAT-induced hyperactivity in these rats (Fig. 3). The results are explainable in terms of an increase in the sensitivity of dopamine D2 receptors following chronic blockade of dopamine D2 receptors by buspirone.

Evidence suggests that serotonin also has a stimulatory influence on motor activity (Haleem et al., 2004). These effects of serotonin are possibly mediated via post synaptic 5-HT-1A receptors. Thus systemic administration of 8-OH-DPAT, a selective serotonin-1A agonist acting via somatodendritic as well as postsynaptic receptors, attenuated haloperidol-induced catalepsy and decreased 5-HT metabolism in the striatum. Although administration of the partial 5-HT-1A agonist buspirone at a dose that preferentially stimulated somatodendritic 5-HT-1A receptors also produced similar effects but anticataleptogenic and not the serotonin metabolism reducing effects of 8-OH-DPAT were greater than buspirone, suggesting a role of postsynaptic 5-HT-1A receptors in the anticataleptogenic profile of 8-OH-DPAT.

Unlike 5-HT-2C receptors which produce an inhibitory influence on the activity of dopaminergic neurons, stimulation of postsynaptic 5-HT-1A receptors may lead to an increase in the activity of dopaminergic neurons is also shown in neurochemical investigations. Thus administration of haloperidol is accompanied by a compensatory dose dependent increase in the concentration of homovanillic acid (HVA), a metabolite of dopamine in the striatum and other brain regions (Haleem et al., 2002). Administration of 8-OH-DPAT but not buspirone (Haleem et al., 2004) prevented haloperidol-induced compensatory increases of dopamine metabolites in many brain regions (Anderson and Kalpitrick, 1996; Ichikawa and Meltzer, 2000; Haleem et al., 2004) suggesting a role of postsynaptic 5-HT-1A receptors in the reversal of haloperidol-induced changes of dopamine metabolism and release.

It may be interesting to investigate the role of somatodendritic and/or post synaptic 5-HT-1A receptors in the attenuation of haloperidol-induced VCMs by the full 5-HT-1A agonist 8-OH-DPAT (Naidu and Kulkarni, 2001) or 5-HT-1A agonist/dopamine-D3/D4 ligand sarizotan ((Rosengarten et al., 2006). The present results on the reversal of haloperidol-induced VCMs by buspirone are largely explainable in terms of the reversal of supersensitivity at somatodendritic receptors. An upregulation of dopamine D2 receptors if also occurs following long term administration of buspirone seems less important in the reversal of haloperidol-induced VCMs because chronic administration of haloperidol that elicits VCMs also increased the sensitivity of dopamine D2 receptors (Halperin et al., 1989).

In conclusion, the present study shows that induction of VCMs and supersensitivity at serotonin-1A receptors by the long term administration of haloperidol is reversed by the coadministration of buspirone at low doses. The results show that a supersensitive somatodendritic serotonergic influence on dopamine neurotransmission may be a contributing factor in the onset of TD. It is suggested that drugs that preferentially stimulate somatodendritic 5-HT-1A receptors may be of use in extending therapeutics in schizophrenia.

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