ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Acta Neurobiol Exp 2007, 67: 389–397

Increase in the effectiveness of somatodendritic 5-HT-1A receptors in a rat model of tardive dyskinesia

Noreen Samad[1], Asma Khan[1], Tahira Perveen[1], Saida Haider[1], Muhammad Abdul Haleem[2], and Darakhshan Jabeen Haleem[1]

[1]Department of Biochemistry, Neurochemistry and Biochemical Neuropharmacology Research Laboratory, University of Karachi, Karachi-75270, Pakistan; [2]Department of Biomedical Engineering, Sir Syed University of Engineering and Technology, Karachi, Pakistan

Abstract. The present study concerns responsiveness of pre- and postsynaptic 5-hydroxytryptamine (5-HT)-1A receptors in a rat model of tardive dyskinesia (TD). Vacuous chewing movements (VCMs) in rats are widely accepted as an animal model of TD. Results show that haloperidol injected at a dose of 1 mg/kg twice a day for 5 weeks elicited VCMs, which increased in a time dependent manner following the drug administration for 3–5 weeks. Tolerance was produced in motor coordination during the potentiation of VCMs. Exploratory activity in an open field and in an activity box decreased in haloperidol treated animals. The effects of 8-hydroxy-2-(di-n-propylamino)tetraline (8-OH-DPAT; 0.5 mg/kg) were monitored 48-h after withdrawal from repeated administration of haloperidol. 8-OH-DPAT-induced locomotion was greater in haloperidol treated rats. 5-HT synthesis increased in haloperidol treated animals, while 8-OH-DPAT-induced decreases of 5-HT synthesis were greater in repeated haloperidol than repeated saline injected animals. The results suggest that an increase in the effectiveness of somatodendritic 5-HT-1A receptors may decrease the inhibitory influence of 5-HT on the activity of dopaminergic neurons to precipitate VCMs. The 5-HT-1A agonist may help to alleviate neuroleptic-induced TD.

Correspondence should be addressed to N. Samad, Email: noreensamad_ku@yahoo.com

Key words: tardive dyskinesia, motor coordination, haloperidol, 8-OH-DPAT, somatodendritic 5-HT-1A receptor

INTRODUCTION

Neuroleptics are used extensively in the treatment of schizophrenia (Korostenskaja et al. 2006). Unfortunately typical antipsychotics such as haloperidol and chlorpromazine often cause distressing side effects involving extrapyramidal systems. These adverse reactions comprise a variety of movement disorders (Grohman et al. 1990) including tardive dyskinesia, which occurs in 20–40% of the patient population (Casey 2000, Kulkarni and Naidu 2001). Tardive dyskinesia, a syndrome of potentially irreversible, involuntary hyperkinetic disorder that occurs during chronic neuroleptic treatment, is a major limitation of neuroleptic therapy (Casey 2000, Egan et al. 1997). Vacuous chewing movements (VCMs) in rats are widely accepted as a rat model of TD. It has been shown that rats repeatedly treated with haloperidol develop VCMs (Ellison and See 1989).

It has been hypothesized that dopamine receptor supersensitivity arising from upregulation of dopamine D2 receptors following neuroleptic therapy could be the reason for the development of TD. In addition to dopamine receptors, serotonin receptors are also important in the etiology of schizophrenia and in the elicitation of extrapyramidal symptoms (EPS). An increase in the responsiveness of postsynaptic as well as presynaptic 5-hydroxytryptamine (5-HT)-1A receptors in rat brain has also been observed following prolonged neuroleptic treatment (Haleem and Khan 2003).

A role for 5-HT-1A receptors in the treatment of TD is also shown in animal research. 5-HT-1A receptors are present on the soma and dendrites of 5-HT neurons and on postsynaptic sites (Verge et al. 1985). Stimulation of somatodendritic receptors by a selective 5-HT-1A agonist such as 8-hydroxy-2-(di-n-propylamino)tetraline (8-OH-DPAT) inhibits 5-HT synthesis to decrease its release from the nerve endings (Haleem 1990, Huston et al. 1989, Koprowska et al. 2002). 8-OH-DPAT-induced decreases of 5-HT synthesis therefore give a measure of presynaptic receptor responsiveness (Haleem 1999). Stimulation of postsynaptic 5-HT-1A receptors by 8-OH-DPAT elicits a hyperactivity syndrome that is taken as a measure of postsynaptic receptor responsiveness (Haleem 1992, Haleem et al. 2002b). Previously it has been reported that 8-OH-DPAT inhibited haloperidol-induced VCMs dose dependently (Naidu and Kulkarni 2001).

It may be hypothesized that 5-HT-1A receptor responses are increased following long term administration of haloperidol and have a significant role in the onset of haloperidol-induced VCMs. The present study was designed to monitor the responsiveness of pre- and postsynaptic 5-HT-1A receptors following long term administration of haloperidol in rats exhibiting TD.

METHODS

Animals

Twenty-four locally bred male albino Wistar rats (age: 18–20 weeks), weighing 220–250 g purchased from the Agha Khan University, Pakistan, were housed individually under a 12 h light-dark cycle (lights on at 6:00 AM) with free access to cubes of standard rodent diet and tap water 2 days before starting the experiment. All experiments were performed according to a protocol approved by a local animal care committee.

Drugs

Haloperidol (Serenace, Searle, USA) purchased as injectable ampoules of 5 mg/ml, was injected intraperitoneally at a dose of 1 mg/ml/kg body weight twice daily. (±)8-OH-DPAT-HBr, purchased from Research Biochemicals (RBI, USA), was dissolved in saline and injected subcutaneously at a dose of 0.5 mg/ml/kg body weight. Control animals were injected with saline in volumes of 1 ml/kg.

Experimental protocol

Twenty-four animals were randomly divided to two equal groups (12 animals in each group): (1) saline injected (1 ml/kg); (2) haloperidol injected (1 mg/kg). The two groups of animals were injected twice a day at 09:00–09:30 AM and 05:00–05:30 PM for 5 weeks. Exploratory activities in an activity box and in open field, and motor coordination, respectively, were monitored 30 min, 40 min, and 60 min post-injection on day 1 and weekly during 5 weeks of drug administration. TD was monitored weekly before the drug administration.

Two days after the haloperidol withdrawal the animals were further divided into four equal groups: (1) repeated saline plus saline; (2) repeated saline plus 8-OH-DPAT; (3) repeated haloperidol plus saline;

(4) repeated haloperidol plus 8-OH-DPAT. They were injected accordingly with saline (1 ml/kg) and 8-OH-DPAT (0.5 mg/kg). Thirty minutes after the injection of saline or 8-OH-DPAT all animals were injected with 3-hydroxybenzyl hydrazine at a dosage of 100 mg/kg.

Postsynaptic 5-HT-1A receptor dependent responses were monitored as the intensity of 5-HT syndrome elicited in 8-OH-DPAT injected animals. Various components of the syndrome were scored for 20 min starting 5 min post injection.

Presynaptic 5-HT-1A receptor dependent responses were monitored as the decrease of 5-HT synthesis following the administration of 8-OH-DPAT. The synthesis of 5-HT was determined as the accumulation of 5-hydroxytryptophan (5-HTP) 30 min after the injection of the decarboxylase inhibitor 3-hydroxybenzyl hydrazine at a dosage of 100 mg/kg, as described elsewhere (Haleem et al. 2002b, Nolan et al. 2000). Thirty min after the injection of saline or 8-OH-DPAT all animals were injected with 3-hydroxybenzyl hydrazine at a dosage of 100 mg/kg. The animals were sacrificed 30 min after the injection of 3-hydroxybenzyl hydrazine, i.e., 1 h after the subcutaneous injection of saline or 8-OH-DPAT, to collect tissue from the striatum, as described previously (Haleem 1990, Haleem and Perveen 1994). The samples were stored at –70°C for the HPLC-EC determination of 5-HTP.

Behavioral analysis

ACTIVITY IN AN ACTIVITY BOX

To monitor activity in a familiar environment, activity boxes were used. The rectangular Perspex activity cage consisted of small square area (26 × 26 × 26 cm) with sawdust-covered floor. Before monitoring the activity an animal was placed in it for 15 min for habituation. Numbers of crossings across the box were monitored for 10 min.

OPEN FIELD ACTIVITY

To monitor activity in a novel environment, an open field apparatus was used. That used in the present investigation consisted of a square area 76 × 76 cm with walls 42 cm high. The floor was divided by lines into 25 equal squares. To determine activity a rat was placed in the center square of the open field. The numbers of squares crossed with all four paws were scored for 5 min.

ROTA-ROD ACTIVITY

Motor coordination was assessed on a Rota-rod (UGO-BASILE, Italy). The Rota-rod (Knurled Perspex) with a drum of 7 cm radius and a speed of 2–20 rpm during training sessions and a fixed speed of 20 rpm during the test session. The surface of the drum is not too glossy and smooth to avoid the slippery effects when a rat was placed on it. A day before the treatment rats were trained in a single session until they attained 150 s on the Rota-rod. The latency to fall in a test session of 150 s was taken as measure of motor coordination.

VACUOUS CHEWING MOVEMENTS (*VCMS*) *QUANTIFICATION*

Animals were placed individually in an activity box (26 × 26 × 26 cm) with sawdust-covered floor and were allowed to adapt to the observation cage for a period of 15 min. VCMs were monitored during 10 min observation periods. For calculation purposes, each burst of purposeless chewing was counted as one, if its duration was at least 3 seconds.

8-OH-DPAT ELICITED 5-HT SYNDROME

Animals were placed individually in rectangular Perspex activity cages (26 × 26 × 26 cm) with sawdust covered floor 15 min before injecting 8-OH-DPAT. Forepaw treading and locomotion elicited by the drug were scored as described earlier (Haleem et al. 2002b). The experiment was conducted on a group of four rats at a time. Saline and haloperidol pre-injected rats were placed in a separate observation cages and injected with 8-OH-DPAT in a balanced design. The number of cage crossings (movement in any direction with all four paws) and forepaw treadings were scored for 1 min, every 5 min up to 25 min, i.e. in 5 sessions of 1 min each. A total of 5 scoring periods was later determined.

Neurochemical analysis

DISSECTION OF STRIATUM

The dissection procedure was essentially same as described before (Haleem et al. 2004). A fresh brain was dipped in ice cold saline and placed with its

ventral site up in molded cavity of a brain slicer. Fine fishing line wire was inserted into the slots of the slicer to give slices of 2 mm thickness. The slices containing striatum were transferred to a slide kept on ice. Punches of 2.5 mm diameter were made bilaterally in the striatum.

HPLC-EC DETERMINATION OF 5-HTP

Samples (striatum) were extracted as described before (Haleem and Perveen 1994). A 5 μm ODS (Shim-Pack) separation column (4.5 mm internal diameter and 15 cm length) was used. The mobile phase comprising methanol (14%), octyl sodium sulfate (0.02%) and EDTA (0.0035%) in 0.1 M phosphate buffer of pH 2.9, was passed at an operating pressure of 2 000–3 000 psi with the help of a Schimadzu LC-6A pump. Electrochemical detection was achieved on a Schimadzu LECD-6A detector at an operating potential of 0.8 volts.

Statistical analysis

Data on haloperidol-induced VCMs, deficits of motor coordination and motor activity were analyzed by two-way ANOVA repeated measure design followed by Newman-Keuls test. Data on 8-OH-DPAT-induced serotonin syndrome in saline and haloperidol treated animals were statistically tested by *t*-test. Neurochemical data on the effects of 8-OH-DPAT on 5-HT synthesis in repeated saline or repeated haloperidol injected animals were analyzed by two-way ANOVA and *t*-test used for *post-hoc* comparison.

RESULTS

Figure 1 shows the effect of haloperidol on activity in a familiar environment (activity box). Two-way ANOVA (repeated measure design) showed significant effect of haloperidol ($F_{1,22}$=273.89, P<0.01) and days ($F_{5,110}$=4.84, P<0.05) and a significant interaction between haloperidol × day ($F_{5,110}$=13.76, P<0.01). *Post-hoc* analysis showed that administration of haloperidol decreased activity on day 1 and weekly during 5 weeks.

Figure 2 shows the effect of haloperidol on the activity in the open field (squares crossed). Two-way ANOVA (repeated measure design) showed significant effect of haloperidol ($F_{1,22}$=515.95, P<0.01) but not significant for day ($F_{5,110}$=0.007, P>0.05). Interaction between haloperidol and day ($F_{5,110}$=3.07, P>0.05) was not significant. *Post-hoc* analysis showed that administration of haloperidol

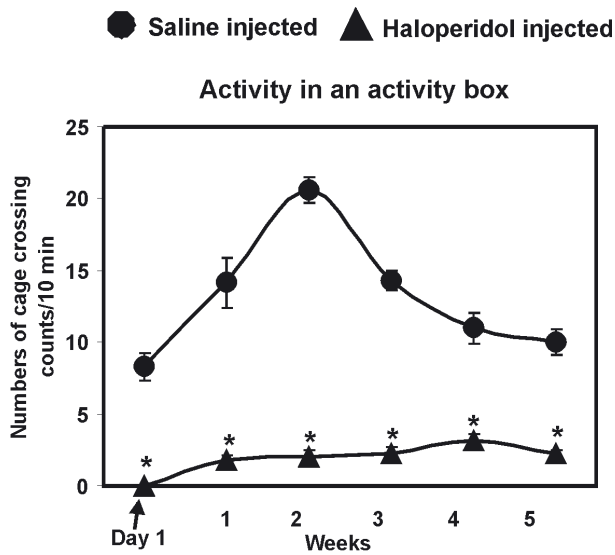

Fig. 1. Effects of haloperidol on activity in an activity box. Values are means ± SEM (n=12) 30 min post-injection. Significant differences by Newman-Keuls test: *P<0.01 in haloperidol injected animals from their respective controls, following two-way ANOVA (repeated measure design).

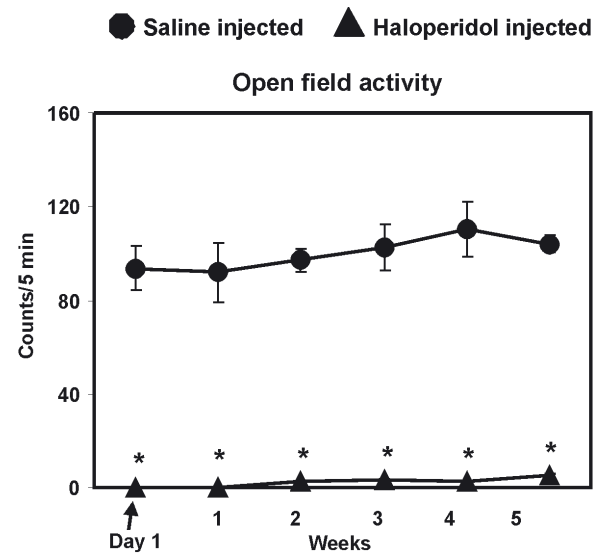

Fig. 2. Effects of haloperidol on ambulatory activity in an open field. Values are means ± SEM (n=12) 40 min post-injection. Significant differences by Newman-Keuls test: *P<0.01 from their respective controls following two-way ANOVA (repeated measure design).

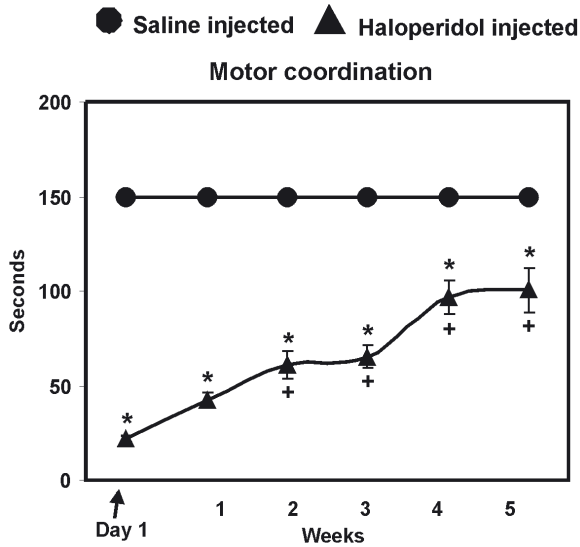

Fig. 3. Effects of haloperidol on motor coordination. Values are means ± SEM (n=12) 60 min post-injection. Significant differences by Newman-Keuls test: *P<0.01 from their respective controls, ^{+}P<0.01from day 1 following two-way ANOVA (repeated measure design).

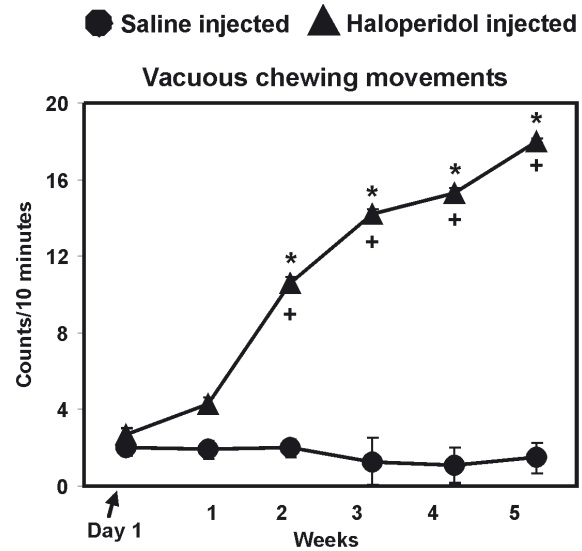

Fig. 4. The intensity of haloperidol-induced vacuous chewing movements (VCMs). Values are means ± SEM (n=12) before haloperidol administration. Significant differences by Newman-Keuls test: *P<0.01 from their respective controls, ^{+}P<0.01 from day 1 following two-way ANOVA (repeated measure design).

decreased activity on day 1 and weekly during 5 weeks.

Figure 3 shows the effect of haloperidol on motor coordination. Two-way ANOVA (repeated measure design) showed significant effect of haloperidol ($F_{1,22}$=408.22, P<0.01), day ($F_{5,110}$=5.17, P<0.05) and a significant interaction between haloperidol × day ($F_{5,110}$=16.67, P<0.01). *Post-hoc* analysis showed that administration of haloperidol impaired motor coordination on day 1 and weekly during 5 weeks. Tolerance was produced in motor coordination during 2–5 weeks of drug administration.

Figure 4 shows the intensity of haloperidol-induced VCMs. Two-way ANOVA (repeated measure design) showed a significant effect of haloperidol ($F_{1,22}$=371.67, P<0.01), days ($F_{5,110}$=13.50, P<0.01) and a significant interaction between haloperidol × days ($F_{5,110}$=56.70, P<0.01). *Post-hoc* analysis showed that administration of haloperidol elicited VCMs after 2 weeks of administration. The intensity of VCMs increased in a time dependent manner during 3-5 weeks of drug administration.

Figure 5 shows the intensity of 5-HT syndrome elicited by 0.5 mg/kg 8-OH-DPAT injected rats 48 h after repeated (two times a day for 5 weeks) injection of saline or haloperidol (1 mg/kg). *T*-test showed that the number of forepaw treadings were not significantly

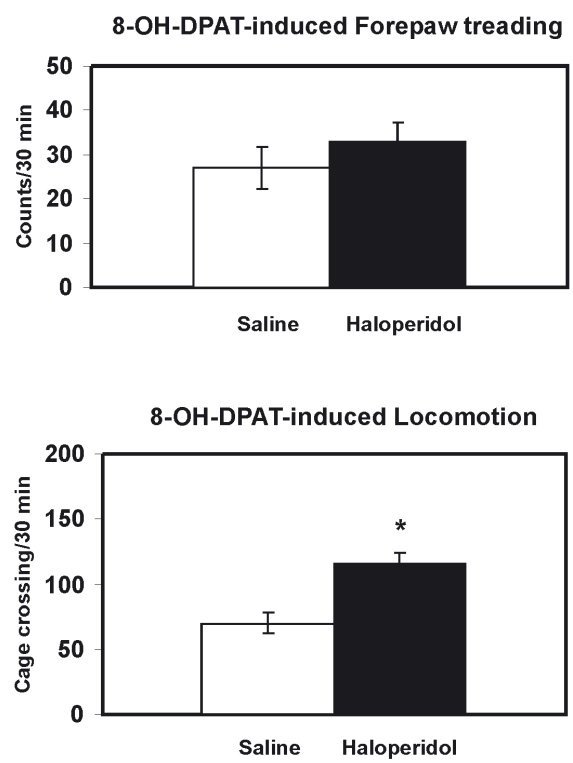

Fig. 5. 8-OH-DPAT (0.5 mg/kg) elicited forepaw treading and locomotion in rats injected repeatedly (two-time a days for 5 weeks) with haloperidol (1.0 mg/kg). 8-OH-DPAT was injected 48-h after the last of the repeated saline or haloperidol injection. Values are means ± SEM (n=6, four scoring periods each of 1-min duration). Significant differences by *t*-test; *P<0.01.

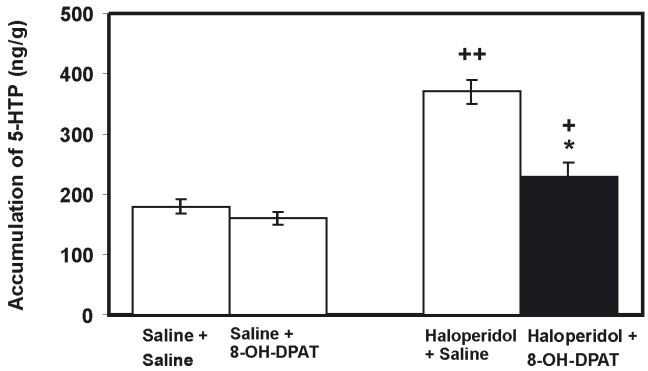

Fig. 6. Effects of 8-OH-DPAT (0.5 mg/kg) on the synthesis of 5-HT (monitored as the accumulation of 5-HTP 30 min after the injection of 3-hydroxybenzyl hydrazine) in rats repeatedly (two-times a day for 5 weeks) injected with haloperidol (1.0 mg/kg). 8-OH-DPAT was injected 48-h after the last of the repeated saline or haloperidol injection. Values are means ± SEM (n=6). Significant differences by t-test: *P<0.01 in haloperidol plus 8-OH-DPAT-injected animals from haloperidol plus saline-injected animals, ^{+}P<0.05 and ^{++}P<0.01 in haloperidol plus 8-OH-DPAT and haloperidol plus saline-injected animals from saline plus 8-OH-DPAT and saline plus saline-injected animals respectively following two-way ANOVA.

(t_{10}=0.94, P>0.05) different in the two groups. Cage crossings were significantly (t_{10}=3.70, P<0.01) greater in the repeated haloperidol than repeated saline injected rats. Because the syndrome was not produced in the saline injected animals, the saline injected group was not included in the statistical analysis.

Figure 6 shows the effect of 8-OH-DPAT on the synthesis of 5-HT in the striatum of repeated saline- or haloperidol-injected rats, 48 h after the last of the repeated injections of saline or haloperidol. Two-way ANOVA showed significant effects of 8-OH-DPAT ($F_{1,20}$=6.3, P<0.05) and haloperidol ($F_{1,20}$=60.9, P<0.01). Interaction between 8-OH-DPAT and haloperidol was also significant ($F_{1,20}$=4.5, P<0.05). *Post-hoc* analysis showed that the injection of 8-OH-DPAT did not significantly decrease 5-HT synthesis in repeated saline injected rats but decreased it in repeated haloperidol injected rats. Repeated haloperidol plus saline and repeated haloperidol plus 8-OH-DPAT injected animals exhibited greater values than their respective repeated saline plus saline and repeated saline plus 8-OH-DPAT injected counterparts.

DISCUSSION

The present study shows a time dependent increase in haloperidol-induced VCMs. VCMs start after 2 weeks of haloperidol administration and are potentiated from 3–5 weeks. Tolerance was produced in motor coordination during the potentiation of VCMs. The aim of the present study was to determine the responsiveness of pre- and postsynaptic 5-HT-1A receptors in rats exhibiting TD. 8-OH-DPAT (a 5-HT-1A receptor agonist) was used for this purpose. Administration of 8-OH-DPAT produces a 5-HT syndrome due to the stimulation of postsynaptic 5-HT-1A receptors (Haleem 1992, Haleem and Khan 2003). A decrease in 5-HT synthesis (Haleem et al. 2004) and release (Haleem 1999) following the administration of 8-OH-DPAT occurs because of the stimulation of somatodendritic 5-HT-1A receptors. Results of the present study show that administration of 8-OH-DPAT produced greater pre- and postsynaptic 5-HT-1A receptor dependent responses in haloperidol treated animals.

It is well established that haloperidol (a dopamine receptor antagonist) prevents hyperactivity induced by amphetamine (Moore 1999) and decreases spontaneous locomotion and exploration (Conceicao and Frussa-Filho 1996, Karl et al. 2006) and elicits a state known as catalepsy (Haleem and Khan 2003, Haleem et al. 2004). Other authors have reported that repeated (chronic and subchronic) administration of haloperidol induced orofacial dyskinesia (Naidu and Kulkarni 2001, Naidu et al. 2002, Tamminga et al. 1990). In the present study treatment with haloperidol at a dose of 1 mg/kg twice a day induced VCMs in 2 weeks that increased in a time dependent manner as the treatment continued for 5 weeks (Fig. 3). An important finding of the present study was that repeated treatment with haloperidol produced tolerance in motor coordination.

It is often suggested that dopamine receptor supersensitivity arising from the upregulation of dopamine D2 receptor following neuroleptic therapy accounts for the development of TD (Klawans and Rubovits 1972). Previous studies have shown that administration of haloperidol increased 5-HT (Johnson et al. 1992) and 5-HIAA concentration in many brain regions including the striatum (Haleem et al. 2002a). Preclinical and clinical studies suggest that an increase in serotonin transmission may be an important contributing factor in the onset of dyskinesia (Melamed et al. 1996, Meltzer and Nash 1991). The present study shows that an increase in

5-HT concentration follows the repeated administration of haloperidol (Fig. 6) and an increase in postsynaptic 5-HT-1A receptor dependent responses.

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, Kulkarni and Naidu 2001) and increased the responsiveness of somatodendritic 5-HT-1A receptors in rats (Haleem and Khan 2003). In the present study tolerance in motor coordination following repeated haloperidol treatment was associated with an increase in the responsiveness of somatodendritic 5-HT-1A receptors, which have an important role in the precipitation of haloperidol-induced VCMs. Numerous investigations of interaction between brain 5-HT and dopamine system, have demonstrated both cooperative (Wadenberg 1996) and antagonistic interactions (Kapur 1996, Neal-Beliveau et al. 1993). Serotonergic projections from the dorsal raphe project directly to the substantia nigra and negatively modulate dopamine neurons in the substantia nigra (Jacobs and Azimitia 1992, Kelland et al. 1990). This inhibitory action seems to be mediated by 5-HT-2A/2C receptors located on the somatodendritic surface of dopamine neurons (Pazos et al. 1987, Ujedo et al. 1989).

5-HT-1A receptors are known to be located both presynaptically, where they functions as somatodendritic autoreceptors, and postsynaptically. Behavioral responses produced by the activation of 5-HT receptors may arise from receptors with either a presynaptic or a postsynaptic localization. It has been reported that electrical stimulation of the dorsal raphe inhibited a subpopulation of nigrostriatal neurons termed "Slow firing" because they are normally under the tonic inhibitory influence of 5-HT (Kelland et al. 1990). Since 8-OH-DPAT is known to suppress the firing rate of the dorsal raphe, it may inhibit 5-HT synthesis and release. 8-OH-DPAT could increase the firing rate of the "Slowly firing" dopamine neurons by releasing the tonic inhibitory influence of 5-HT (Kelland et al. 1990).

Elicitation of the 5-HT syndrome by the administration of 8-OH-DPAT was reported by Hjorth and coauthors (1982). The behavior is independent of presynaptic machinery, as it was not blocked by the inhibition of 5-HT synthesis. Increase in motor activity, forepaw treading, head weaving and flat body posture are some of the distinct behavioral components of the syndrome (Haleem 1992). Stimulation of the somatodendritic 5-HT-1A receptor resulting in a decrease in the inhibitory influence of 5-HT on dopaminergic neurons, (Shireen and Haleem 2005) as well as postsynaptic 5-HT-1A, is known to be involved in hyperlocomotion (Haleem et al. 2002b). The present study shows that 5 weeks administration of haloperidol at a dose of 1 mg/kg when injected with 0.5 mg/kg 8-OH-DPAT 48-h after the withdrawal of haloperidol exhibited an increase in the intensity of locomotion (Fig. 5).

Subsequent studies showed a selective increase in dopamine D2 receptor binding in rat following prolonged neuroleptic treatment (Porceddu et al. 1986, Uronova et al. 1991). Thus chronic haloperidol treatment induced dopamine receptor hypersensitivity in rats, as measured by enhanced hyperactivity and stereotypy to apomorphine after withdrawal of the neuroleptic (Halperin et al. 1989). Previously it has been reported that stimulation of the somatodendritic 5-HT-1A receptor induces a decrease in the inhibitory influence of 5-HT on dopamine neurotransmission (Haleem et al. 2004). The effects of chronic administration of haloperidol are explainable in terms of either an increase in the responsiveness of both pre- and postsynaptic 5-HT-1A receptors and postsynaptic dopamine D2 receptors.

The striatum, a region of the brain involved in the control of motor activity, is rich in dopamine nerve terminals. Factors that modulate brain serotonin metabolism have been shown to produce little effect in this region of the brain. Thus, the synthesis of 5-HT following a tryptophan load increased in the whole brain (Haleem 1990, Haleem et al. 1998) and many brain regions except the striatum (Chauloff et al. 1989).

Stimulation of 5-HT-1A receptors located on cell body dendrites decreases the activity of tryptophan hydroxylase, the rate-limiting enzyme in the biosynthesis of 5-HT. A decrease in 5-HT turnover following the administration of 8-OH-DPAT (Haleem 1990, 1999) or other 5-HT agonists (Haleem et al. 2004) acting *via* presynaptic 5-HT receptors has been shown in several studies. It has also been shown that the decreases are much smaller in the striatum (Haleem 1999) and do not always reach significance (Haleem 1990).

The present effects of 8-OH-DPAT on 5-HT synthesis in the striatum are consistent with our previous report (Haleem 1990). Previous results from our laboratory provide evidence that administration of 8-OH-DPAT decrease 5-HT metabolism in the striatum of

rats singly injected with haloperidol (Haleem et al. 2004). In addition the present results show that administration of 8-OH-DPAT at a dose of 0.5 mg/kg decreases 5-HT synthesis in the striatum of rats repeatedly injected with haloperidol (Fig. 6) 48-h after the withdrawal of haloperidol, and shows an increase in the effectiveness of somatodendritic 5-HT-1A receptors controlling the synthesis and release of 5-HT in this brain region.

CONCLUSION

The results of the present study suggest that an increase in the effectiveness of somatodendritic as well postsynaptic 5-HT-1A receptors is a major contributing factors in the pathophysiology of TD. An increase in the effectiveness of somatodendritic 5-HT-1A receptor would be expected to decrease the inhibitory influence of serotonin on the activity of dopaminergic neurons. On the other hand, an increase in the effectiveness of postsynaptic 5-HT-1A may be directly involved in the elicitation of VCMs.

ACKNOWLEDGMENTS

The authors would like to thank the Higher Education Commission (HEC) and Pakistan Science foundation (PSF) for a grant.

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Received 1 December 2006, accepted 14 April 2007