ELSEVIER

European Journal of Pharmacology 428 (2001) 81–86

ejp

www.elsevier.com/locate/ejphar

Effect of 5-HT_{1A} and 5-$HT_{2A/2C}$ receptor modulation on neuroleptic-induced vacuous chewing movements

Pattipati S. Naidu, Shrinivas K. Kulkarni *

Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh 160 014, India

Received 15 February 2001; received in revised form 3 August 2001; accepted 7 August 2001

Abstract

Tardive dyskinesia is a serious motor side effect of chronic neuroleptic therapy. Chronic treatment or rats with neuroleptics leads to the development of abnormal oral movements called vacuous chewing movements. Vacuous chewing movements in rats are widely accepted as an animal model of tardive dyskinesia. Atypical antipsychotics such as clozapine and rispiridone are associated with a lower incidence of extrapyramidal side effects and tardive dyskinesia. The present study was aimed to explore the role of 5-HT_{1A}, 5-$HT_{2A/2C}$ receptors in the expression of neuroleptic-induced orofacial dyskinesia. In the present study rats were chronically (for 21 days) treated with haloperidol (1.5 mg/kg, i.p.) to elicit vacuous chewing movements. The neuroleptic-induced vacuous chewing movements, viz., vertical jaw movements, tongue protrusions and bursts of jaw tremors, were counted during a 5-min observation period. Acute treatment with 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT), a 5-HT_{1A} receptor agonist, dose-dependently (0.05, 0.1 and 0.2 mg/kg, i.p.) reduced the haloperidol-induced vacuous chewing movements and headshakes. Both acute and chronic administration of seganserin, ketanserin and ritanserin, 5-$HT_{2A/2C}$ receptor antagonists, also reduced haloperidol-induced vacuous chewing movements in a dose-dependent (0.05, 0.1 and 0.2 mg/kg, i.p.) manner. In acute studies a higher dose of ritanserin (1 mg/kg) but not ketanserin (1 mg/kg) increased vacuous chewing movements, whereas a higher dose of seganserin (1 mg/kg) did not have any effect on vacuous chewing movements. All the drugs reduced haloperidol-induced headshakes in a dose-dependent fashion. These findings indicate that the serotonergic system, and particularly 5-HT_{1A} and 5-$HT_{2A/2C}$ receptors, may be involved in haloperidol-induced orofacial dyskinesia, and that 5-HT receptors may provide novel targets for the development of drugs that can be used to reverse or prevent the extrapyramidal side effects associated with long-term antipsychotic treatment.

Keywords: Tardive dyskinesia; Vacuous chewing movement; Neuroleptic; 5-HT_{1A} receptor; 5-$HT_{2A/2C}$ receptor

1. Introduction

Tardive dyskinesia, a syndrome of potentially irreversible, involuntary hyperkinetic disorders that occurs during chronic neuroleptic treatment, is a major limitation of neuroleptic therapy (Egan et al., 1997; Casey, 1995). In spite of its high frequency of occurrence, relatively little is known about the pathophysiological basis of the syndrome. Dopamine receptor supersensitivity has been proposed as one of the pathological factors responsible for tardive dyskinesia, but this does not adequately explain the time course of onset of tardive dyskinesia or the persistence of the syndrome after neuroleptic withdrawal (Fibiger and Lloyd, 1984; Tarsy and Baldessarini, 1977; Casey, 2000; Andreassen and Jorgessen, 2000). Several other alternative hypotheses have been proposed, but most of them are inconclusive. Different suppressive agents have been tried with limited success (Egan et al., 1997; Gupta et al., 1999).

Atypical antipsychotics such as clozapine and rispiridone are associated with a lower incidence of extrapyramidal side effects and tardive dyskinesia. All these drugs show 5-HT receptor antagonistic properties along with dopamine receptor antagonism. A number of reports have suggested that the limited extrapyramidal side effect profile of these drugs might be at least in part due to their 5-HT receptor antagonistic property. The high density of 5-HT receptors, especially 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_4 receptors, in the basal ganglia region and their interaction with other neurotransmitter systems, especially with

* Corresponding author. Tel.: +91-172-534114; fax: +91-172-541142, +91-172-541409.

E-mail address: skpu@yahoo.com (S.K. Kulkarni).

0014-2999/01/$ - see front matter
PII: S0014-2999(01)01284-5

dopamine, leads to the hypothesis that serotonin may play a significant role in the pathophysiology of movement disorders of basal ganglia origin. Clozapine, a prototype atypical antipsychotic shows more affinity for 5-HT_2 receptors (Seeman et al., 1993; Farde et al., 1994), than for dopamine D_2 receptors and is associated with fewer extrapyramidal side effects than conventional antipsychotics. More recently, ritanserin, an atypical antipsychotic that shows 5-HT_2 antagonistic properties along with dopamine D_2 receptor antagonism, etc., was reported to produce few extrapyramidal side effects (Chouinard et al., 1993; Peuskens, 1995). The purposeless chewing behavior induced by pilocarpine is antagonized by clozapine and methiopin, mixed D_2/5-HT_2 receptor antagonists, and by mianserine, a 5-HT_2 receptor antagonist but not by sulpiride or thioridazone, suggesting that a serotonergic component may be involved in the mediation of this behavior and in tardive dyskinesia (Stewart et al., 1988). The presence of 5-HT_{2C} receptors in the ventrolateral striatum, the internal pallidum and substantia nigra pars reticulata, the regions thought to participate in the generation of orofacial dyskinesias (Eberle-Wang et al., 1993; Mengod et al., 1990), further supports the role of 5-HT in mediating these behaviors.

The present study was aimed to investigate the effect of 5-HT_{1A}, 5-$HT_{2A/2C}$ receptor modulation on haloperidol-induced abnormal oral behaviors.

2. Materials and methods

2.1. Animals

Male Wistar rats, bred in the Central Animal House facility of the Panjab University and weighing between 180 and 220 g, were used. The animals were housed under standard laboratory conditions, maintained on a 12-h light and dark cycle and had free access to food and water. Animals were acclimatized to laboratory conditions before the test. Each animal was used only one time in the experiments. All experiments were carried out between 0900 and 1500 h. The experimental protocols were approved by the Institutional Ethics Committee and conducted according to the Indian National Science Academy Guidelines for the use and care of experimental animals.

2.2. Induction of orofacial dyskinesia

Haloperidol (1.5 mg/kg i.p.) was given chronically to rats for a period of 21 days to induce oral dyskinesia (Sasaki et al., 1995). Chronic haloperidol-treated animals were challenged with different drugs 24 h after the last haloperidol injection and behavioral assessments were carried out 30 min after drug challenge.

2.3. Assessment of vacuous chewing movements

Rats were placed individually in a small ($30 \times 20 \times 30$ cm) Plexiglass cage for the assessment of vacuous chewing movements. Animals were allowed 5 min to get used to the observation cage before behavioral assessment. Vacuous chewing movements were counted for 5 min with the help of a mechanical counter. Counting stopped whenever the rat began grooming, and restarted when grooming stopped. Three types of oral behaviors were recorded: vertical jaw movements (each vertical opening and closing of jaw is regarded as one vacuous chewing movement), bursts of jaw tremor and tongue protrusions. For calculation purposes, each burst of jaw tremor was regarded as being equal to two vacuous chewing movements (Gunne et al., 1982). A vacuous chewing movement consisted of a rapid movement of the jaw that resembled chewing, but did not appear to be directed at any particular stimulus. In all the experiments the rater was blind to the treatment given to the rats.

2.4. Measurement of headshakes

Numbers of headshakes were counted during a 5-min observation period with the help of a mechanical counter. In all experiments the rater was blind to the treatment given to the rats.

2.5. Drugs

The following drugs were used in the present study. Haloperidol (serenace® inj., Searle India, India) was diluted with distilled water. Ritanserin was dissolved in a few drops of HCl and the volume was made up with distilled water. pH was adequately adjusted. Ketanserin tartrate, seganserin hydrochloride, (all gifts from Janssen Research Foundation, Belgium) and 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) (Sigma, St. Louis, MO) were dissolved in distilled water.

2.6. Treatment schedule

All drugs were administered intraperitonially in a constant volume of 0.5 ml per 100 g of body weight of rat. In acute studies all the drugs were administered 30 min prior to the behavioral assessment.

2.7. Statistical analysis

One specific group of rats was assigned to one specific drug treatment condition and each group comprised six rats ($n = 6$). All the values are expressed as means ± S.E.M. The data were analyzed by using analysis of variance (ANOVA) followed by Dunnett's test. In all tests, the criterion for statistical significance was $P < 0.05$.

3. Results

3.1. Behavioral effects of chronic haloperidol treatment

Animals repeatedly treated with haloperidol (for a period of 21 days) developed profound vacuous chewing movements $F(9,50) = 38.283$ ($n = 6$, $P < 0.05$) (Fig. 1A) and tongue protrusions $F(9,50) = 70.866$ ($n = 6$, $P < 0.05$) (Fig. 1B) in a time-dependent fashion, showing a maximum count after 21 days. The effects persisted for more than 40 days after treatment. Chronic haloperidol treatment also induced headshakes in rats in a statistically significant manner as compared to vehicle treatment $F(9,50) = 73.205$ ($n = 6$, $P < 005$) (Fig. 1C).

3.2. Effect of single 8-OH-DPAT-, seganserin-, ketanserin- and ritanserin on the various behavioral parameters in haloperidol-treated rats

Acute treatment with 8-OH-DPAT (0.05, 0.1 and 0.2 mg/kg) reduced the haloperidol-induced vacuous chewing movements $F(4,25) = 153.909$ ($n = 6$, $P < 0.05$) (Fig. 2A), tongue protrusions $F(4,25) = 106.370$ ($n = 6$, $P < 0.05$) (Fig. 2B) and headshakes $F(4,25) = 21.23$ ($n = 6$, $P < 0.05$) (Fig. 2C) in a dose-dependent manner. Seganserin (0.05, 0.1 and 0.2 mg/kg), ketanserin (0.05, 0.1 and 0.2 mg/kg) and ritanserin (0.05, 0.1 and 0.2 mg/kg) dose-dependently reduced haloperidol-induced vacuous chewing movements. A higher dose of seganserin (1 mg/kg) had no effect on vacuous chewing movements, but a higher dose of ritanserin (1 mg/kg) increased the vacuous chewing movements, even though slightly, in a statistically significant fashion $F(13,70) = 55.923$ ($n = 6$, $P < 0.05$)(Fig. 3A). Seganserin, ketanserin, and ritanserin dose-dependently reduced the chronic haloperidol-induced tongue protrusions $F(13,70) = 55.835$ ($n = 6$, $P < 0.05$) (Fig. 3B) and headshakes $F(13,70) = 18.289$ ($n = 6$, $P < 0.05$). All drugs were effective at lower doses on vacuous

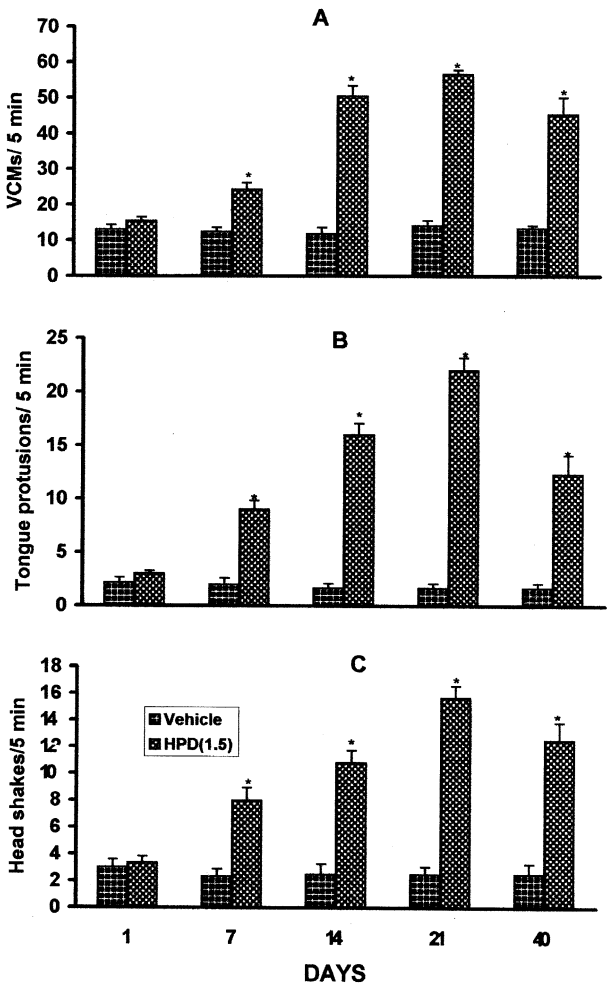

Fig. 1. Effect of chronic haloperidol (1.5 mg.kg, i.p., for 21 days) treatment on vacuous chewing movements (VCMs) (A), tongue protrusions (B) and head shakes (C) in rats. Values expressed as means ± S.E.M. * $P < 0.05$ as compared to vehicle-treated group. (ANOVA followed by Dunnett's test.)

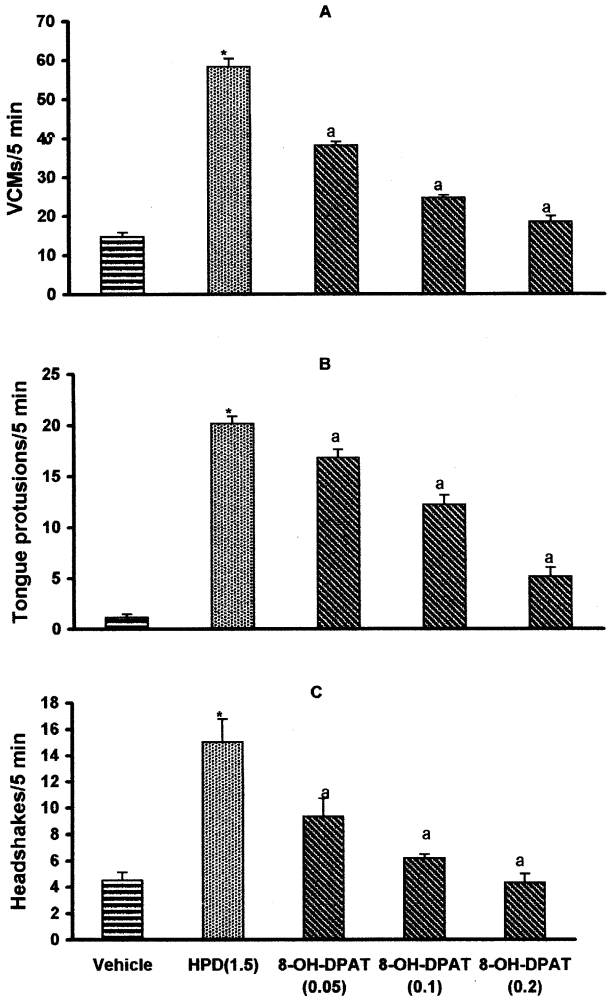

Fig. 2. Effect of acute treatment with 8-OH-DPAT on haloperidol-induced (HPD) vacuous chewing movements (VCMs) (A), tongue protrusions (B) and head shakes (C) in rats. All values expressed as means ± S.E.M. * $P < 0.05$ as compared to vehicle-treated group. [a] $P < 0.05$ as compared to haloperidol-treated group (ANOVA followed by Dunnett's test.)

chewing movements whereas higher doses were needed for the suppression of tongue protrusions.

3.3. Effect of chronic 5-HT_2 receptor antagonist administration on haloperidol-induced vacuous chewing movements, tongue protrusions, and headshakes

Haloperidol-treated animals developed significant vacuous chewing movements in a time-dependent fashion, showing a ceiling effect after 21 days (Fig. 1). Chronic treatment with seganserin (0.2 mg/kg) and ketanserin (0.2 mg/kg) reduced the haloperidol-induced vacuous chewing movements after 7, 14, and 21 days of treatment, whereas ritanserin (0.2 mg/kg) reduced vacuous chewing movements after 7 days but did not have any effect after 14 days, and significantly increased the vacuous chewing movements after 21 days of treatment $F(19,100) = 84.536$ ($n = 6$, $P < 0.05$) (Fig. 4A). Both seganserin (0.2 mg/kg) and ketanserin (0.2 mg/kg) reduced haloperidol-induced tongue protrusions significantly after 7, 14, and 21 days of treatment, whereas ritanserin (0.2 mg/kg) did not have an effect after 7 and 14 days, but it aggravated the tongue protrusions after 21 days of treatment $F(19,100) = 62.375$ ($n = 6$, $P < 0.05$) (Fig. 4B). Seganserin, ketanserin, and ritanserin (0.2 mg/kg) significantly reduced the haloperidol-induced headshakes after 7, 14, and 21 days of treatment $F(19,100) = 28.532$ ($n = 6$, $P < 0.05$) (Fig. 4C).

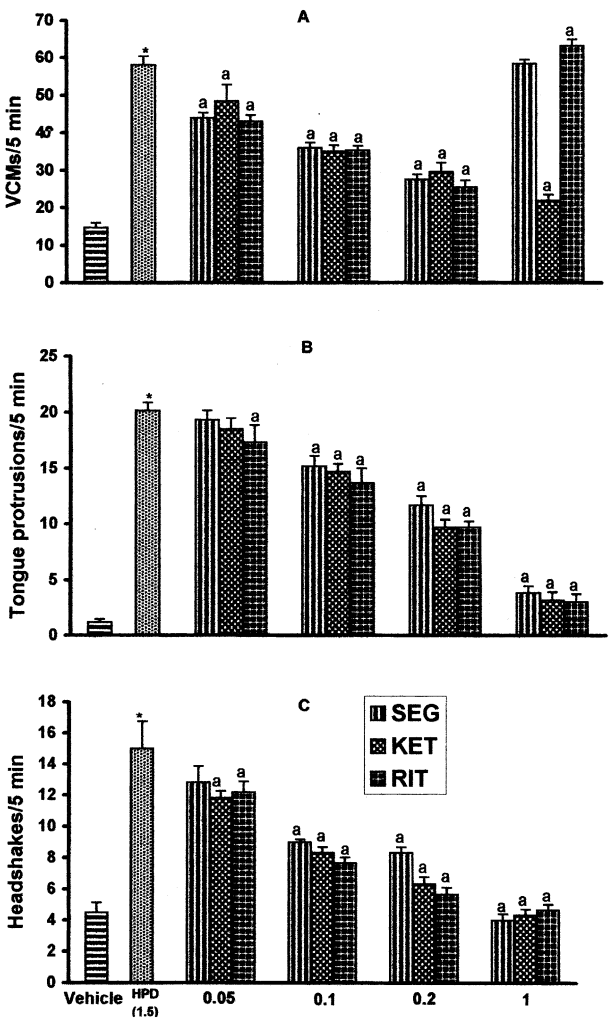

Fig. 3. Effect of acute treatment with seganserin (SEG), ketanserin (KET) and ritanserin (RIT) on haloperidol-induced vacuous chewing movements (VCMs) (A), tongue protrusions (B) and head shakes (C) in rats. All values expressed as means ± S.E.M. $^{*}P < 0.05$ as compared to vehicle-treated group. $^{a}P < 0.05$ as compared to haloperidol-treated group (ANOVA followed by Dunnett's test.)

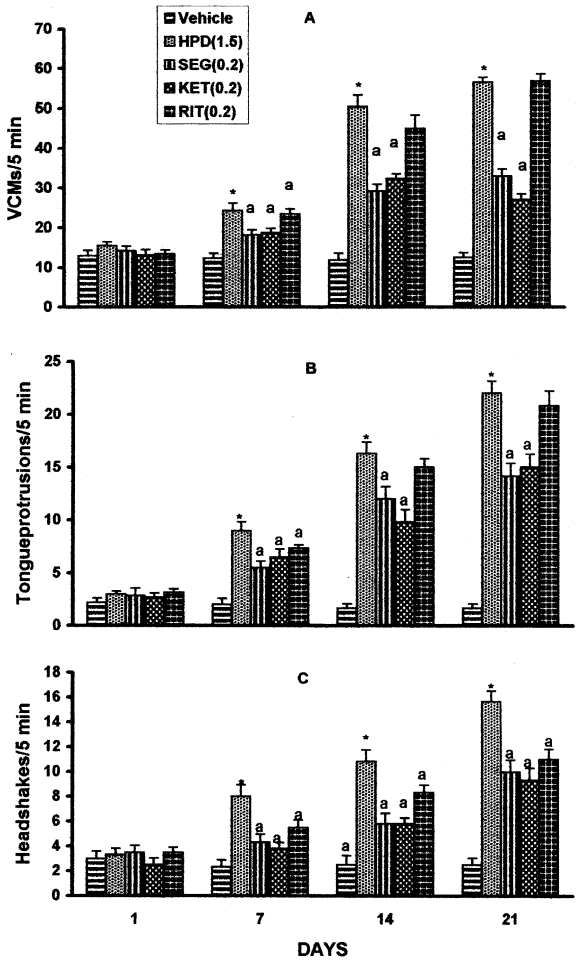

Fig. 4. Effect of chronic treatment with seganserin (SEG), ketanserin (KET) and ritanserin (RIT) on haloperidol-induced (HPD) vacuous chewing movements (VCMs) (A), tongue protrusions (B) and head shakes (C) in rats. All values expressed as means ± S.E.M. $^{*}P < 0.05$ as compared to vehicle-treated group. $^{a}P < 0.05$ as compared to haloperidol-treated group (ANOVA followed by Dunnett's test.)

4. Discussion

The results of the present study demonstrate that acute administration of 8-OH-DPAT, a 5-HT_{1A} receptor agonist, dose-dependently reduced haloperidol-induced vacuous

chewing movements. Both acute and chronic treatment with seganserin, ketanserin, and ritanserin 5-$HT_{2A/2C}$ receptor antagonists, reduced haloperidol-induced vacuous chewing movements. All of the drugs reduced vacuous chewing movements at lower doses than those needed to reduce the number of tongue protrusions. This leads to the speculation that these two behaviors may involve different mechanisms.

Numerous investigations of interactions between brain 5-HT and dopamine systems, have demonstrated both cooperative (Waddington and Crow, 1979; Wandenberg, 1996) and antagonistic interactions (Neal-Beliveau et al., 1993; Kapur, 1996). Serotonergic projections from the dorsal raphe project directly to the substantia nigra and negatively modulate dopamine neurons in the substantia nigra (Jacobs and Azmitia, 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).

In the present study, 8-OH-DPAT dose-dependently reversed the haloperidol-induced vacuous chewing movements. 5-HT_{1A} receptor agonists are known to reverse haloperidol-induced catalepsy (Neal-Beliveau et al., 1993). However, there are no data available in the literature regarding the effect of 8-OH-DPAT on neuroleptic-induced vacuous chewing movements. 5-HT_{1A} receptors are known to be located both presynaptically, where they function as somatodendritic autoreceptors, and postsynaptically. Behavioral responses produced by the activation of 5-HT_{1A} receptors may arise from receptors with either a presynaptic or a postsynaptic localization. It was reported that electrical stimulation of the dorsal raphe inhibited a subpopulation of nigrostriatal neurons termed "slow firing" neurons, because they are normally under the tonic inhibitory influence of 5-HT (Dray et al., 1978; Kelland et al., 1990). Since 8-OH-DPAT is known to suppress the firing rate of dorsal raphe neurons by acting at somatodendritic autoreceptors and to 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). Increased dopamine release would then act competitively to counteract the effects of the postsynaptic dopamine receptor blockade in the striatum, which is responsible for the development of vacuous chewing movements. 8-OH-DPAT, acting through corticofrontal and tegmental 5-HT_{1A} receptors, facilitates the firing of mesocortical dopamine neurons, which in turn inhibit corticostriatal glutamatergic inputs (Espejo and Gil, 1997). Since vacuous chewing movements are also thought to be mediated by striatal glutamate receptors (Jorgensen and Andreassen, 1995), the protective effect of 8-OH-DPAT could be related to reduced striatal glutamatergic activity.

Acute as well of chronic concomitant treatment with the 5-HT_2 receptor antagonists ketanserin, seganserin and ritanserin reduced haloperidol-induced vacuous chewing movements significantly in a dose-dependent manner, but at a higher dose acute seganserin (1 mg/kg) had no effect on vacuous chewing movements, whereas ritanserin even significantly increased vacuous chewing movements. Administered chronically, a higher dose of seganserin and ritanserin (1 mg/kg), but not of ketanserin increased haloperidol-induced vacuous chewing movements. Ritanserin is known to have dopamine D2 receptor antagonistic activity along with serotonin antagonism. The augmentation of neuroleptic-induced vacuous chewing movements by ritanserin might be due to its dopamine antagonistic activity, but how a higher dose of seganserin increased vacuous chewing movements is not known, but it might be due to a compensatory mechanism in the serotonergic or dopaminergic system. 5-HT_{2C} receptors are present in the ventolateral striatum, internal pallidum, and substantia nigra pars reticulata, and these regions are thought to be involved in the generation of vacuous chewing movements. This further supports the role of the serotonergic system in mediating vacuous chewing movements (Mengod et al., 1990). 5-HT_2 receptor antagonists have been reported to increase nigrostriatal DA activity (Ujedo et al., 1989; Saller et al., 1990). Blockade of dopamine D_2 receptors is thought to be responsible for both the antipsychotic action and the induction of detrimental side effects such as tardive dyskinesia. The 5-HT_2 receptor antagonism reportedly compensates for the dopamine D_2 receptor blockade in areas responsible for the induction of extrapyramidal side effects, by increasing dopamine activity within the striatum (Saller et al., 1990).

Headshake behavior in rats is thought to be mediated by the 5-HT_2 receptor subtype (Yap and Taylor, 1983; Goodwin and Green, 1985). Chronic haloperidol treatment also produced a significant number of headshakes in rats. 8-OH-DPAT, seganserin, ketanserin, and ritanserin dose-dependently decreased the number of headshakes. This further supports the role of 5-HT_2 receptors in the headshake behavior induced by chronic haloperidol treatment. The augmented headshake behavior might be due to an increased number of 5-HT receptors, because chronic treatment with neuroleptics tends to increase the number of 5-HT receptor sites (Dawbarn et al., 1981).

Taken together, the results of the present study strongly suggest the involvement of the serotonergic system, specifically 5-HT_{1A} and 5-$HT_{2A/2C}$ receptors, in neuroleptic-induced vacuous chewing movements. These receptors can serve as potential targets for the development of novel drug candidates for the treatment of tardive dyskinesia.

Acknowledgements

Financial support provided by Sun Pharmaceuticals, Mumbai, is gratefully acknowledged.

References

Andreassen, O.A., Jorgessen, H.A., 2000. Neurotoxicity associated with neuroleptic induced oral dyskinesias in rats implications for tardive dyskinesia? Prog. Neurobiol. 61, 525–541.

Casey, D.E., 1995. Tardive dyskinesia: pathophysiology. In: Floyd, E., Bloom, Kupfer, D.J. (Eds.), Psychopharmacology. The Fourth Generation of Progress. Raven Press, New York, pp. 1497–1502.

Casey, D.E., 2000. Tardive dyskinesia: pathophysiology and animal models. J. Cin. Psychiatry 61, 5–9.

Chouinard, G., Jones, B., Remington, G., Bloom, D., Addington, D., MacEwan, G.W., Labelle, A., Beaucleir, L., Arnott, W., 1993. A Canadian multicentre placebo controlled study of fixed doses of respiridone and haloperidol in the treatment of chronic schizophrenic patients. J. Clin. Psychopharmacol. 13, 25–40.

Dawbarn, D., Long, S.K., Pycock, C.J., 1981. Increased central 5-hydroxytryptamine receptor mechanisms in rats after chronic neuroleptic treatment. Br. J. Pharmacol. 73, 149–156.

Dray, A., Davies, J., Oakley, N.R., Tongroach, P., Vellucci, S., 1978. The dorsal and medial raphe projections to the substantia nigra in the rat: electrophysiological, biochemical and behavioral observations. Brain Res. 151, 431–442.

Eberle-Wang, K., Mikeladze, Z., Chesselet, M.F., 1993. Expression of 5-HT_{1C} receptor mRNA in the basal ganglia of rats. Soc. Neurosci. Abstr. 19, 132.

Egan, M.F., Apud, J., Wyatt, R.J., 1997. Treatment of tardive dyskinesia. Schizophr. Bull. 23, 583–609.

Espejo, E.F., Gil, E., 1997. Single restrained stress sensitizes acute chewing movements induced by haloperidol, but not if the 5-HT_{1A} agonist 8-OH-DPAT is given prior to stress. Brain Res. 755, 351–355.

Farde, N., Nordstrom, A.L., Nyberg, S., Halldin, C., Sedvall, G., 1994. D_1-, D_2-, and 5-HT_2 receptor occupancy in clozapine treated patients. J. Clin. Psychiatry 55, 1–3.

Fibiger, H.C., Lloyd, K.G., 1984. Neurobiological substrates of tardive dsykinesia: the GABA hypothesis. Trends. Neurol. Sci. 7, 462–464.

Goodwin, G.M., Green, A.R., 1985. A behavioral and biochemical study in mice and rats of putative selective agonists and antagonists for 5-HT_1 and 5-HT_2 receptors. Br. J. Pharmacol. 84, 743–753.

Gunne, L.M., Growdon, J., Glaeser, B., 1982. Oral dyskinesia in rats following brain lesions and neuroleptic drug administration. Psychopharmacology 77, 134–139.

Gupta, S., Mosnik, D., Black, D.W., Berry, S., Masand, P.S., 1999. Tardive dyskinesia: review of treatments past. Present, and future. Ann. Clin. Psychiatry 11, 257–266.

Jacobs, B.L., Azmitia, E.C., 1992. Structure and function of the brain serotonin system. Physiol. Rev. 72, 165–229.

Jorgensen, H.A., Andreassen, O.A., 1995. Memantine inhibits the development of haloperidol-induced persistent oral movements. Soc. Neurosci. Abstr., 470.

Kapur, S., 1996. 5-HT_2 antagonism and EPS benefits: is there a causal connection? Psychopharmacology 124, 35–39.

Kelland, M.D., Freeman, A.S., Chiodo, I.A., 1990. Serotonergic afferent regulation of the basic physiology and pharmacological responsiveness of nigrostriatal dopamine neurons. J. Pharmacol. Exp. Ther. 253, 803–811.

Mengod, G., Nguyen, H., Le, H., Waeber, C., Lubbert, H., Palacios, J.M., 1990. The distribution and the cellular localization of the serotonin$_{1C}$ receptor mRNA in the rodent brain examined by in situ hybridization histochemistry. Comparison with receptor binding distribution. Neuroscience 35, 577–591.

Neal-Beliveau, B.S., Joyce, J.N., Lucki, I., 1993. Serotonergic involvement in haloperidol-induced catalepsy. J. Pharmacol. Exp. Ther. 265, 207–217.

Pazos, A., Probst, A., Palacios, J.M., 1987. Serotonin receptors in the human brain: IV. Autoradiographic mapping of serotonin-2 receptors. Neuroscience 21, 123–139.

Rispiridone study group, Peuskens, J., 1995. Rispiridone in the treatment of chronic schizophrenic patients: a multi-national, multi-center, double-blind, parallel-group study versus haloperidol. Br. J. Psychiatry 166, 712–726.

Saller, C.F., Czupryna, M.J., Salama, A.I., 1990. 5-HT_2 receptor blockade by ICI 169,369 and other 5-HT_2 antagonists modulates the effects of D_2 dopamine receptor blockade. J. Pharmacol. Exp. Ther. 253, 1162–1170.

Sasaki, H., Hashimoto, K., Maeda, Y., Inada, T., Kitao, Y., Fukui, S., Iyo, M., 1995. Rolipram, a selective c-AMP phosphodiesterase inhibitor suppresses oro-facial dyskinetic movements in rats. Life Sci. 56, 443–447.

Seeman, P., Guan, H.C., Van Tol, H.H.M., 1993. Dopamine D_4 receptors elevated in schizophrenia. Nature 365, 441–445.

Stewart, B.R., Jenner, P., Marsden, C.D., 1988. The pharmacological characterization of pilocarpine-induced purposeless chewing behavior in the rat. Psychopharmacology 96, 55–62.

Tarsy, D., Baldessarini, R., 1977. The pathophysiological basis of tardive dsykinesia. Biol. Psychiatry 12, 431–450.

Ujedo, I., Grenhoff, J., Syensson, T.H., 1989. Ritanserin, a 5-HT_2 receptor antagonist, activates midbrain dopamine neurons by blocking serotonergic inhibition. Psychopharmacology 98, 45–50.

Waddington, J.L., Crow, T.J., 1979. Rotational responses to serotonergic and dopaminergic agonists after unilateral dihydroxytryptamine lesions of the medial forebrain bundle: co-operative interactions of serotonin and dopamine in neostriatum. Life Sci. 25, 1307–1314.

Wandenberg, M.L., 1996. Serotonergic mechanisms in neuroleptic-induced catalepsy in the rat. Neurosci. Biobehav. Rev. 20, 325–339.

Yap, C.Y., Taylor, D.A., 1983. Involvement of 5-HT_2 receptors in wet-dog shake behavior induced by 5-hydroxytryptamine in the rat. Neurophramacology 22, 801–804.