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Reversal of neuroleptic-induced orofacial dyskinesia by 5-HT_3 receptor antagonists

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Abstract

Tardive dyskinesia, a syndrome of abnormal, involuntary hyperkinetic movements that occurs during long-term neuroleptic therapy is a major limitation of chronic neuroleptic therapy. The pathophysiology of tardive dyskinesia is still an enigma. The objective of the present study was to elucidate the role of 5-HT_3 receptor involvement in neuroleptic-induced vacuous chewing movements in rats. Rats chronically (for 21 days) treated with haloperidol (1.5 mg/kg, i.p.) significantly developed vacuous chewing movements, as compared to vehicle-treated controls. Both ondansetron and tropisetron dose-dependently (0.25, 0.5 and 1.0 mg/kg, i.p.) reversed the haloperidol-induced vacuous chewing movements. Serotonin acting through 5-HT_3 receptors might play a significant role in the pathophysiology of tardive dyskinesia, and 5-HT_3 receptor ligands can be exploited as novel therapeutic agents for the treatment of tardive dyskinesia.

Keywords: Tardive dyskinesia; Vacuous chewing movement; Neuroleptic; 5-HT (5-hydroxytryptamine, serotonin); 5-HT_3 receptor antagonist

1. Introduction

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

The therapeutic success of clozapine and other newer atypical antipsychotics has focused its attention on the role of the serotonergic system in the pathophysiology of schizophrenia and extrapyramidal side-effects. Electrophysiological, biochemical and behavioural evidence shows that serotonin modulates the dopaminergic system. This modulation is most evident when the dopaminergic system has been activated (Palfreyman et al., 1993). Clozapine has previously been shown to interact with multiple receptors (Watling et al., 1990). Clozapine shows more affinity towards 5-HT_2 and 5-HT_3 receptor subtypes (Seeman, 1992; Farde et al., 1994), and is virtually devoid of extrapyramidal side-effects at therapeutic doses. A high density of serotonin receptors, especially 5-HT_1, 5-HT_2 and 5-HT_3 receptor subtypes in the basal ganglia region, and their interactions with the dopaminergic system leads to the hypothesis that serotonin might play a significant role in movement disorders of basal ganglia origin. Biochemical studies showed that there are interactions between dopamine and serotonin in the central nervous system. The ventral striatum and nucleus accumbens septi receive a serotonergic input from the raphe nucleus (Fuxe, 1965), as do the dopaminergic cell bodies in the substantia nigra and ventral tegmental area, the important areas involved in movement control (Neal-Beliveau et al., 1993). This serotonergic input has been shown to make direct

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synaptic contact with dopaminergic neurones in both substantia nigra and ventral tegmental area (Nedergaard et al., 1988). Alterations in the serotonergic neurotransmission area are also known to alter dopamine-mediated behaviours such as stereotypy and hyperactivity (Fink and Oelssner, 1981; Lucki and Harvey, 1979). Serotonin modulates striatal dopamine release and could influence dyskinetic movements (Seibyl et al., 1989; Egan et al., 1997). Cyprohepatdine, a non-selective 5-HT receptor antagonist, is reported to improve dyskinetic symptoms (Goldman, 1976). 5-HT_3 receptors in the CNS appear to subserve a number of important modulatory actions of serotonin. The ability of dopamine to inhibit the firing rate of medial prefrontal neurones can be potentiated by 5-HT_3 receptor agonists and is blocked by 5-HT_3 receptor antagonists. 5-HT_3 receptor agonists stimulate dopamine release (Balandina et al., 1988) and potentiate dopamine-mediated behaviors, and antagonists reverse these effects (Palfreyman et al., 1993). However, very little is known about the role of 5-HT_3 receptors in mediating vacuous chewing movements. Stimulation of 5-HT_3 receptors gave mixed results. The highly selective 5-HT receptor agonist, biguanide, had no effect on oral behaviour, while another agonist, 2-Me-5-HT, increased vacuous chewing movement frequency (Liminga et al., 1993). The ability of 5-HT_3 receptor antagonists to modulate cerebral dopaminergic function in rats and primates has provided a rationale for the evaluation of 5-HT_3 receptor antagonists in disorders where excessive dopaminergic activity has been postulated.

We have now examined the efficacy of selective 5-HT_3 receptor antagonists, namely ondansetron and tropisetron, to ameliorate the dyskinetic symptoms in a putative animal model of tardive dyskinesia.

2. Materials and methods

2.1. Animals

Male Wistar rats, bred in the Central Animal House facility of Panjab University and weighing between 180–220 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. The animals were allowed to adapt to laboratory conditions before the test. All experiments were carried out between 0900 and 1500 h. The experimental protocols were approved by the Institutional Ethical Committee and conducted according to the Indian National Science Academy Guidelines for the use and care of experimental animals.

2.2. Induction of vacuous chewing movements

For the induction of vacuous chewing movements, the animals received daily injections of haloperidol (1.5 mg/kg, i.p.) for a period of 21 days, as described previously by Sasaki et al. (1995).

2.3. Measurement of vacuous chewing movements

Vacuous chewing movements were measured 24 h after the last dose of haloperidol. The animals were placed individually in a small ($30 \times 20 \times 30$) plexiglass cage, and were allowed to adapt to the observation cage for a period of 5 min. Vacuous chewing movements were scored during a 5-min observation period, and counting of VCMs was stopped whenever the animal began grooming and restarted when grooming stopped (Gunne et al., 1982). Two types of jaw movements were recorded; i.e. vacuous jaw movements and bursts of jaw tremor. For calculation purposes, each burst of jaw tremor was regarded as being two vacuous chewing movements. A vacuous chewing movement consisted of a rapid movement of the jaw, which resembled chewing but did not appear to be directed at any particular stimulus. In all the experiments, the experimenter was blind to the treatment given to the rats.

2.4. Measurement of wet dog shakes

Wet dog shakes were counted during a 5-min observation period. In all the experiments, the experimenter was blind to the treatment given to the rats.

2.5. Treatment schedule

All the test drugs were administered intraperitoneally in a constant volume of 0.5 ml per 100 g of body weight. All the test drugs were administered 30 min before behavioural assessment.

2.6. Drugs

Haloperidol (Searle India, India), ondansetron (Cipla, India) and tropisetron (Sandoz Pharma, Switzerland) were used in the present study. All drugs were dissolved in distilled water.

2.7. Statistical analysis

All results were expressed as means $\pm$ S.E.M. The data were analysed by one-way analysis of variance followed by Dunnett's test, and a P value $p < 0.05$ was considered statistically significant.

3. Results

Animals repeatedly treated with haloperidol developed profound vacuous chewing movements, in a time-depen-

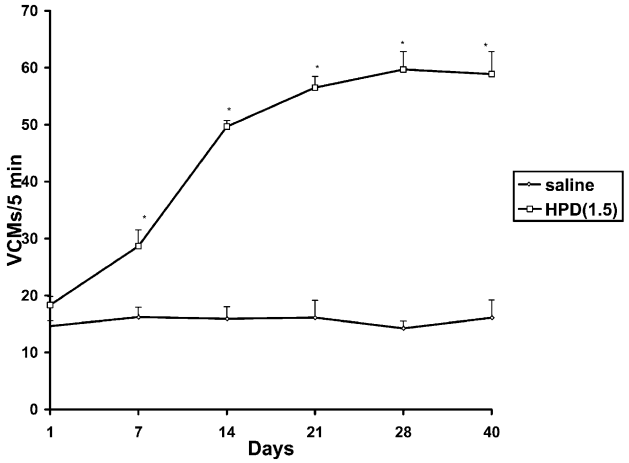

Fig. 1. Effect of chronic haloperidol (1.5 mg/kg) treatment on vacuous chewing behaviour in rats at different time intervals. Values expressed as means ± S.E.M. $^{*}P < 0.05$ as compared to first day score (ANOVA followed by Dunnett's test).

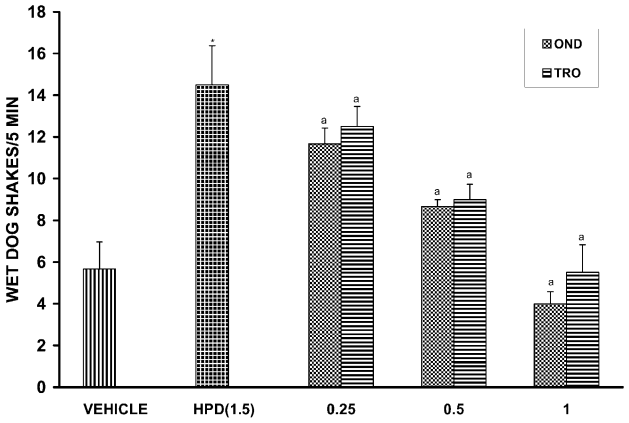

Fig. 3. Effect of ondansetron (OND) and tropisetron (TRO) on haloperidol-induced wet dog shakes in rats. Values expressed as means ± S.E.M. $^{*}P < 0.05$ as compared to vehicle-treated group. $^{a}P < 0.05$ as compared to haloperidol (HPD)-treated group (ANOVA followed by Dunnett's test).

dent fashion, which plateaued after 21 days and persisted for more than 40 days post-treatment (Fig. 1). Ondansetron (0.25, 0.5 and 1 mg/kg) dose-dependently reduced haloperidol-induced vacuous chewing movements (Fig. 2). Tropisetron (0.25, 0.5 and 1.0 mg/kg) similarly reversed the haloperidol-induced vacuous chewing movements in a dose-dependent manner, with a ceiling effect at 0.5 mg/kg (Fig. 2), $F(7,40) = 73.205$ ($n = 6$, $P < 0.05$). Ondansetron was found to be more potent in reducing vacuous chewing movements than tropisetron, whereas both drugs were equally effective to reduce haloperidol-induced wet dog shakes. Haloperidol treatment also produced significant wet dog shakes behaviour in rats. Both ondansetron and tropisetron dose-dependently reduced the haloperidol-induced wet dog shakes (Fig. 3), $F(7,40) = 12.071$ ($n = 6$, $P < 0.05$). The protective effect of these agents lasted for 8–10 h.

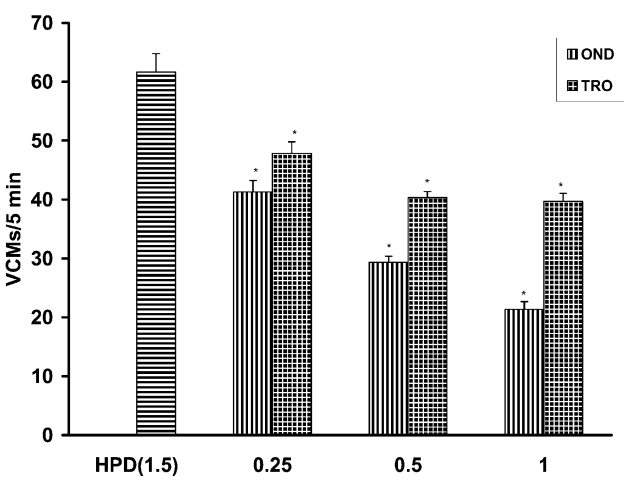

Fig. 2. Effect of ondansetron (OND) and tropisetron (TRO) on haloperidol-induced VCMs. Values expressed as means ± S.E.M. $^{*}P < 0.05$ as compared to haloperidol (HPD)-treated group (ANOVA followed by Dunnett's test).

4. Discussion

In the present study, both ondansetron and tropisetron, selective 5-HT_3 antagonists, dose-dependently reduced haloperidol-induced vacuous chewing movements.

The involvement of the serotonergic system in the modulation of extrapyramidal motor effects is suggested by the absence of extrapyramidal side-effects with atypical anti-psychotics like clozapine. These agents are known to have high affinity towards 5-HT_{1C}, 5-HT_2 receptors (Stockmeier et al., 1993; Lieberman, 1993), a high ratio of 5-HT_2 to dopamine D2 receptor blockade and 5-HT_3 receptor antagonism (Palfreyman et al., 1993; Hoyer et al., 1994). 5-HT_3 receptor antagonism of clozapine could contribute to its antipsychotic action and reduced EPS (Wang et al., 1994). The serotonergic system interacts directly with dopaminergic neurones in the substantia nigra and ventral tegmental area (Barnes et al., 1992), areas with a major involvement in movement control. Serotonergic projections from the dorsal raphe project directly to the substantia nigra and inhibit the firing of the dopaminergic neurones (Jacobs and Azmitia, 1992; Nedergaard et al., 1988). Stimulation of dorsal raphe serotonergic fibres releases serotonin in the substantia nigra, and this is associated with a decrease of dopamine-mediated behaviours, suggesting inhibitory modulation of the dopamine neurones in the substantia nigra by serotonin (Kapur and Remongton, 1996).

5-HT_3 receptors have been identified in the cell body and terminal regions of both the nigrostriatal and mesolimbicocortical dopaminergic systems (Palfreyman et al., 1993). Much evidence suggests a strong interaction be-

tween 5-HT_3 receptors and dopaminergic system (Kulkarni and Roychoudhury, 1996; Palfreyman et al., 1993; Hoyer et al., 1994). Ondansetron, a selective 5-HT_3 receptor antagonist, has been reported to block locomotor hyperactivity induced by central administration of amphetamine and dopamine (Costall et al., 1987). Ondansetron also is reported to have an antipsychotic effect in acute schizophrenia, even at lower doses (4–12 mg/kg). Ondansetron inhibits the dopamine infusion-induced hyperactivity response without affecting dopamine receptor sensitivity, but is reported to attenuate the rebound hyperactivity induced by withdrawal from combined dopamine infusion and haloperidol treatment (Costall et al., 1987). Ondansetron was reported to reduce psychotic symptoms by 50% after 3-weeks treatment without causing any extra pyramidal syndrome (Zoldan et al., 1995), and led to significant improvement in tardive dyskinesia patients (Sirota et al., 2000).

Haloperidol-treated animals showed significant wet dog shake behaviour when compared with vehicle-treated controls. The serotonergic system was reported to be involved in this behaviour. Both ondansetron and tropisetron dose-dependently reduced haloperidol-induced wet dog shakes, further supporting the possibility of an alteration in the serotonergic system after chronic haloperidol treatment.

Ondansetron was found to be more potent in reducing vacuous chewing movements than was tropisetron, whereas in the case of wet dog shakes, even though tropisetron had less effect than ondansetron, the values were not statistically significant. This difference may be due to a difference in potency. As wet dog shakes is a serotonin-mediated phenomenon, both drugs are equally effective, but vacuous chewing movements may involve other neurotransmitter systems, which could be a reason for the difference in activities between the two antagonists.

The exact mechanism of the 5-HT_3 receptor antagonist action to reduce vacuous chewing movements is not fully known. These drugs might be acting by modulating the release of dopamine, but further studies are needed to find the exact mechanism by which these drugs reduce the neuroleptic-induced vacuous chewing movements.

In conclusion, the results of the present study indicate that serotonin acting through 5-HT_3 receptors might play a significant role in the pathophysiology of tardive dyskinesia. These 5-HT_3 receptors can serve as potential therapeutic targets for the development of novel molecules for the treatment and prevention of tardive dyskinesia.

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