ELSEVIER

European Journal of Pharmacology 430 (2001) 295–298

ejp

www.elsevier.com/locate/ejphar

Short communication

Possible involvement of prostaglandins in haloperidol-induced orofacial dyskinesia in rats

Pattipati S. Naidu, Shrinivas K. Kulkarni *

Division of Pharmacology, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh-160014, India

Received 12 July 2001; received in revised form 30 August 2001; accepted 7 September 2001

Abstract

Dopaminergic abnormality is one of the pathological mechanisms involved in the pathophysiology of tardive dyskinesia, a late complication of neuroleptic treatment. Prostaglandins modulate the dopamine release in the striatum, the principle area involved in the pathophysiology of tardive dyskinesia. Rats were chronically treated with haloperidol (HPD) (1.5 mg/kg) for a period of 21 days, to induce orofacial dyskinesia. Behavioural assessment of orofacial dyskinesia was done 24 h after the last dose of haloperidol. Catalepsy was induced in rats by acute treatment with haloperidol (1 mg/kg), and catalepsy was scored for the next 4 h. Chronic haloperidol treatment induced profound vacuous chewing movements in rats. Indomethacin, a nonselective cyclooxygenase inhibitor dose-dependently (5–20 mg/kg) suppressed the vacuous chewing movements count in haloperidol-treated animals. In conclusion, the results of the present study infer that prostaglandins might play a significant role in the haloperidol-induced vacuous chewing movements, and prostaglandin synthesis inhibitors can serve as novel drug candidates for the treatment of tardive dyskinesia.

Keywords: Tardive dyskinesia; Dopamine; Indomethacin; Prostaglandin; Vacuous chewing movement

1. Introduction

Tardive dyskinesia is a late complication of prolonged neuroleptic treatment characterized by involuntary movements preferentially that of the oral region (Kulkarni and Naidu, 2001). Despite much research, the pathogenesis of tardive dyskinesia remains elusive. The proximal cause of these symptoms is unknown; however, chronic blockade of dopamine D2 receptor is clearly the initiating stimulus (Eyles et al., 2000). So far, various neurochemical hypotheses have been proposed for the development of tardive dyskinesia. Those include dopaminergic supersensitivity, disturbed balance between dopaminergic and cholinergic systems, dysfunction of striatonigral γ-amino butyric acid (GABA) ergic mechanisms, and excitotoxicity (Kulkarni and Naidu, 2001; Casey, 2000).

Prostaglandins are the lipid mediators derived from arachidonic acid via the cyclooxygenase pathway. The presence of prostaglandins have been identified in the central nervous system of several mammalian species, and several considerable evidences show that prostaglandins may play a role as putative transmitters or as modulators in the central nervous system (Ono et al., 1986). Prostaglandins have been reported to modulate catacholaminergic, serotonergic and cholinergic neurons in the central nervous system (Saito et al., 1986). Prostaglandins are reported to induce cataleptic behaviour in rats by modulating the presynaptic dopamine receptors (Ono et al., 1992). With this observation in view, we examined the possible role of prostaglandins that might be involved in the pathophysiology of the movement disorders of the basal ganglia origin.

The nonsteroidal antiinflammatory drugs (NSAIDs) are known to inhibit prostaglandin synthesis in a variety of tissues, including the central nervous system. We have earlier reported about the vacuous chewing movements in rats on chronic treatment with haloperidol, and now attempted to study the effect of indomethacin, a nonselective cyclooxygenase inhibitor on haloperidol-induced vacuous chewing movements.

* 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)01385-1

2. Materials and methods

2.1. Animals

Male Wistar rats (Central Animal House, Panjab University, Chandigarh) weighing between 200 and 250 g were used for the study. They were housed under standard laboratory conditions with a 12 h light and dark cycle (lights on at 06:00). Experiments were performed between 09:00 and 12:00. Each animal was used only once in the experiments. 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 orofacial dyskinesia

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

2.3. Assessment of vacuous chewing movements

Behavioural assessments were carried out 24 h after the last injection of haloperidol according to Gunne et al. (1982). Briefly, rats were placed individually in a Plexiglas cage ($30 \times 20 \times 30$ cm), and were allowed to accommodate to the observation cage for 10 min before behavioural assessment. Vacuous chewing movements were counted for 5 min with the help of a mechanical counter. The count stopped whenever the rat began grooming, and restarted when grooming stopped. After the baseline vacuous chewing movements of all the animals, vehicle or indomethacin (Micro Labs, India) suspended in distilled water wetted with Tween 80 was administered intraperitonially, and behavioural assessment was done 30 min later. In all the experiments, the rater was blind to the treatment given to the rats.

2.4. Measurement of catalepsy

A cataleptic behaviour was measured with a high bar test method. Catalepsy score was measured each hour for 4 h after haloperidol administration by gently placing both the forepaws of the rat over a metal bar (0.5–1-cm diameter) suspended 10 cm above the tabletop. The intensity of catalepsy was assessed by counting the time in seconds until the rat brought both forepaws down to the tabletop, with a maximum cutoff time of 180 s. Finally, scores at different time intervals were added and expressed as cumulative catalepsy score for comparison purposes. In all the experiments, the rater was blind to the treatment given to the rats.

2.5. Drugs and drug treatment

Haloperidol (Searle India) was diluted with distilled water. Indomethacin (Micro Labs) was suspended in distilled water wetted with Tween 80. All drugs were administered intraperitonially in a constant volume of 0.5 ml/100 g of body weight of the rat. Drug doses were selected on the bases of previous studies conducted in our laboratory and those reported in the literature.

2.6. Statistical analysis

One specific group of rats was assigned to one specific drug treatment condition and each group comprises six rats ($n = 6$). All the values were expressed as mean ± S.E.M. The data was analyzed by Analysis of Variance (ANOVA) followed by Dunnett's *t*-test. In all the tests, the criterion for the statistical significance was $P < 0.05$.

3. Results

Chronic administration of haloperidol (1.5 gm/kg) to rats induced pronounced vacuous chewing movements and tongue protrusions. Acute administration of indomethacin (10–20 mg/kg), a nonselective cyclooxygenase inhibitor, significantly suppressed the severity of haloperidol-induced vacuous chewing movements $F(5,30) = 116.321$ ($n = 6$, $P < 0.05$) (Fig. 1A) and tongue protrusions $F(5,30) = 60.897$ ($n = 6$, $P < 0.05$) (Fig. 1B) in a dose-

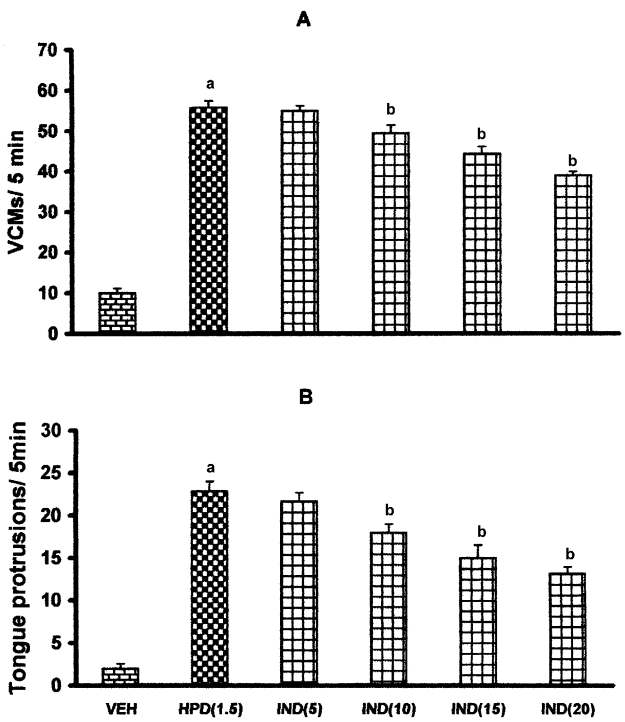

Fig. 1. Effect of indomethacin (IND) on haloperidol-induced (HPD) vacuous chewing moments (A) and tongue protrusions (B) in rats. Values expressed as mean ± S.E.M. [a]$P < 0.05$ as compared to vehicle-treated group. [b]$P < 0.05$ as compared to haloperidol-treated group (ANOVA followed by Dunnett's *t*-test).

Table 1
Effect of indomethacin on cumulative catalepsy score (s) in haloperidol-treated animals

S.No.	Treatment (mg/kg)	Cumulative catalepsy score (s), mean ± S.E.M.
1	Vehicle	8.73 ± 1.015
2	Haloperidol (1)	586.50 ± 17.642[a]
3	Indomethacin (5)	560.26 ± 15.162
4	Indomethacin (10)	400.261 ± 16.926[b]
5	Indomethacin (15)	329.873 ± 14.822[b]
6	Indomethacin (20)	234.853 ± 12.941[b]

Values expressed as mean ± S.E.M.
[a] $P < 0.05$ as compared to vehicle-treated group.
[b] $P < 0.05$ as compared to haloperidol-treated group $F(5,30) = 160.53$ ($n = 6$, $P < 0.05$) (ANOVA followed by Dunnett's t-test).

dependent manner. Indomethacin reversal of haloperidol-induced vacuous chewing movements is short-lived, animals showed baseline (haloperidol-treated group) vacuous chewing movements count after 10–12 h (data not shown). The pharmacokinetic profile of indomethacin may explain this time-dependent decline in its action. Acute treatment with haloperidol induced a strong cataleptic state starting at the first hour after its injection, reaching a maximal plateau after the second hour. Vehicle-treated animals did not display catalepsy as they remained less than 5 s on the bar at each time point. Indomethacin, a nonspecific cyclooxygenase inhibitor dose-dependently (10–20 mg/kg) reduced the catalepsy score in haloperidol-treated animals at all time intervals $F(5,30) = 160.53$ ($n = 6$, $P < 0.05$) (Table 1).

4. Discussion

The results presented here show that chronic administration of indomethacin reverses chronic haloperidol-induced vacuous chewing movements. However, the effect of indomethacin on vacuous chewing movements is short-lived and animals regained their baseline vacuous chewing movements count after 10–12 h.

Nigrostriatal dopaminergic system is reported to be the primary pathway playing an important role in the control of movements and complex motor behaviour. Abnormal dopaminergic transmission in these areas may lead to the development of several movement disorders, such as Parkinsonism and tardive dyskinesia (Kulkarni and Ninan, 1996). A functional interaction exists between prostaglandins and dopaminergic system in this area. Dopamine reported to increase the prostaglandin synthesis (Tada et al., 1991). Prostaglandins induced cataleptic behaviour by modulating the dopamine neuronal systems (Ono et al., 1992). Pretreatment with prostaglandin synthesis inhibitors aspirin, paracetamol and indomethacin, significantly reversed neuroleptic-induced catalepsy (Lall et al., 1984; Ono et al., 1988, 1992). The results of the present study are in accordance with the previous reports. An important mechanism in the regulation of dopaminergic activity is the autoreceptors found on dopaminergic terminals (Cebeddu and Comar, 1983). Evidences indicate that prostaglandins may exert their effects on the striatum by inhibiting these striatal dopamine autoreceptors. Prostaglandins may interact not only with the autoreceptors but also with the postsynaptic dopamine receptors (Ono et al., 1992). At postsynaptic terminals, prostaglandins are reported to inhibit the depolarization-induced release of dopamine, and antagonize the physiological effects of dopamine receptor activation (Schwarz et al., 1982; Westfall and Kitay, 1977). Prostaglandins, through a modulatory action on dopaminergic system, might play a significant role in mediating the haloperidol-induced vacuous chewing movements.

Understanding the mechanism(s) underlying the antidyskinetic effect of indomethacin could have important implications, particularly in conditions where dopaminergic abnormality was implicated as pathological mechanism, such as Parkinsonism and tardive dyskinesia. In conclusion, the present study showed that indomethacin reverses haloperidol-induced vacuous chewing movements, probably by modulating the dopaminergic activity via prostaglandin-dependent mechanisms.

Acknowledgements

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

References

Casey, D.E., 2000. Tardive dyskinesia: pathophysiology and animal models. J. Clin. Psychiatry 61 (Suppl. 4), 5–9.
Cebeddu, A., Comar, C.L., 1983. Frequency dependent effects of neuronal uptake inhibitors on the autoreceptor mediated modulation of dopamine and acetylcholine release from the rabbit striatum. J. Pharmacol. Exp. Ther. 226, 85–94.
Eyles, D.W., Pond, S.M., Van der Schyf, C.J., Halliday, G.M., 2000. Mitochondrial ultra structure and density in a primate model of persistent tardive dyskinesia. Life Sci. 66, 1345–1350.
Gunne, L.M., Growdon, J., Glaeser, B., 1982. Oral dyskinesia in rats following brain lesions and neuroleptic drug administration. Psychopharmacology 77, 134–139.
Kulkarni, S.K., Naidu, P.S., 2001. Tardive dyskinesia: an update. Drugs Today 37, 97–119.
Kulkarni, S.K., Ninan, I., 1996. Current concepts in the molecular diversity and pharmacology of dopamine receptors. Methods Find. Exp. Clin. Pharmacol. 18, 599–613.
Lall, S.B., Tekur, U., Sen, P., 1984. Effect of drugs influencing synthesis of prostaglandins on haloperidol-induced catalepsy. Indian J. Physiol. Pharmacol. 28, 219–222.
Ono, N., Saito, R., Abiru, T., Kamiya, H., Furukawa, T., 1986. Possible involvement of prostaglandins in cataleptic behaviour in rats. Pharmacol., Biochem. Behav. 25, 463–467.
Ono, N., Saito, R., Abiru, T., Mstdudhita, Y., Kamiya, H., 1988. Effect

of aspirin on haloperidol-induced cataleptic behavior in mice. Neuropharmacology 27, 327–329.

Ono, N., Abiru, T., Sugiyama, K., Kamiya, H., 1992. Influence of cyclooxygenase inhibitors on the cataleptic behaviour induced by haloperidol in mice. Prostaglandins, Leukotrienes Essent. Fatty Acids 46, 59–63.

Saito, R., Fujiwara, M., Kamiya, H., Ono, N., 1986. The effect of neurotransmitters on cataleptic behaviour induced by PG D_2 in rats. Pharmacol., Biochem. Behav. 26, 543–546.

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.

Schwarz, R.D., Uretsky, N.J., Bianchine, J.R., 1982. Prostaglandin inhibition of amphetamine-induced circling in mice. Psychopharmacology 78, 317.

Tada, K., Kudo, T., Kishimoto, Y., 1991. Effects of L-dopa or dopamine on human decidual prostaglandin synthesis. Acta Med. Okayama 45, 333–338.

Westfall, T.C., Kitay, D., 1977. The effects of prostaglandins on the release of ^{3}H-dopamine from superfused slices of rat striatum following electrical stimulation. Proc. Soc. Exp. Biol. Med. 155, 305.