EFFECT OF DOPAMINERGIC DRUGS ON RIVASTIGMINE INDUCED VACUOUS CHEWING MOVEMENTS AND TONGUE PROTRUSION IN RATS

M.D. KHARJUL[1], AMJAD A. PATHAN[1], M. MOHAN[1], M. S. KARCHULI[2], S.B. KASTURE [2*]

[1]Department of Pharmacology, MGV's Pharmacy College, Panchavati, Nashik-422003, Maharashtra, India, [2]Pinnacle Biomedical Research Institute, Bhopal, India

* Corresponding author
S. B. Kasture
Division of Pharmacology
Pinnacle Biomedical Research Institute, Bhopal, India
e-mail: Kasture_sb@hotmail.com
Mobile: 9822951098

Summary

The objective of this study was to study the effect of dopaminergic drugs on rivastigmine induced vacuous chewing movements and tongue protrusion in rats. Albino rats divided into 5 groups, each containing 5 animals received vehicle, amantadine (10mg/kg, i.p.), apomorphine (2mg/kg, s.c.), bromocriptine (5mg/kg, i.p.), or L-dopa (100mg/kg, i.p.) 30 min before rivastigmine (1.25mg/kg, i.p). The number of vacuous chewing movements, orofacial bursts and tongue protrusions were observed for 45 min after rivastigmine. The L-DOPA, amantadine, apomorphine, and bromocriptine treated groups significantly ($P < 0.05$) reduced vacuous chewing movements, orofacial bursts, and tongue protrusions induced by rivastigmine. The study concludes that rivastigmine induced chewing movements and tongue protrusions in rats can be used to characterize dopaminergic antiparkinsonian agents.

Key Words: Rivastigmine, vacuous chewing movements, tongue protrusions, dopaminergic, antiparkinsonian

Running title: DOPAMINERGIC DRUGS INHIBIT RIVASTIGMINE INDUCED VACUOUS CHEWING MOVEMENTS AND TONGUE PROTRUSION

Introduction

Several antiparkinsonian drugs inhibit vacuous chewing movements (VCMs) induced by various categories of drugs (1, 2). Considerable evidence suggests that cholinomimetic-induced tremulous jaw movements in rats are similar with human Parkinsonian tremor (3). Carlson et al., (4) have shown that antihistamines such as diphenhydramine, which are used as antiparkinsonian agents, reduce cholinomimetic-induced vacuous chewing movements. These data are generally interpreted to mean that dopamine and acetylcholine (ACh) systems interact in the production of Parkinsonian symptoms (5). Salamone and Buskin (6) have reported that coadministration of the monoamine-depleting agent reserpine with a low dose of apomorphine results in high levels of vacuous chewing movements in rats and scopolamine produced a dose-related decrease in vacuous chewing movements. They further showed that most of the vacuous chewing movements shown by rats treated with reserpine and apomorphine occurred in rapid bursts of chewing movements with a local frequency in the range of 3-7 Hz.
Rivastigmine is a cholinesterase inhibitor known to induce vacuous chewing movements (VCMs) and tongue protrusions (TPs) in rats. In the present communication, we have studied effect of amantadine, apomorphine, bromocriptine, and L-dopa on rivastigmine-induced vacuous chewing movements and tongue protrusions in rats.

Materials and Methods

Animals: Male Wistar rats weighing 120-150 g were purchased from Serum Institute, Pune. The animals were housed in groups of five and had free access to feed and water. A light: dark cycle of 12 h was maintained and all experiments were carried out between 10:00 – 14:00 hrs. The experiments were carried out as per the guidelines of committee for the purpose of control and supervision of experiments in animals (CPCSEA) and the protocol of this study was approved by the Institutional Animal Ethical Committee.

Drugs: Rivastigmine (Sun Pharma, Mumbai), L-Dopa (Sun Pharma, Mumbai), bromocriptine (Novartis, Mumbai), apomorphine (Sigma, USA), amantadine (Cipla, Mumbai).

Rivastigmine-induced vacuous chewing movements and tongue protrusions
Rats were placed individually in a small (30 x 20 x 30 cm) Plexiglas cage and allowed to habituate for 30 min. various doses of rivastigmine ranging from 0.5 – 2 mg/kg i.p. were tested for the induction of VCMs and TPs and a dose of 1.25 mg/kg was selected for further study. Rats were treated with vehicle or amantadine (10mg/kg, i.p.), apomorphine (2mg/kg, s.c.) bromocriptine (5mg/kg, i.p.) or L-dopa (100mg/kg, i.p.) 30 min before rivastigmine (1.25 mg/kg, i.p.). The no. of vacuous chewing movements, orofacial bursts and tongue protrusions were observed for 45 min immediately after rivastigmine injection. VCMs were counted with the help of a hand operated counter by trained observers. VCMs were referred to as single mouth openings in the vertical plane not directed toward a physical object. If VCMs occurred during a period of grooming, they were not taken into account. Counting was stopped whenever the rat began grooming, and restarted when grooming was over. VCMs were measured continuously for a period of 5 min. In all the experiments the scorer was unaware of the treatment given to the animals (7).

Statistical Analysis: All the values were expressed as MEAN ± SEM. All the data were subjected to one-way ANOVA followed by Dunnett's test, *P< 0.05 were considered significant as compared with control.

Results

Rivastigmine induced orofacial bursts, VCMs and TPs in rats. Dopaminergic drugs showed significant inhibition of rivastigmine induced vacuous chewing movements ($F_{4,20}$= 1306.13, P< 0.0001), orofacial bursts ($F_{4,20}$= 41.91, P< 0.001) and tongue protrusions ($F_{4,20}$ = 33.05, P< 0.0001). Bromocriptine and apomorphine were more effective in reducing the VCMs, orofacial bursts, and TPs. The observations are given in Table 1.

Table 1: Effect of dopaminergic drugs on rivastigmine induced vacuous chewing movements, orofacial bursts and tongue protrusions in rats

Group	No. of Vacuous Chewing Movements	No. of Orofacial Bursts	No. of Tongue Protrusions
Control (Rivastigmine 1.25mg/kg, i.p.)	791.8 ± 10.81	109.8 ± 5.82	58.2 ± 4.40
Amantadine (10mg/kg, i.p.)	252.0 ± 6.08*	54.2 ± 2.72*	30.4 ± 3.12*
L-DOPA (100mg/kg, i.p.)	255.1 ± 5.84*	53.2 ± 2.90*	27.1 ± 2.89*
Bromocriptine (5mg/kg, i.p.)	175.4 ± 5.60*	39.8 ± 2.78*	18.1 ± 1.84*
Apomorphime (2mg/kg, i.p.)	177.2 ± 6.42*	36.4 ± 6.89*	16.2 ± 1.46*
F(4,20)	1306.13	41.91	33.05

n=5, All the values are in MEAN ± SEM, All the data were subjected to one-way ANOVA followed by Dunnett's test, *P< 0.05 as compared with control

Discussion

Several drugs are known to induce vacuous chewing movements in rats. Earlier studies suggest that the VCMs can be used as a model of Parkinsonian tremor (5). Baskin et al., (8) showed that repeated scopolamine injections sensitize rats to pilocarpine-induced vacuous jaw movements and enhance striatal muscarinic receptor binding. Salamone et al., (3) suggested that cholinomimetic-induced tremulous jaw movements in rats are similar to human Parkinsonian tremors.

Mayorga et al., (1) used the rodent model of pilocarpine-induced VCMs to characterize the putative antiparkinsonian effects of the full D_1 dopamine receptor agonist, SKF 82958. SKF 82958 reduced the tremulous jaw movements induced by pilocarpine. The suppressive effects of SKF 82958 on jaw movements were dose-dependently reversed by systemic pretreatment with the selective D_1 dopamine receptor antagonist SCH 23390. Intracranial injection of SCH 23390 into the ventrolateral striatum, the rodent homologue of the human ventral putamen, and also substantia nigra pars reticulata reversed the reduction of pilocarpine-induced jaw movements produced by SKF 82958. These data suggest that the antiparkinsonian actions of SKF 82958 may be due to stimulation of D_1 receptors in the ventrolateral striatum and substantia nigra pars reticulata.

Adenosine A_{2A} receptor antagonists have antiparkinsonian activity. Since adenosine A_{2A} receptors are largely expressed throughout the striatum, Simola et al., (9) studied effect of A_{2A} antagonists injected into rat dorsomedial (DMS) and ventrolateral striatum (VLS) to investigate whether A_{2A} antagonists could act at this level. The A_{2A} antagonists effectively reduced the magnitude of tremulous jaw movements induced in rats by acute tacrine, mainly by an action in VLS and suggested that A_{2A} antagonists might be used as specific agents against Parkinsonian tremor.

Rivastigmine is acetylcholinesterase inhibitor used to treat Alzheimer's disease (10). Rivastigmine crosses blood brain barrier and precipitates Parkinsonian symptoms in rats, like vacuous jaw movements and tongue protrusions. In the present study all the dopaminergic drugs significantly inhibited rivastigmine induced VCMs and TPs suggesting that rivastigmine induced vacuous jaw movements and tongue protrusions in rats can be used as putative model for Parkinsonian in rats, same like tacrine induced tremulous jaw movements. The study also showed that apomorphine and bromocriptine were more potent than amantadine and L-DOPA. A similar potency order has been observed in inhibition by dopaminergic drugs in the tacrine-induced VCMs. Therefore it is concluded that rivastigmine-induced VCMs and TPs can be used to evaluate antiparkinsonian drugs.

References

1 Mayorga AJ, Trevitt JT, Conlan A, Gianutsos G, Salamone JD. Striatal and nigral D1 mechanisms involved in the antiparkinsonian effects of SKF 82958 (APB): studies of tremulous jaw movements in rats. Psychopharmacology (Berl). 1999; **143**: 72-81

2 Salamone JD, Betz AJ, Ishiwari K, Felsted J, Madson L, Mirante B, Clark K, Font L, Korbey S, Sager TN, Hockemeyer J, Muller CE. Tremorolytic effects of adenosine A2A antagonists: implications for Parkinsonism. Front Biosci. 2008;**13**: 3594-605

3 Salamone JD, Carlson BB, Rios C, Lentini E, Correa M, Wisniecki A, Betz A. Dopamine agonists suppress cholinomimetic-induced tremulous jaw movements in an animal model of Parkinsonism: tremorolytic effects of pergolide, ropinirole and CY 208-243. Behav Brain.Res. 2005; **156**: 173-179.

4 Carlson BB, Trevitt JT, Salamone JD. Effects of H_1 antagonists on cholinomimetic-induced tremulous jaw movements: studies of diphenhydramine, doxepin, and mepyramine. Pharmacol. Biochem. Behav. 2000; **65**: 683-689.

5 Salamone J.D., Mayorga A. J., Trevitt J. T., Cousins M. S., Conlan A., Nawab A. Tremulous jaw movements in rats: A model of Parkinsonian tremor. Progress in Neurobiology 1998; **56**: 591-611.

6 Salamone J, Baskin P. Vacuous jaw movements induced by acute reserpine and low-dose apomorphine: possible model of parkinsonian tremor. Pharmacol Biochem Behav. 1996 53:179-83.

7 Naidu PS., Kulkarni SK. Excitatory mechanisms in neuroleptic-induced vacuous chewing movements (VCMs): Possible involvement of calcium and nitric oxide. Behav. Pharmacol. 2001; **12**, 209 - 216.

8 Baskin, P., Gianutsos G., Salamone J.D. Repeated scopolamine injections sensitize rats to pilocarpine-induced vacuous jaw movements and enhance striatal muscarinic receptor binding. Pharmacol. Biochem. Behav. 1994; **49**: 437.

9 Simola N, Fenu S, Baraldi PG, Tabrizi MA, Morelli M. Blockade of adenosine A_{2A} receptors antagonizes Parkinsonian tremor in the rat tacrine model by an action on specific striatal regions. Exp. Neurol. 2004;**189**: 182-8.

10 Spencer, Caroline M.; Noble, Stuart. Rivastigmine: A Review of its Use in Alzheimer's Disease. Drugs & Aging: 1998: **13**; 391-411