ELSEVIER

European Journal of Pharmacology 356 (1998) 105–108

ejp

Short communication

Reserpine does not induce orofacial dyskinesia in spontaneously hypertensive rats

Claudio M.T. Queiroz, Ronaldo D. Piovezan, Roberto Frussa-Filho *

Departamento de Farmacologia, Escola Paulista de Medicina / Universidade Federal de São Paulo, Rua Botucatu 862, Edificio Leal Prado, CEP: 04023-062, São Paulo, SP, Brazil

Received 18 May 1998; revised 16 July 1998; accepted 21 July 1998

Abstract

The nigrostriatal dopaminergic system seems to be involved in both reserpine-induced orofacial dyskinesia in normal rats and in the pathogenesis of hypertension in spontaneously hypertensive rats. In the present study, repeated reserpine administration (1.0 mg/kg, s.c., every other day, for 3 days) increased tongue protrusion and vacuous chewing frequencies as well as the duration of facial twitching in Wistar normotensive but not in spontaneously hypertensive rats. These results suggest that genetic hypertension and drug-induced orofacial movements may be inversely modulated by similar mechanisms in the nigrostriatal dopaminergic system. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Reserpine; Spontaneously hypertensive rat (SHR); Orofacial dyskinesia; Tardive dyskinesia; Dopamine

1. Introduction

Tardive dyskinesia is a syndrome characterized by repetitive involuntary movements, usually involving mouth, face and tongue and sometimes limb and trunk musculature. The syndrome is considered to be an adverse effect of prolonged administration of antipsychotic drugs. It usually persists for months after the neuroleptic has been stopped and may be irreversible (Kane, 1995). Recently, Neisewander et al. (1994) have suggested that reserpine-induced oral dyskinesia may provide a new animal model of tardive dyskinesia. Rats treated with this monoamine-depleting agent for at least 3 days develop orofacial dyskinesia characterized by twitching of the facial musculature, vacuous chewing movements and tongue protrusion (Neisewander et al., 1991a,b, 1994, 1996; Vital et al., 1997; Bergamo et al., 1997). In this regard, although reserpine is not classified as a neuroleptic, it has been used as an antipsychotic agent and has been associated with the development of tardive dyskinesia (see Uhrbrand and Faurbye, 1960). This reserpine-induced orofacial dyskinesia in rats has also other features that are consistent with tardive dyskinesia, including persistence following termination of administration and dose-dependent blockade by a dopamine D_2 receptor antagonist (Neisewander et al., 1991a,b). Furthermore, whereas the orofacial dyskinesia is of insidious onset at low doses of reserpine, the response develops very rapidly at high doses, a fact offering an outstanding methodological advantage over long-term neuroleptic administration. Finally, consistent to the clinical situation (Wolfarth and Ossowska, 1989), we have recently verified that in old rats, the persistence of reserpine-induced orofacial dyskinesia was increased when compared to adult animals (Bergamo et al., 1997).

Besides being attenuated by a dopamine D_2 receptor antagonist (Neisewander et al., 1991b), reserpine-induced orofacial dyskinesia is reversed by nigrostriatal 6-hydroxydopamine lesions and exacerbated by acute administration of amphetamine (Neisewander et al., 1996). These findings suggest that residual endogenous dopamine in the nigrostriatal system may play a crucial role in this orofacial syndrome. In this respect, several lines of evidence support the notion of an altered function of the nigrostriatal dopaminergic system in spontaneously hypertensive rats, which seems to be involved in the pathogenesis of hypertension in that model. For example, while brain dopamine depletion by lesion in the nigrostriatal dopamine system attenuates the development of hypertension in the sponta-

* Corresponding author. Tel.: +55-11-549-4122; Fax: +55-11-576-4449; E-mail: frussa.farm@epm.br

0014-2999/98/$19.00 © 1998 Elsevier Science B.V. All rights reserved.
PII: S0014-2999(98)00546-9

neously hypertensive rat (Van den Buuse et al., 1986; Linthorst et al., 1994), in vitro autoradiography studies have shown that the amounts of striatal dopamine D_1 receptors (Kirouac and Ganguly, 1993) as well as of the dopamine transporter (Watanabe et al., 1997) are increased in spontaneously hypertensive rats at both pre- and posthypertensive stages.

This study was undertaken to compare the orofacial movements of spontaneously hypertensive rats with those of normotensive Wistar EPM-1 rats (derived from a local Wistar strain), after repeated reserpine administration.

2. Materials and methods

2.1. Subjects

Five-month old Wistar EPM-1 and spontaneously hypertensive rats were used. Groups of six animals were kept in Plexiglass cages with free access to food and water in a room with controlled temperature ($22 \pm 1°C$) and in 12 h light/dark cycle with lights on at 7:00 AM. Blood pressures of spontaneously hypertensive rats were hypertensive at the time of experiment (200–235 mmHg). The animals were maintained and used in accordance to the guidelines of the Committee on Care and Use of Experimental Animal Resources, School of Veterinary Medicine and Animal Science of the University of São Paulo, Brazil.

2.2. Drugs

Reserpine (RBI) was dissolved in glacial acetic acid and then diluted in distilled water. Vehicle consisted of the same amount of acetic acid and water as in the reserpine solution. Both reserpine and control solutions were administered in the volume of 1.0 ml/kg body weight.

2.3. Experimental procedure

Twenty Wistar EPM-1 and 20 spontaneously hypertensive rats were randomly divided into two groups of 10 animals each, respectively, which received a total of two administrations of 1.0 mg/kg reserpine or vehicle given s.c. every other day. Animals were observed for quantification of orofacial dyskinesia 24 h after the second injection of reserpine or vehicle.

2.4. Behavioral testing

To quantify the occurrence of orofacial dyskinesia, hand operated counters were employed to score tongue protrusion and vacuous chewing frequencies and stopwatches were employed to score the duration of twitching of the facial musculature. In the present study, vacuous chewing movements are referred to as single mouth openings in the vertical plane not directed towards physical material. If tongue protrusion, vacuous chewing, or twitching of the facial musculature occurred during a period of grooming they were not taken into account. The behavioral

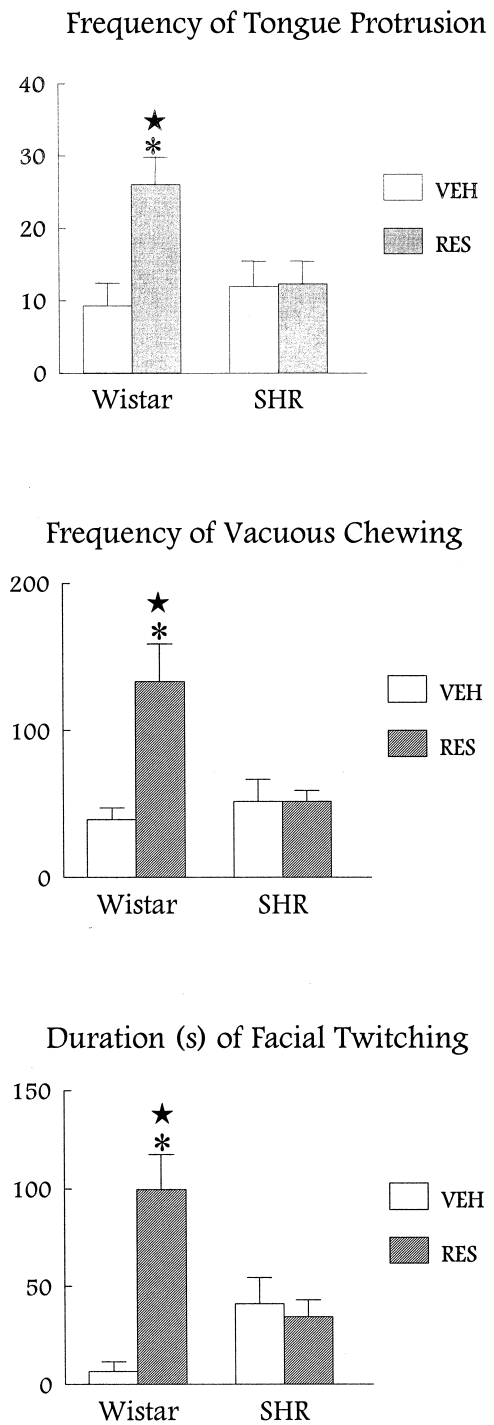

Fig. 1. Effects of repeated administration of reserpine (RES, 1.0 mg/kg, s.c., every other day, for 3 days) or vehicle (VEH) on reserpine-induced tongue protrusion and vacuous chewing frequencies and duration of twitching of the facial musculature in spontaneously hypertensive (SHR) or normotensive Wistar EPM-1 rats. Data (mean ± SEM, $n = 10$) were analyzed by the two-way analysis of variance followed by the Student–Newman–Keuls. $* P < 0.05$ compared to the respective vehicle-treated strain, $★P < 0.05$ compared to reserpine- and vehicle-treated SHR.

parameters of orofacial dyskinesia were measured continuously for 15 min. During the observation sessions, mirrors were placed under the floor and behind the backwall of the experimental cage to permit observation when the animal was faced away from the observer. The behavioral tests were always conducted blind.

2.5. Statistical analysis

The data were analyzed by two-way analysis of variance followed by the Student–Newman–Keuls test. A probability of $P < 0.05$ was considered to show significant differences for all comparisons made.

3. Results

Two-way analysis of variance for tongue protrusion, vacuous chewing and facial twitching revealed significant drug ($F(1,36) = 6.03$, 7.53 and 11.46, respectively, $P < 0.05$) and drug vs. strain interaction ($F(1,36) = 5.57$, 7.50 and 15.36, respectively, $P < 0.05$) effects. As depicted in Fig. 1, post-hoc analysis revealed that repeated administration of reserpine to normotensive Wistar EPM-1 rats increased tongue protrusion and vacuous chewing frequencies, as well as the duration of twitching of the facial musculature when compared to the respective saline-treated animals. However, there were no differences in the orofacial parameters between reserpine- and saline-treated spontaneously hypertensive rats. In addition, whereas reserpine-treated spontaneously hypertensive rats showed significant decreases in the three orofacial parameters when compared to reserpine-treated Wistar EPM-1 rats, there were no differences between saline-treated Wistar EPM-1 and spontaneously hypertensive rats.

4. Discussion

The present study demonstrates that as opposed to normotensive Wistar EPM-1 animals, spontaneously hypertensive rats were not able to develop orofacial dyskinesia after repeated treatment with reserpine.

As mentioned earlier, there is convincing evidence that stimulation of dopamine receptors by residual endogenous dopamine in the nigrostriatal system plays a fundamental role in reserpine-induced orofacial syndrome (Neisewander et al., 1996). In this respect, there is growing evidence that striatal dopamine D_1 and/or D_2 receptors as well as dopamine transporter densities and tyrosine hydroxylase activity are increased in spontaneously hypertensive rats when compared to different normotensive rat strains (Nagaoka and Lovenberg, 1977; Lim et al., 1989; Kujirai et al., 1990; Kirouac and Ganguly, 1993; Watanabe et al., 1997; but see Linthorst et al., 1993). However, in spite of these enhanced biochemical dopaminergic parameters, vehicle-treated spontaneously hypertensive rats did not show increased spontaneous basal orofacial movements when compared to normotensive Wistar EPM-1 rats. In line with this finding, Neisewander et al. (1996) verified that normal rats treated with amphetamine do not exhibit a reserpine-like orofacial dyskinesia. These data suggest that a quantitative increase in nigrostriatal dopaminergic transmission is not a sufficient phenomenon to produce orofacial dyskinesia. In further support of this assumption, although repeated treatment with reserpine produces an up-regulation of both striatal dopamine D_1 and D_2 receptors (Neisewander et al., 1991a), different lines of evidence suggest that this phenomenon is not directly related to the orofacial syndrome. First, the increase in the striatal dopamine D_1 receptor density is not correlated with the persistence of the oral dyskinesia (Neisewander et al., 1991a). Second, whereas reserpine-induced oral dyskinesia is more persistent in old rats (Bergamo et al., 1997), it is well known that the number of striatal dopamine D_2 receptors declines linearly with age in rodents (Wolfarth and Ossowska, 1989).

Taken together, the findings described above suggest that dopamine depletion may cause qualitative (in addition to quantitative) changes in nigrostriatal postsynaptic receptor mechanisms, resulting in altered responses to residual endogenous dopamine, including orofacial dyskinesia. The present data suggest that these hypothetical reserpine-induced qualitative changes in postsynaptic mechanisms would be absent in spontaneously hypertensive rats. Within this context, whereas a modification of the dopamine D_2 receptor supersensitivity hypothesis for tardive dyskinesia suggests that it develops from an imbalance between dopamine D_1 and D_2 receptor-mediated effects in the basal ganglia (see Peacock and Gerlach, 1997), LaHoste and Marshall (1992) have demonstrated that reserpine administration can produce a dopamine receptor supersensitivity that is independent of dopamine D_1 and D_2 receptor density and that is associated with a breakdown in D_1/D_2 synergism. Interestingly, selective agonists of dopamine D_1-like and D_2-like receptors have been reported to produce behavioral effects in spontaneously hypertensive rats that were quantitatively and qualitatively different from those produced in normotensive controls (Linthorst et al., 1992; Van den Buuse et al., 1992). Clearly, however, more extensive experimentation is necessary to characterize dopamine D_1/D_2 receptor synergism in spontaneously hypertensive rats.

Irrespective from the exact mechanism by which abnormal dopaminergic nigrostriatal function avoid reserpine-induced orofacial dyskinesia in spontaneously hypertensive rats, this abnormality could also be related to the development of hypertension. Indeed, chemical or electrolytic lesions of the nigrostriatal dopaminergic system in spontaneously hypertensive rats during the pre-hypertensive stage attenuate the development of hypertension (Van den Buuse et al., 1986; Linthorst et al., 1994). In this regard, although

clinical interpretations from animal models must always be made with caution, it is tempting to speculate if the present findings may be related to the fact that reports of reserpine-induced tardive dyskinesia in hypertensive patients are exceedingly rare in literature. Indeed, since dose is not a strong risk factor for drug-induced tardive dyskinesia (Gardos and Cole, 1997) a much greater incidence of the syndrome in reserpine-treated hypertensive patients should be expected.

Acknowledgements

This research was supported by fellowship from Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP, Proc 1995/9462-7) and from Conselho Nacional de Pesquisa (CNPq, Proc 522975/95-0). The authors would like to thank Mrs. Teotila R.R. Amaral and Mr. Cleomar S. Ferreira for capable technical assistance.

References

Bergamo, M., Abilio, V.C., Queiroz, C.M.T., Barbosa, H.M. Jr., Abdanur, L.R.A., Frussa-Filho, R., 1997. Effects of age on a new animal model of tardive dyskinesia. Neurobiol. Aging 18, 623–629.

Gardos, G., Cole, J.O., 1997. Neuroleptic treatment and tardive dyskinesia. In: Yassa, R., Nair, N.P.V., Jeste, D.V. (Eds.), Neuroleptic-induced Movements Disorders. Cambridge Press, Cambridge, pp. 104–116.

Kane, J.M., 1995. Tardive dyskinesia: epidemiological and clinical presentation. In: Bloom, F.E., Kupfer, D.J. (Eds.), Psychopharmacology: The Fourth Generation of Progress. Raven Press, New York, pp. 1485–1495.

Kirouac, G.J., Ganguly, P.K., 1993. Up-regulation of dopamine receptors in the brain of spontaneously hypertensive rats: an autoradiographic analysis. Neuroscience 52, 135–141.

Kujirai, K., Przendborski, S., Kostic, V., 1990. Autoradiography of dopamine receptors in dopamine uptake sites in the spontaneously hypertensive rats. Brain Res. Bull. 25, 703–709.

LaHoste, G.J., Marshall, J.F., 1992. Dopamine supersensitivity and D_1/D_2 synergism are unrelated to changes in receptor density. Synapse 12, 14–26.

Lim, D.K., Ito, Y., Hoskins, B., Rockhold, R.W., Ho, I.K., 1989. Comparative studies of muscarinic and dopamine receptors in three strains of rat. Eur. J. Pharmacol. 165, 279–287.

Linthorst, A.C.E., Broekhoven, M.H., De Jong, W., Van Wimersma Greidanns, T.B., Versteeg, D.H.G., 1992. Effect of SCH 23390 and quinpirole on novelty-induced grooming behaviour in spontaneously hypertensive rats and Wistar-Kyoto rats. Eur. J. Pharmacol. 219, 23–28.

Linthorst, A.C.E., De Jong, W., De Boer, T., Versteeg, D.H.G., 1993. Dopamine D_1 and D_2 receptors in the nucleus of spontaneously hypertensive rats and normotensive Wistar–Kyoto rats. Brain Res. 602, 119–125.

Linthorst, A.C.E., Giersbergen, P.L.M., Gras, M., Versteeg, D.H.G., 1994. The nigrostriatal dopamine system: role in the development of hypertension in spontaneously hypertensive rats. Brain Res. 639, 261–268.

Nagaoka, A., Lovenberg, W., 1977. Regional changes in the activities of aminergic biosynthetic enzymes in the brains of hypertensive rats. Eur. J. Pharmacol. 43, 297–306.

Neisewander, J.L., Lucki, I., McGonigle, P., 1991a. Neurochemical changes associated with the persistence of spontaneous oral dyskinesia in rats following chronic reserpine treatment. Brain Res. 558, 27–35.

Neisewander, J.L., Lucki, I., McGonigle, P., 1991b. Behavioral and neurochemical effects of chronic administration of reserpine and SKF-38393 in rats. J. Pharmacol. Exp. Ther. 257, 850–860.

Neisewander, J.L., Castañeda, E., Davis, D.A., 1994. Dose-dependent differences in the development of reserpine-induced oral dyskinesia in rats: support for a model of tardive dyskinesia. Psychopharmacology 116, 79–84.

Neisewander, J.L., Castañeda, E., Davis, D.A., Elson, H.J., Sussman, A.N., 1996. Effects of amphetamine and 6-hydroxydopamine lesions on reserpine-induced oral dyskinesia. Eur. J. Pharmacol. 305, 13–21.

Peacock, L., Gerlach, J., 1997. A reanalysis of the dopamine theory of tardive dyskinesia: the hypothesis of dopamine D_1/D_2 imbalance. In: Yassa, R., Nair, N.P.V., Jeste, D.V. (Eds.), Neuroleptic-induced Movements Disorders. Cambridge Press, Cambridge, pp. 141–160.

Uhrbarnt, L., Faurbye, A., 1960. Reversible and irreversible dyskinesia after treatment with perphenazine, chlorpromazine, reserpine and electroconvulsive therapy. Psychopharmacology 1, 408–418.

Van den Buuse, M., Versteeg, D.H.G., Jong, W.D., 1986. Brain dopamine depletion by lesion in substantia nigra attenuates the development of hypertension in the spontaneously hypertensive rats. Brain Res. 368, 69–78.

Van den Buuse, M., Jones, C.R., Wagner, J., 1992. Brain dopamine D_2 receptor mechanisms in spontaneously hypertensive rats. Brain Res. Bull. 28, 289–297.

Vital, M.A.B.F., Frussa-Filho, R., Palermo-Neto, J., 1997. Effects of monosialoganglioside on a new model of tardive dyskinesia. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 21, 1169–1179.

Watanabe, Y., Fujita, M., Ito, Y., Okada, T., Kusuoka, H., Nishimura, T., 1997. Brain dopamine transporter in spontaneously hypertensive rats. J. Nucl. Med. 38, 470–474.

Wolfarth, S., Ossowska, K., 1989. Can supersensitivity of rodents to dopamine be regarded as a model of tardive dyskinesia?. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 13, 789–840.