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Short communication

Acute reserpine administration elicits long-term spontaneous oral dyskinesia

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Abstract

Chronic reserpine administration produces persistent oral dyskinesia accompanied by severe dopamine depletion in the caudate-putamen. The present study examined whether these behavioral and neurochemical effects would persist following acute reserpine administration. Acute administration of reserpine (1 mg/kg, s.c.) produced spontaneous oral dyskinesia that persisted above control levels for at least 84 days. Reserpine also produced a 74% depletion of dopamine in the caudate-putamen relative to vehicle treatment at 3 days post-injection, but did not significantly alter dopamine in the caudate-putamen at 84 days post-injection. The finding that reserpine-induced oral dyskinesia persisted despite repletion of dopamine in the caudate-putamen suggests that the persistent neuropathological change underlying this behavior occurs in a neural pathway other than the dopaminergic nigrostriatal pathway. © 1997 Elsevier Science B.V.

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1. Introduction

Tardive dyskinesia is defined as a motor disorder resulting from chronic neuroleptic treatment that is characterized primarily by involuntary orofacial movements (Baldessarini et al., 1980). Repeated administration of reserpine in rats produces spontaneous oral dyskinesias similar to the symptoms of tardive dyskinesia in humans, including twitching of the facial musculature, jaw movements, and tongue protrusions (Neisewander et al., 1991a,b). 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 (Shonecker, 1957; Uhrbrand and Faurbye, 1960). Based on these parallels, reserpine-induced oral dyskinesia provides an animal model of tardive dyskinesia. Additional evidence to support the validity of this model is that reserpine-induced oral dyskinesia is dose-dependently blocked by the dopamine D_2 receptor antagonist spiroperidol (Neisewander et al., 1991a), consistent with the ability of dopamine receptor antagonists to alleviate the symptoms of tardive dyskinesia in humans (Kazamatsuri et al., 1972; Klawans, 1973). Also, at high doses (1 mg/kg) reserpine-induced oral dyskinesia emerges within 3 days, whereas at low doses (0.05 mg/kg) the dyskinesia is not evident until approximately 6–8 weeks of treatment (Neisewander et al., 1994). The delayed development at low doses is similar to the protracted onset of tardive dyskinesia in humans (Gerlach and Casey, 1988). Lastly, reserpine-induced oral dyskinesia persists for at least 60 days following termination of reserpine administration (Neisewander et al., 1991b), similar to the persistence of tardive dyskinesia in humans (Smith and Baldessarini, 1980).

The persistence of reserpine-induced oral dyskinesia following termination of chronic reserpine administration is accompanied by a persistent dopamine depletion in the caudate-putamen (Neisewander et al., 1991b). However, it is unclear whether these persistent changes require chronic reserpine administration. Therefore, the aim of the present study was to assess reserpine-induced oral dyskinesia and dopamine depletion both early and late following an acute injection of reserpine.

2. Materials and methods

2.1. Animals, drug administration and behavioral testing

Male Sprague–Dawley rats weighing between 350–450 g were housed 2 per cage in a climate-controlled animal

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colony with a 12 h light/dark cycle. They were acclimated to handling for 5–7 days, and were then randomly assigned to treatment groups that received an acute subcutaneous injection of either vehicle (dilute acetic acid) or 1 mg/kg reserpine. In order to minimize dehydration and weight loss, reserpine-treated animals received a 5 ml injection of sucrose (13.6%) subcutaneously for the first two days post-injection. They were also given access to a palatable mixture of ground Purina rat chow moistened with 200 ml of tap water, 100 ml sweetened condensed milk, and 1 package of chocolate flavored instant breakfast mix. Some of the animals were tested 3 days after the injection ($n = 8$ per group). The other animals were tested on days 21, 56, and 84 after the injection ($n = 12$ for vehicle; $n = 18$ for reserpine). On each test day, animals were placed into a clear Plexiglas cage ($44 \times 24 \times 20$ cm high) that had a metal bar floor and a perforated metal lid. The incidence of tongue protrusions was recorded continuously during a 30 min observation period. Tongue protrusions were operationally defined as a visible extension of the tongue outside of the mouth and not directed at anything. Individual tongue protrusions during a bout of oral dyskinesia were each preceded by visible retraction of the tongue. A mirror was placed behind the back wall of the cage to enable observation of tongue protrusions when the animal was faced away from the observer.

2.2. Monoamine assay

All animals were decapitated within 2 h after behavioral testing was completed on either day 3 or 84 post-injection. The brains were rapidly removed and immersed in isopentane at -20°C for 2 min to promote uniform freezing, and then stored at -70°C. The brains were later thawed, cut coronally at the caudal border of the olfactory tubercle, and the caudate-putamen was dissected from the anterior portion. Levels of dopamine and dopamine metabolites, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), were assayed using high performance liquid chromatography with electrochemical detection (HPLC-EC) as described previously (Neisewander et al., 1994).

2.3. Data analysis

Tongue protrusion data were analyzed using an unpaired t test for animals tested on day 3 post-injection, and using analysis of variance (ANOVA) with drug group as a between subjects factor and test day as a repeated measures factor for animals tested on days 21, 56, and 84 post-injection. Levels of dopamine, dopamine metabolites, and the ratios of metabolite to dopamine were analyzed using two-way factorial ANOVAs with drug group and test day as between subjects factors. Newman–Keuls tests were performed for pairwise comparisons.

3. Results

3.1. Reserpine-induced changes in behavior

The mean number of tongue protrusions across days post-injection is shown in Fig. 1. In animals tested 3 days post-injection, reserpine produced a significant increase in the number of tongue protrusions relative to vehicle ($t(14) = -2.459$, $P < 0.05$). Similarly, in animals tested repeatedly, the overall ANOVA indicated a main effect of drug group ($F(1,28) = 17.5$, $P < 0.001$), but no main effect of test day or group by test day interaction. These findings indicate that reserpine-treated animals demonstrated a significant increase in the number of tongue protrusions relative to vehicle-treated animals regardless of test day.

3.2. Dopamine and dopamine metabolite levels

Table 1 illustrates the mean level of striatal dopamine, dopamine metabolites, and metabolite to dopamine ratios in animals treated with an acute injection of reserpine. The ANOVAs revealed a main effect of drug group for each measure ($P < 0.01$). Additionally, a main effect of test day and a drug group by test day interaction was obtained for dopamine and metabolite to dopamine ratios ($P < 0.0001$). Subsequent pairwise comparisons indicated that an acute injection of reserpine produced a significant decrease in dopamine levels (74%) and a significant increase in metabolite to dopamine ratios (DOPAC/dopamine 154% and HVA/dopamine 131%) relative to vehicle in animals examined 3 days post-injection (Newman–Keuls test, $P < 0.01$). In contrast, reserpine did not alter dopamine or metabolite to dopamine ratios relative to vehicle in animals examined 84 days post-injection. Furthermore, there was a significant decrease in dopamine and a significant increase

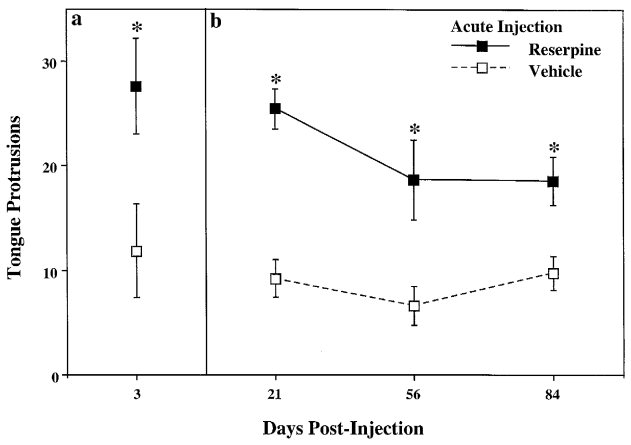

Fig. 1. Incidence of tongue protrusions ($\pm$S.E.M.) during the 30 min test periods following various post- injection intervals. Asterisks (*) represent a significant difference from vehicle-treated animals, t-test, $P < 0.05$ (a) or ANOVA main effect of reserpine, $P < 0.001$ (b).

Table 1
Levels of dopamine, dopamine metabolites (ng/mg tissue ± S.E.M.) and metabolite to dopamine ratios from striata of rats that received an acute injection of either vehicle or reserpine (1 mg/kg, s.c.)

	Acute injection, 3 days post-injection		% Change	Acute injection, 84 days post-injection		% Change
	Vehicle ($n = 8$)	Reserpine ($n = 8$)		Vehicle ($n = 10$)	Reserpine ($n = 18$)	
Dopamine	11.35 ± 0.89	2.97 ± 0.17 [b]	74	13.96 ± 1.26	12.20 ± 0.78	13
DOPAC	2.91 ± 0.31	1.97 ± 0.21 [a]	32	2.67 ± 0.17	2.47 ± 0.17 [a]	7
HVA	1.42 ± 0.14	0.88 ± 0.08 [a]	38	1.45 ± 0.12	1.10 ± 0.08 [a]	24
DOPAC/Dopamine	0.26 ± 0.31	0.66 ± 0.06 [b]	154	0.21 ± 0.03	0.21 ± 0.02	0
HVA/Dopamine	0.13 ± 0.02	0.03 ± 0.02 [b]	131	0.12 ± 0.02	0.10 ± 0.01	17

[a] Represents a significant difference from vehicle-treated groups, $P < 0.01$, ANOVA main effect.
[b] Represents a significant difference from all groups, $P < 0.01$, Newman–Keuls test.

in metabolite to dopamine ratios in reserpine-treated animals examined 3 days post-injection relative to those tested 84 days post-injection, (Newman–Keuls test, $P < 0.01$), whereas there were no differences between vehicle-treated groups.

4. Discussion

An acute reserpine administration produced oral dyskinesia by day 3 post-injection that persisted above control levels for at least 84 days post-injection. Consistent with our previous findings, the magnitude of the oral dyskinesia did not differ across test days. These findings suggest that the oral dyskinesia is not an acute reserpine-elicited effect, but is instead a spontaneous oral dyskinesia that develops as a result of reserpine administration, similar to tardive dyskinesia which develops as a result of neuroleptic administration. Acute reserpine administration also produced a significant dopamine depletion and an increase in metabolite to dopamine ratios in the caudate-putamen in animals examined 3 days post-injection. However, dopamine levels and ratios of metabolite to dopamine returned to control levels by 84 days post-injection.

Previous research indicates that dopamine is involved in reserpine-induced oral dyskinesia. For example, reserpine-induced oral dyskinesia is reversed by administration of the dopamine D_2 receptor antagonist spiroperidol (Neisewander et al., 1991a). Additionally, reserpine-induced oral dyskinesia is exacerbated by a challenge injection of amphetamine and attenuated by nigrostriatal 6-hydroxydopamine lesions (Neisewander et al., 1996). These findings indicate that reserpine-induced oral dyskinesia is mediated, at least in part, by residual endogenous dopamine. Furthermore, reserpine-induced oral dyskinesia, dopamine depletion, and up-regulation of dopamine D_2 receptors in the caudate-putamen persist for 60 days following termination of chronic reserpine administration, suggesting that supersensitivity of dopamine receptors in the caudate-putamen may be involved in the dyskinesia. In contrast, the present finding that dopamine in the caudate-putamen returns to control levels 84 days post-injection suggests a return to homeostasis in the nigrostriatal dopaminergic pathway. Collectively, these findings suggest that dopamine may initiate reserpine-induced oral dyskinesia, but the persistent neuropathology may occur in a system efferent to the nigrostriatal dopamine pathway.

There are several hypotheses suggesting that tardive dyskinesia involves altered functioning in systems efferent to the nigrostriatal dopaminergic system. For example, Gunne et al. (1984) reported a reduction in γ-aminobutyric acid (GABA) levels and a decrease in glutamic acid decarboxylase activity in the internal segment of the globus pallidus, subthalamic nucleus, and the substantia nigra reticulata in monkeys who exhibited oral dyskinesia from chronic neuroleptic treatment. In addition, Gunne and Andrén (1993) found reduced synaptic activity in the globus pallidus and the ventral-anterior and ventral-lateral thalamus in monkeys 4 months after neuroleptic drug withdrawal. The reduced synaptic activity is hypothesized to reflect excitoxic lesions within the ventral-anterior/ventral-lateral thalamic afferents possibly due to the chronic upregulation of glutamatergic neurotransmission. Thus, it is possible that reserpine-induced oral dyskinesia may be initiated by altered striatal dopaminergic function, but the persistent neuropathological change involves GABAergic outputs efferent to striatal dopamine. Additional insight into the mechanism of reserpine-induced oral dyskinesia may be gained by examining whether GABAergic and glutamatergic systems are altered in a manner consistent with the changes produced by long-term neuroleptic administration. In light of the similarities between reserpine- and neuroleptic-induced oral dyskinesia, we propose that these drugs may produce similar neuropathological changes but at different rates due to differences in their pharmacologic action. If reserpine- and neuroleptic-induced dyskinesias involve similar mechanisms, then the rapid development of reserpine-induced oral dyskinesia elicited by acute administration of reserpine offers a tremendous advantage over long-term neuroleptic administration, and may expedite research investigating the etiology and prevention of tardive dyskinesia.

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