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Suppression of oro-facial movements by rolipram, a cAMP phosphodiesterase inhibitor, in rats chronically treated with haloperidol

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Abstract

We investigated the effects of rolipram, a selective cyclic adenosine 3′,5′-monophosphate phosphodiesterase type IV inhibitor, and isobutylmethylxanthine, a nonselective phosphodiesterase inhibitor, on purposeless spontaneous chewing movements and tongue protrusions produced by 24 weeks treatment with haloperidol decanoate (25 mg/kg every 4 weeks i.m.) in rats, to examine our hypothesis that restoration of striatal cyclic adenosine 3′,5′-monophosphate levels previously reduced due to dopamine D_2 receptor supersensitivity, may suppress these movements. Tests were performed 8 weeks after the final injection. Haloperidol treatment significantly increased dyskinetic movements and striatal dopamine D_2 receptor density compared with controls. Rolipram (0.1–1.0 mg/kg i.p.) suppressed these movements in a dose-dependent manner, whereas isobutylmethylxanthine (2 mg/kg i.p.) only slightly suppressed the syndrome and doses higher than 5 mg/kg i.p. produced other intensive movements. These results support our hypothesis and suggest that rolipram may have a therapeutic effect on tardive dyskinesia.

Keywords: Tardive dyskinesia, rat; cAMP; Phosphodiesterase; Rolipram; Ageing

1. Introduction

Neuroleptics such as haloperidol have been used in the treatment of mental disorders such as schizophrenia for about four decades. While their anti-psychotic effects have been widely accepted, prolonged administration has the potential to cause tardive dyskinesia characterized by late-onset persistent movements, mainly involving the peri-oral region. A significant number (10–30%) of neuroleptic-treated schizophrenic patients suffer from this disorder (Baldessarini et al., 1980). However, no reliable therapy has yet been established despite extensive research (Inada et al., 1991). The currently recommended treatment is either a gradual reduction in dosage of neuroleptics or a change to neuroleptics with relatively weak antidopaminergic effects (Jeste and Caligiuri, 1993).

Long-term treatment with neuroleptics in rats induces purposeless spontaneous oro-facial movements which persist for a long time following withdrawal (Waddington et al., 1983). As the characteristics of these movements and the time-course of their appearance resemble those observed in human tardive dyskinesia, this syndrome has been used as a model of tardive dyskinesia in rats, though there is still some debate about its suitability (see Waddington, 1990).

Neuroleptics have proved to be the most effective suppressors of tardive dyskinesia symptoms up to now, but this suppression may be temporary and they are not recommended for treatment (Jeste and Caligiuri, 1993). It is well known that most neuroleptics act on dopamine D_2 receptors (Seeman, 1980). A recent positron emission tomography study has suggested a positive correlation between the severity of tardive dyskinesia and the density of striatal dopamine D_2 receptors (Blin et al., 1989). In rats, long-term administration of neuroleptics increases the number of dopamine D_2, but not D_1, receptors in the striata (Johansson et al., 1987; Rupniak et al., 1984, 1985;

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Ellison and See, 1989; Prosser et al., 1989; See et al., 1989). These suggest that hyperactivity of dopamine D_2 receptors in the striatum may be involved in the etiology of tardive dyskinesia (Neisewander et al., 1991).

Stimulation of dopamine D_1 receptors increases cyclic adenosine 3′,5′-monophosphate (cAMP) levels through the activation of adenylate cyclase, whereas stimulation of dopamine D_2 receptors decreases cAMP levels by inhibiting this enzyme (Kebabian and Calne, 1979; Seeman, 1980). Therefore, we hypothesized that hyperactivity of striatal dopamine D_2 receptors due to long-term treatment with neuroleptics may decrease cAMP levels in the striatum and induce involuntary oro-facial movements, and that a restoration of cAMP levels by exogenous manipulation may reduce these movements. In order to explore this hypothesis, we preliminarily demonstrated that rolipram (Wachtel, 1982), which selectively inhibits cAMP phosphodiesterase type IV (Lowe and Cheng, 1992) and increases cAMP levels in the brain, suppressed involuntary oro-facial movements in rats after daily administration of haloperidol for 21 days (Sasaki et al., 1995). In the present study, we examined the effects of rolipram and isobutylmethylxanthine, a nonselective phosphodiesterase inhibitor, on these movements in rats treated with haloperidol decanoate for a much longer period of 6 months. Furthermore, we measured the number of striatal dopamine D_1 and D_2 receptors in the rats, to confirm D_2 receptor supersensitivity in this tardive dyskinesia model.

2. Materials and methods

2.1. Subjects and drugs

Forty-five male, Sprague-Dawley rats, weighing 230–250 g, were housed in groups of three in cages and maintained under standard laboratory conditions of lighting (12-h light/dark cycle: 7:00 a.m., 7:00 p.m.), temperature (23 ± 0.5°C) and humidity (55 ± 5%) with free access to food and water. Haloperidol decanoate (25 mg/kg), or the equivalent volume of sesame oil (0.1 ml per 100 g body weight) was injected into each rat's thigh muscle once every 4 weeks for 24 weeks. Rolipram (a gift from Meiji Seika Kaisha, Tokyo, Japan) and isobutylmethylxanthine were suspended in physiological sodium chloride solution containing 10% w/v Cremophor^{ELR} (polyethoxylated castor oil) before injection. [^{3}H]SCH23390 (7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride; 80.4 Ci/mmol) and [^{3}H]spiperone (17.5 Ci/mmol) were purchased from New England Nuclear, Boston, MA, USA. Other chemicals were purchased commercially.

2.2. Behavioral assessments

Behavioral assessments (Sasaki et al., 1995) were carried out 16 and 24 weeks after the first injection and 8 weeks after the final injection by a well-trained observer (H.S.), who was unaware of the treatment administered. All behavioral tests were conducted during the light phase. Individual rats were placed into transparent Plexiglas cages (25 × 15 × 12 cm). Following a 30 min habituation period, purposeless spontaneous oro-facial movements, which consisted of chewing movements and tongue protrusions, were counted over 15 min. These movements were recorded only if they appeared to be purposeless, that is, if they did not occur in the context of goal-directed activity, such as licking or biting of objects, or grooming. To test the effects of the phosphodiesterase inhibitors, the rats received intraperitoneal (i.p.) injections of either rolipram (0.1, 0.5 or 1.0 mg/kg), isobutylmethylxanthine (2.0 mg/kg) or the appropriate vehicle. Following a 15 min acclimatization period, these movements were again assessed over 15 min.

2.3. Radioligand binding assays

The rats which had been challenged with 1.0 mg/kg rolipram were decapitated the day after the behavioral assessment. Their striata were removed on ice. The radiobinding assay was performed following the method of Hatta et al. (1993) with slight modification. Each

Table 1
The effects of chronic haloperidol treatment on oro-facial movements

Time after the initial haloperidol injection	Chewing movements		Tongue protrusions	
	Vehicle [a]	Haloperidol	Vehicle	Haloperidol
16 weeks	28 ± 6	212 ± 26 [b]	3.0 ± 0.9	18.5 ± 2.6 [b]
24 weeks	101 ± 17	257 ± 25 [b]	3.6 ± 0.9	25.3 ± 3.3 [b]
32 weeks	94 ± 17	230 ± 28 [b]	4.7 ± 1.7	19.7 ± 4.6 [b]

Haloperidol treatment significantly increased both types of movement at each time point compared with vehicle treatment. In the vehicle-treated rats, chewing movements at 24 and 32 weeks were significantly increased compared with those at 16 weeks. The values indicate mean ± S.E.M. counts/15 min. [a] $P < 0.001$ by Kruskal-Wallis test within the group. [b] $P < 0.001$ by Mann-Whitney *U*-test compared with vehicle. $n = 12$ in each group.

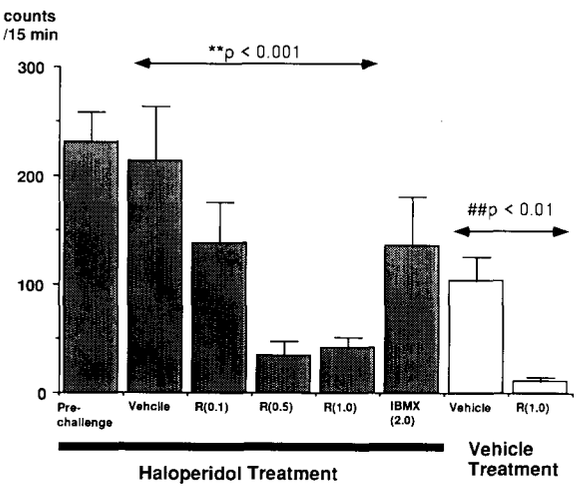

Fig. 1. The effects of the two phosphodiesterase inhibitors on chewing movements in rats. The test was performed after an 8-week withdrawal period following the final haloperidol decanoate (closed columns) or vehicle injection (open columns). Observations were carried out over 15 min following a 15 min habituation period after the challenge. Rolipram (0.1–1.0 mg/mg/kg i.p.) significantly suppressed these movements in both the haloperidol-treated and vehicle-treated rats. Isobutylmethylxanthine (2.0 mg/kg i.p.) slightly suppressed these movements but the effect was not significant. Error bars indicate S.E.M. R(x) and IBMX(x) indicate x mg/kg rolipram and x mg/kg isobutylmethylxanthine respectively. $^{**}P < 0.001$ by Kruskal-Wallis test. $^{\#\#}P < 0.01$ by Mann-Whitney U-test. $n = 12$ in the pretreatment group and $n = 6$ in each group.

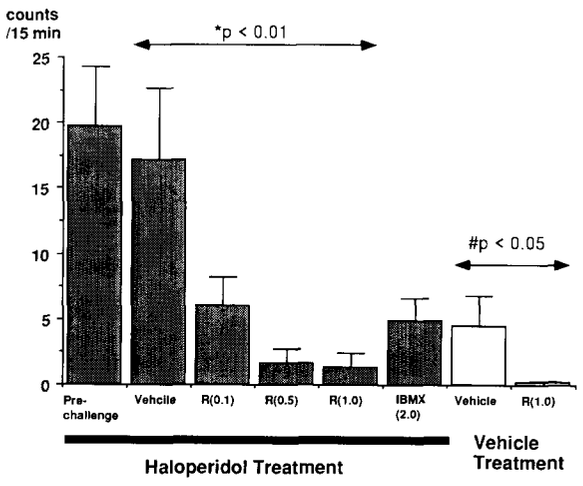

Fig. 2. The effects of the two phosphodiesterase inhibitors on tongue protrusions in rats. The test was performed after an 8-week withdrawal period following the final haloperidol decanoate (closed columns) or vehicle injections (open columns). Observations were carried out over 15 min following a 15 min habituation period after the challenge. Rolipram (0.1–1.0 mg/kg i.p.) significantly suppressed these movements in both the haloperidol-treated and the vehicle-treated rats. Isobutylmethylxanthine (2.0 mg/kg i.p.) slightly suppressed these movements but the effect was not significant. Error bars indicate S.E.M. R(x) and IBMX(x) indicate x mg/kg rolipram and x mg/kg isobutylmethylxanthine respectively. $^{*}P < 0.01$ by Kruskal-Wallis test. $^{\#}P < 0.05$ by Mann-Whitney U-test. $n = 12$ in the pretreatment group and $n = 6$ in each group.

striatum was homogenized in 50 volumes of 50 mM Tris-HCl buffer (pH 7.4) at 37°C and the homogenates were centrifuged (48 000 × g, 20 min, at 4°C). The homogenization and centrifugation procedures were repeated 3 times using fresh buffer. The final pellet was resuspended in the same buffer. Aliquots of membrane suspension were incubated with six different concentrations of [^{3}H]SCH23390 (0.01–2.0 nM) for dopamine D_1 receptor studies or [^{3}H]spiperone (0.01–2.0 nM) for dopamine D_2 receptor studies at 37°C for 15 min. Nonspecific binding of [^{3}H]SCH23390 or [^{3}H]spiperone was determined by the addition of 10 μM SCH23390 or 100 μM (−)-sulpiride, respectively. After incubation, the homogenates were filtered rapidly through Whatman GF/B filters pretreated with 0.5% polyethyleneimine using a 24-channel cell harvester (Brandel, Gaithersburg, MD, USA). The filters were washed 3 times with 5 ml ice-cold 50 mM Tris-HCl buffer. Radioactivity trapped by the filters was determined by a liquid scintillation counter (Aloka, LSC-1000). All determinations were carried out in duplicate. Protein concentrations were measured by Bradford's method (Bradford, 1976). B_{max} and K_d values for D_1 and D_2 receptors in each rat were calculated by Scatchard analysis.

2.4. Statistical analysis

The data from the behavioral assessments were analyzed using the Kruskal-Wallis test or Mann-Whitney

Table 2
The results of radiobinding assays for striatal dopamine D_1 receptors ([^{3}H]SCH23390) and D_2 receptors ([^{3}H]spiperone) in the rats after an 8-week withdrawal period following haloperidol decanoate treatment for 24 weeks

	[^{3}H]SCH23390 binding in D_1 receptors		[^{3}H]Spiperone binding in D_2 receptors	
	B_{max} (fmol/mg protein)	K_d (nM)	B_{max} (fmol/mg protein)	K_d (nM)
Vehicle	2994 ± 372	0.59 ± 0.10	937 ± 41	0.064 ± 0.012
Haloperidol	3185 ± 495	0.61 ± 0.07	1669 ± 192 [a]	0.075 ± 0.008

The striatal B_{max} for [^{3}H]spiperone significantly increased in the haloperidol-treated rats. The values indicate mean ± S.D. [a] $P < 0.0001$ by Student's t-test compared with vehicle. $n = 6$ in each group.

U-test. B_{max} and K_d values were analyzed using the two-tailed Student's t-test for unpaired data.

3. Results

The results of the assessment of oro-facial movements from the day before the 5th and 7th injections, i.e., 16 and 24 weeks after the initial haloperidol-decanoate injection, and 8 weeks after the final injection (32 weeks after the initial injection) are shown in Table 1. A significantly higher frequency of both chewing movements and tongue protrusions was observed in the haloperidol-treated rats than in the control at each time point ($P < 0.001$). In the haloperidol-treated group, increased chewing movements and tongue protrusions were observed during treatment, i.e., 16 and 24 weeks after the initial injection. This increase was still apparent even 8 weeks after the final injection. In the control group, the duration of treatment did not affect the number of tongue protrusions, but a significant increase in chewing movements was observed at 24 and 32 weeks compared with week 16 ($P < 0.001$).

Fig. 1 shows the effects of the two phosphodiesterase inhibitors on chewing movements. Rolipram dose-dependently suppressed these movements in the rats treated with haloperidol ($P < 0.001$), whereas the vehicle did not alter their frequency. Fig. 2 shows the effects of the two phosphodiesterase inhibitors on tongue protrusions. Rolipram also dose-dependently suppressed these movements ($P < 0.01$), while the vehicle did not. Doses higher than 0.5 mg/kg rolipram suppressed the frequencies of chewing movements and tongue protrusions to less than 20% and 10%, respectively. In the control rats, rolipram (1.0 mg/kg) almost completely suppressed both chewing movements ($P < 0.01$; Fig. 1) and tongue protrusions ($P < 0.05$; Fig. 2). Although rolipram tended to sedate the rats slightly at 1.0 mg/kg, but not at 0.1 nor 0.5 mg/kg, no other prominent behavioral changes were observed following rolipram injections.

As a preliminary study, we observed isobutylmethylxanthine (2, 5 and 10 mg/kg i.p.)-induced behavior in rats ($n = 1$ or 2 at each dose; data not shown). 5 and 10 mg/kg of isobutylmethylxanthine induced intensive face scratching, jumping and locomotion, which made it impossible to assess the oro-facial movements. Therefore, we tested 2.0 mg/kg isobutylmethylxanthine in the haloperidol-treated rats ($n = 6$) in this study. Although isobutylmethylxanthine seemed to suppress the involuntary movements, there was no significant difference in chewing movements ($0.35 > P > 0.1$; Fig. 1) or tongue protrusions ($0.06 > P > 0.05$; Fig. 2) compared with the vehicle-treated groups.

The results of the receptor binding assays are shown in Table 2. For dopamine D_2 receptors, there was a significant increase in B_{max} without any change in K_d in the haloperidol-treated rats compared with controls ($P < 0.0001$), whereas there were no significant differences in B_{max} and K_d for dopamine D_1 receptors between the two groups.

4. Discussion

Various modes of assessment and quantification of oro-facial movements in rats have been used as models of tardive dyskinesia. However, there is still some debate regarding their suitability (Ellison and See, 1989; Waddington, 1990). In the present study, we counted the frequency of purposeless, spontaneous chewing movements and tongue protrusions, which were strictly distinguished from movements in the context of goal-directed activity, such as licking or biting of objects, or grooming, as indicators of abnormal oro-facial movements (Waddington, 1990; Rupniak et al., 1985). We found that administration of haloperidol for 24 weeks produced significant increases in these movements compared with vehicle administration. These results agree with those of previous studies (Waddington, 1990; See et al., 1988; Glassman and Glassman, 1980). The movements observed in this study were identical to those in our previous study in which rats were treated with haloperidol (1.5 mg/kg i.p. once a day) for 21 days (Sasaki et al., 1995), but the frequency was higher by about 95% for chewing movements and about 31% for tongue protrusions than previously observed. Furthermore, the increases in the present study appeared 16 weeks after the initial administration of haloperidol and persisted even 8 weeks after the final injection, though appreciable levels of the drug might remain after even this drug-free period due to the use of the decanoate preparation. Therefore, we consider that these movements form a reasonable model of tardive dyskinesia not only because of the phenomenology but also from the point of view of the time course of their emergence and persistence.

We evaluated B_{max} and K_d values for striatal dopamine D_1 and D_2 receptors 8 weeks after the final administration of haloperidol decanoate. The B_{max} of striatal D_2 receptors increased without any alteration in K_d following chronic haloperidol treatment, whereas there was no significant alteration of the B_{max} or K_d of striatal D_1 receptors. This agrees with the results of previous studies (See et al., 1989,1990; Prosser et al., 1989; Rupniak et al., 1985; Severson et al., 1984). These results suggest that dopamine D_2 receptor hypersensitivity is responsible for tardive dyskinetic movements (Laruelle et al., 1992; Seeman, 1988; Neisewander et al., 1991). However, some researchers have suggested that dopamine D_1 receptors might be involved in the etiology of tardive dyskinesia (Spooren et

al., 1991; Diana et al., 1992; Ellison et al., 1988), because administration of D_1 receptor agonists causes spontaneous oro-facial movements while D_1 receptor antagonists alleviate these movements. It cannot be concluded that dopamine D_2 supersensitivity is solely responsible for these movements from the present study.

Stimulation of dopamine D_2 receptors has been reported to inhibit adenylate cyclase activity (Kebabian and Calne, 1979). If striatal D_2 receptor supersensitivity is responsible for the development of oro-facial movements, and decreases intracellular cAMP levels via suppression of adenylate cyclase, restoration of the striatal cAMP level may suppress these movements. In fact, it has been reported that chronic treatment with haloperidol suppresses the activation of cAMP by dopamine in the rat striatum (Rupniak et al., 1984), and that ceruletide, which is thought to relieve the abnormal oro-facial movements in rats, restores the lowered cAMP level through modification of dopamine receptors (Hatta et al., 1993). In man, postmortem studies have indicated that chronic administration of neuroleptics increases the number of striatal dopamine D_2 receptors (Machay et al., 1982). The results of a positron emission tomography study suggested that the severity of tardive dyskinesia depends on the density of striatal dopamine D_2 receptors (Blin et al., 1989). Furthermore, cAMP levels in cerebrospinal fluid in patients with tardive dyskinesia have been reported to be significantly lowered compared with those in schizophrenics without tardive dyskinesia (Bowers et al., 1979).

Rolipram is a selective cAMP phosphodiesterase type IV inhibitor (Lowe and Cheng, 1992). It permeates the brain well (Schmiechen et al., 1990) and increases striatal cAMP levels by 50 and 70% at 0.3 and 3.0 mg/kg i.p., respectively (Schneider, 1984) by inhibiting cAMP metabolism (Wachtel, 1982) without directly stimulating neurotransmitter receptors (Schneider, 1984), or altering dopamine release and metabolism rates (Kehr et al., 1985). Therefore, we predicted that a cAMP phosphodiesterase inhibitor would suppress tardive dyskinetic movements. As we had already found that 1.0 mg/kg rolipram almost totally suppressed oro-facial movements in rats treated with haloperidol daily for 21 days (Sasaki et al., 1995), we tested doses of 0.1–1.0 mg/kg rolipram in this tardive dyskinesia model in rats and observed dose-dependent suppression of the abnormal movements. Although it has been reported that large doses of rolipram induce motor depressant effects (Wachtel, 1982), in the present study there was no prominent behavioral change other than suppression of the oro-facial movements, which agrees with the results of our previous studies (Iyo et al., 1995; Sasaki et al., 1995). We tested a nonspecific phosphodiesterase inhibitor, isobutylmethylxanthine. The dose of this drug, i.e., 2.0–10 mg/kg i.p., was selected according to a report that the inhibitory potency of isobutylmethylxanthine on the in vivo binding of [^{3}H]rolipram in rat brain is 30 times lower than that of rolipram (Schmiechen et al., 1990). 5–10 mg/kg isobutylmethylxanthine induced intensive face scratching and jumping, making it impossible to assess oro-facial movements. Although 2 mg/kg isobutylmethylxanthine did not lead to such behavior, it produced only slight suppression of the oro-facial movements which was almost equivalent to that produced by 0.1 mg/kg rolipram (see Fig. 1 and Fig. 2). Isobutylmethylxanthine increases cAMP levels in the brain (Schneider and Prozesky, 1979), but does not selectively act on phosphodiesterase IV and has a much lower inhibitory potency for the enzyme. Consequently, this drug may produce only slight suppression of oro-facial movements while causing other prominent behavioral changes. These results suggest that restoration of cAMP levels by inhibition of brain cAMP metabolism suppresses dyskinetic movements, although we did not measure cAMP levels in the brain. However, as we have reported that rolipram has anti-methamphetamine effects (Iyo et al., 1995) and it has been shown to have antidepressant properties in humans (Bobon et al., 1988), it may prove useful for tardive dyskinesia in schizophrenic patients.

In the control rats, oro-facial movements also developed during vehicle treatment, but the frequency was less than one-half of that in the haloperidol-treated rats. It has been reported that aging increases abnormal oro-facial movements (Johansson et al., 1987; Waddington et al., 1983; Kane et al., 1992) and our results may reflect this process. It is unclear whether the mechanisms underlying neuroleptic-induced tardive dyskinesia and age-related abnormal oro-facial movements are the same. However, rolipram suppressed these movements in the control rats as well as in the haloperidol-treated rats. This may indicate that oro-facial movements in senile rats are caused by a similar mechanism to those observed in haloperidol-treated rats.

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