

5-HT_{1A} and 5-HT_{1B} receptors in the ventrolateral striatum differentially modulate apomorphine-induced jaw movements in rats

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Abstract: The ability of serotonin 5-HT_{1A} and 5-HT_{1B} receptors in the ventrolateral striatum to modulate dopamine receptor-mediated jaw movements was investigated in freely moving rats, using a magnet-sensing system combined with an intracerebral drug microinjection technique. Apomorphine (1 mg/kg i.v.) has been found to elicit repetitive jaw movements. Bilateral injections of the 5-HT_{1A} receptor agonist 8-OH-DPAT (1 and 4 µg/0.2 µl in each side) into the ventrolateral striatum partially but significantly reduced apomorphine-induced repetitive jaw movements. The 5-HT_{1A} receptor antagonist WAY-100635 (1 µg), which alone did not affect the effects of apomorphine, antagonized the inhibitory effects of 8-OH-DPAT (4 µg). Bilateral injections of the 5-HT_{1B} receptor agonist CP93129 (1 and 10 µg) also reduced apomorphine-induced repetitive jaw movements in a dose-dependent manner. However, the 5-HT_{1B} receptor antagonist GR55562 (1 and 10 µg) did not antagonize the inhibitory effects of CP93129 (10 µg). These results suggest that 5-HT_{1A}, but not 5-HT_{1B}, receptors in the ventrolateral striatum play a modulatory role in the production of dopamine receptor-mediated jaw movements. (J. Oral Sci. 50, 387-395, 2008)

Keywords: 5-HT_{1A} receptor; 5-HT_{1B} receptor; apomorphine; repetitive jaw movements; ventrolateral striatum; rat.

Introduction

There is a considerable body of evidence for the important role of the basal ganglia in the regulation of orofacial movements (1-4). Particular attention is focused on the role of the dopamine D₁-like receptor family and its functional interactions with dopamine D₂-like counterparts (2,5-9). Bilateral stimulation of dopamine D₁ and D₂ receptors, particularly in the ventrolateral portion of the striatum, readily elicits repetitive jaw movements in rats (2,4,10,11).

Although dopamine clearly plays a role in orofacial movements, it is important to consider the possible role of other neurotransmitters in this region. For example, there are dense serotonergic projections arising from the midbrain raphe nuclei, especially the dorsal nucleus (12-14), which particularly innervate the ventrolateral striatum (13). Several anatomical studies have reported that both 5-hydroxytryptamine (5-HT)_{1A} and 5-HT_{1B} receptors are present in the striatum (15-17). Regarding the functional effects of these serotonergic receptors on the activity of dopaminergic neurons, Ichikawa et al. (18) reported that 5-HT_{1A} receptor stimulation inhibits basal DA release in the striatum using *in vivo* microdialysis. A similar reduction due to 5-HT_{1A} receptor stimulation was also seen in 6-hydroxydopamine-lesioned rats, in which the 5-HT_{1A}

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receptor agonist 8-OH-DPAT decreases release of dopamine formed from exogenous levodopa (19-21). This finding is also supported by clinical findings that stimulation of 5-HT_{1A} receptors in levodopa-treated patients with Parkinson's disease can modulate striatal dopaminergic function and reduce levodopa-induced dyskinesias (22).

In contrast to the role of 5-HT_{1A} receptors on dopaminergic activity, studies describing the role of 5-HT_{1B} receptors on dopaminergic activity are rather inconsistent. For instance, K⁺-evoked overflow of dopamine is inhibited by CP93129, a 5-HT_{1B} agonist, in a concentration-dependent manner in rat striatal synaptosomes loaded with dopamine (23), whereas an opposite effect has been reported in microdialysis studies in that CP93129 increases striatal dopamine release (24).

In the present study, we have therefore hypothesized first that repetitive jaw movements induced by dopamine D₁ and D₂ receptor stimulation can be under inhibitory control of 5-HT_{1A} receptors in the ventrolateral striatum. Secondly, we have hypothesized that 5-HT_{1B} receptors in the ventrolateral striatum may have some modulatory role in dopamine receptor-mediated jaw movements. For examining these hypotheses, the ability of 5-HT_{1A} and 5-HT_{1B} receptors in the ventrolateral striatum to affect dopamine receptor-mediated jaw movements was investigated in freely moving rats using a magnet-sensing system combined with an intracerebral drug microinjection technique (25-27). To stimulate both dopamine D₁ and D₂ receptors simultaneously, the non-selective dopamine receptor agonist apomorphine was chosen at a dose (1 mg/kg) known to readily produce repetitive jaw movements in rats when administered intravenously (25,26).

Materials and Methods

Animals

Male Sprague-Dawley rats (NRC Haruna, Gunma, Japan) weighing 180-190 g were housed in cages (27 × 45 × 20 cm). The animals were kept in a temperature (23 ± 2°C) and humidity (55 ± 5%) controlled environment under a 12 h light/dark cycle (lights on at 07.00 h; off at 19.00 h), with free access to food and water.

Surgical procedures

The surgical and recording procedures were as described previously (25-27). Briefly, rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and a neodymium magnet (5.0 mm diameter, 2.0 mm thick, 350mT; N-39SH, Niroku Seisakusyo, Shiga, Japan) was fixed to the mandible with dental acrylic cement. Bipolar electrodes were placed into the masseter and digastric muscles to record electromyographic (EMG) activity. Then the rats were

placed in a stereotaxic frame to fix a Hall-effect transducer (NW-300B, Asahikasei Electronics, Tokyo, Japan) to the skull with stainless screws and dental acrylic cement. Guide cannulae (0.5mm o.d., 0.3mm i.d., 6.0 mm length), with wire stylets inserted to prevent occlusion, were also implanted bilaterally into the brain as described previously (2). The coordinates according to the atlas of Paxinos and Watson (28) for the ventrolateral striatum were: anterior: 8.6mm from interaural line; vertical: 3.0 mm from interaural line; and lateral: 4.0 mm from midline. Damage to the target site was minimized by implanting the tips of the guide cannulae 1.5 mm above the desired injection sites. Rats were allowed to recover from the operation for one week. On the day of behavioral observation, the rats were placed individually in a rectangular activity box (40 × 40 × 40 cm) with Perspex sides and wire-mesh floor at least 30 min before commencing assessment.

Jaw movement analysis

Vertical (opening and closing) jaw movement trajectory and EMG activity were recorded on an eight-channel tape recorder (RD-180T; TEAC, Tokyo, Japan) for automatic off-line analysis with a spike trigger that counted vertical jaw movements per 5 min. After administering apomorphine (1 mg/kg i.v.) rats not only elicit vertical jaw movements of the typical dopaminergic movement pattern reported previously (25) (see also Fig. 1) but also elicit several other types of orofacial behaviors that are associated with vertical component of jaw movements. Such behaviors, e.g. sniffing, grooming, vacuous chewing and yawning, were easily detected by their characteristic patterns of jaw movements and EMG activities of masseter and digastric muscles (Fig. 1) and were carefully removed by trained observers from the above-mentioned automatically-counted number of vertical jaw movements. In other words, we counted only vertical jaw movements that occur during stereotyped licking and gnawing directed onto the wire-mesh floor.

The experiments were approved by the Animal Experimentation Committee of Nihon University School of Dentistry and were performed in accordance with institutional guidelines for the care and use of experimental animals, based on the UK Animals Scientific Procedures Act 1986. All efforts were made to minimize animal suffering and to reduce the number of animals used.

Drugs

The animals (n = 6-9 per experiment) received intravenous injections of the non-selective dopamine receptor agonist *R*(-)-apomorphine hydrochloride (apomorphine; Sigma, St. Louis, MO, USA) and

intraatrial injection of the selective 5-HT_{1A} receptor agonist *R*-(+)-2-dipropylamino-8-hydroxy-1,2,3,4-tetrahydronaphthalene (8-OH-DPAT; Sigma), the selective 5-HT_{1A} receptor antagonist WAY-100635 maleate (WAY-100635; Sigma), the selective 5-HT_{1B} receptor agonist 1,4-dihydro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-5H-pyrrol[3,2-b]pyridine-5-one dihydrochloride (CP93129; TOCRIS, Ellisville, MO, USA) and the selective 5-HT_{1B} receptor antagonist 3-[3-(dimethylamino)propyl]-4-hydroxy-*N*-[4-(4-pyridinyl)phenyl]benzamide dihydrochloride (GR55562; TOCRIS). 8-OH-DPAT and

WAY-100635 were dissolved in distilled water and other drugs were dissolved in saline immediately before use. Intravenous injections were made 20 min (for CP93129 and GR55562) or 30 min (for 8-OH-DPAT and WAY-100635) after intraatrial injections *via* the tail vein in a volume of 1 ml/kg. Intraatrial injections were made slowly in a volume of 0.2 µl per side over 20 sec, with the needle left *in situ* for an additional 20-sec period after completion of the injection. The doses employed in this study were based on previously published studies (25,26,29-32). Each animal was used only once.

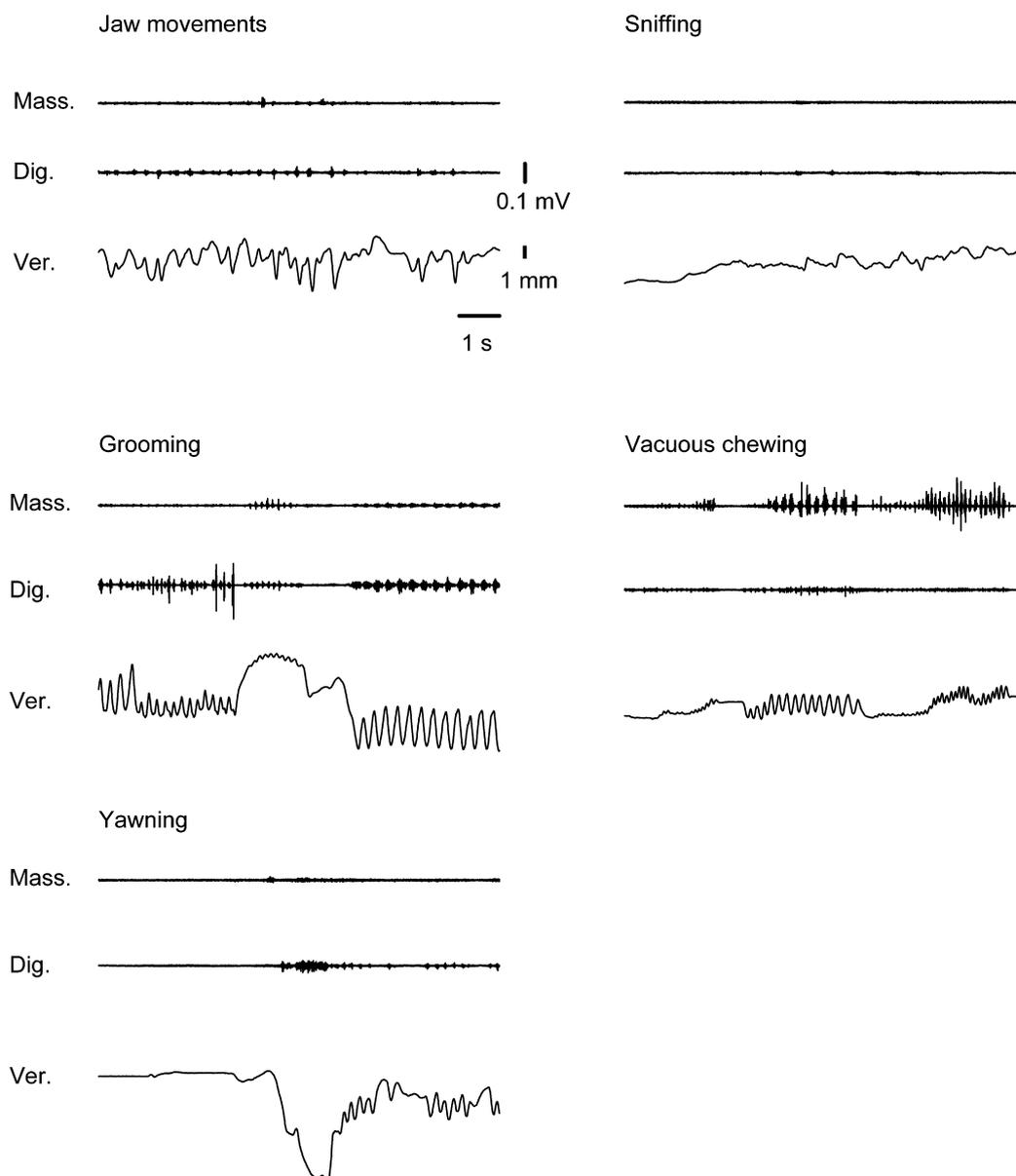


Fig. 1 Characteristic patterns of vertical jaw movements (Ver.) and EMG activities of the digastric (Dig.) and masseter (Mass.) muscles seen during repetitive vertical jaw movements (including licking and gnawing), sniffing, grooming, vacuous chewing and yawning induced by apomorphine (1 mg/kg i.v.). During grooming, the rat initially showed face grooming followed by trunk licking.

Histology

At the end of each experiment, the rats were deeply anesthetized with sodium pentobarbital (80 mg/kg i.p.) and perfused transcardially with 10% formalin. The brains were removed, sectioned at 50 μ m and stained with Cresyl violet to visualize the injection sites.

Data analysis

All values are expressed as means \pm S.E.M. The time-course of jaw movements counted during a 60-min observation period was analyzed using a two-way (group \times time) analysis of variance (ANOVA). A probability value of $P < 0.05$ was considered statistically significant.

Results

Histology

Figure 2 indicates the location of injection sites in the ventrolateral striatum. The total number of rats used was 132 and only data from rats with injection sites in the desired region ($n = 81$) were used in subsequent behavioral analyses.

Effects of 5-HT_{1A} receptor agonist and antagonist into the ventrolateral striatum on apomorphine-induced jaw movements

In agreement with previous studies using the same Hall-effect transducer system (25), intravenous injection of

apomorphine (1 mg/kg; $n = 7$) in freely moving rats receiving bilateral distilled water injections into the ventrolateral striatum 30 min beforehand induced repetitive jaw movements. The jaw movements occurred almost immediately after apomorphine injection, reached a maximum about 20 min and then declined gradually over the 60-min observation period (Fig. 3). Bilateral injections of 8-OH-DPAT (1 μ g, $n = 7$; 4 μ g, $n = 7$) into the ventrolateral striatum 30 min beforehand modestly but significantly reduced apomorphine-induced repetitive jaw movements ($F(2,216) = 5.72$, $P < 0.01$, two-way ANOVA; Fig. 3). Bilateral injections of WAY-100635 (1 μ g, $n = 7$) into the ventrolateral striatum 30 min beforehand did not modify apomorphine-induced repetitive jaw movements (Fig. 4). The reduction by 8-OH-DPAT (4 μ g) of apomorphine-induced repetitive jaw movements was antagonized by co-administration of WAY-100635 (1 μ g, $n = 8$) ($F(1,156) = 19.06$, $P < 0.001$, two-way ANOVA; Fig. 4).

Effects of 5-HT_{1B} receptor agonist and antagonist into the ventrolateral striatum on apomorphine-induced jaw movements

Intravenous injection of apomorphine (1 mg/kg; $n = 9$) in freely moving rats receiving bilateral saline injections into the ventrolateral striatum 20 min beforehand induced repetitive jaw movements similar to those after distilled

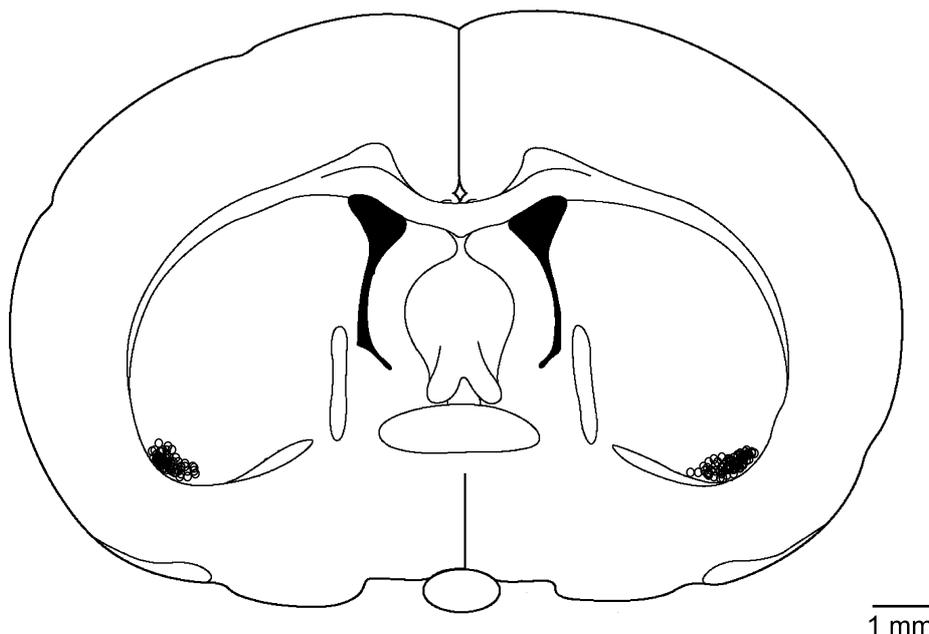


Fig. 2 Location of injection sites in the ventrolateral striatum. Plane is a composite of two or three sections through the ventrolateral striatum from the atlas of Paxinos and Watson (28); coordinate of ventrolateral striatum is 8.6 mm anterior to the interaural line ($n = 81$).

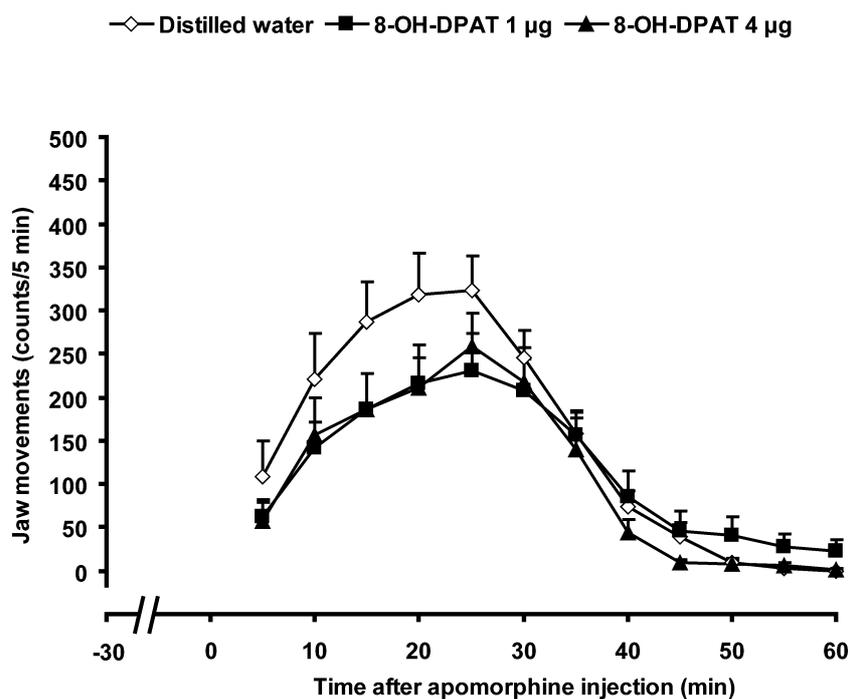


Fig. 3 Effects of bilateral injections of 8-OH-DPAT or distilled water into the ventrolateral striatum on apomorphine (1 mg/kg i.v.)-induced repetitive jaw movements. The data are expressed as the mean number of jaw movements occurring in 5-min observation periods ($n = 7$). Vertical bars indicate S.E.M.

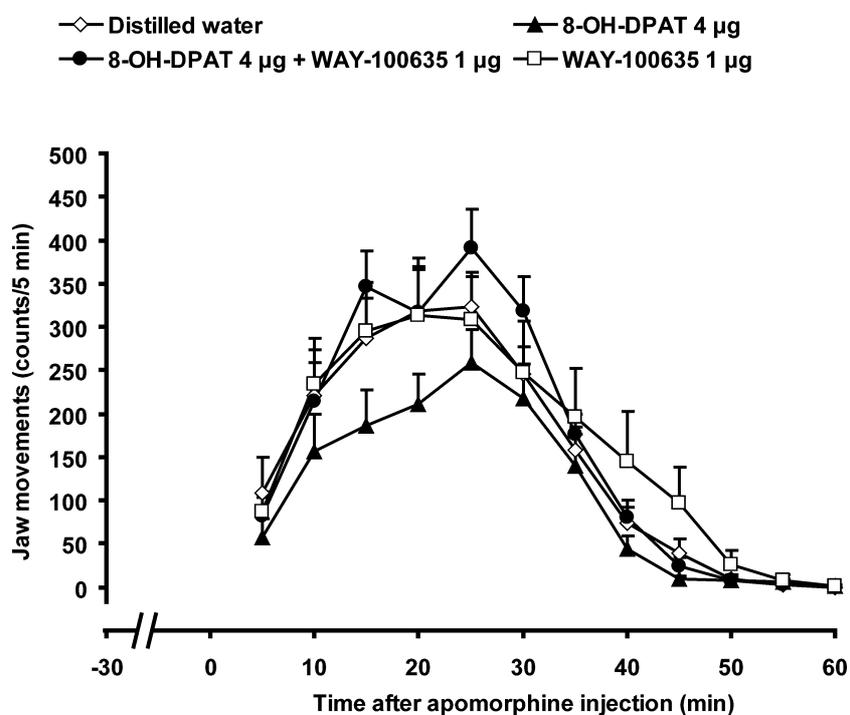


Fig. 4 Effects of bilateral injections into the ventrolateral striatum of WAY-100635 on 8-OH-DPAT-induced reduction in apomorphine (1 mg/kg i.v.)-induced repetitive jaw movements. The data are expressed as the mean number of jaw movements occurring in 5-min observation periods ($n = 7-8$). Vertical bars indicate S.E.M.

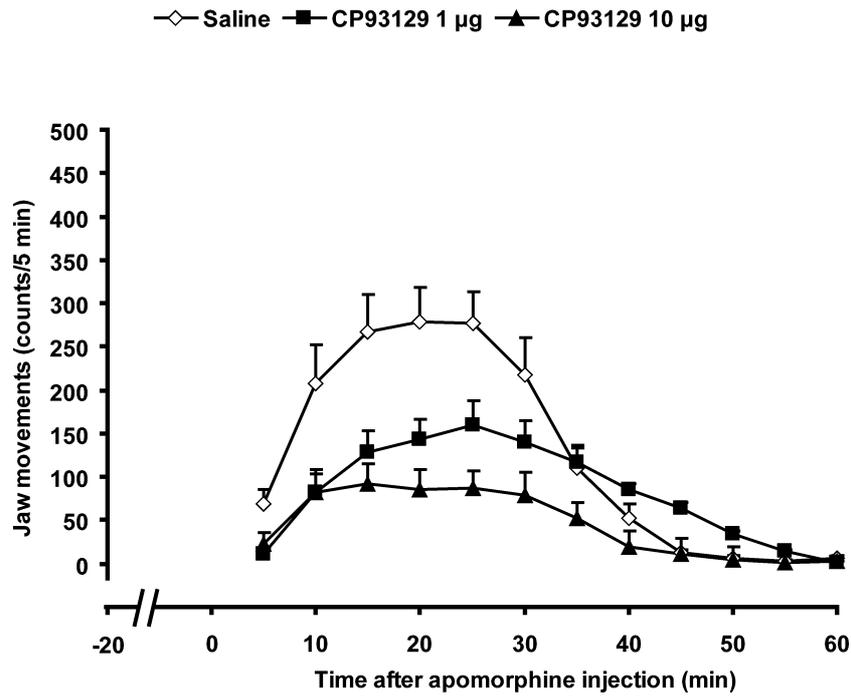


Fig. 5 Effects of bilateral injections of CP93129 or saline into the ventrolateral striatum on apomorphine (1 mg/kg i.v.)-induced repetitive jaw movements. The data are expressed as the mean number of jaw movements occurring in 5-min observation periods (n = 6-9). Vertical bars indicate S.E.M.

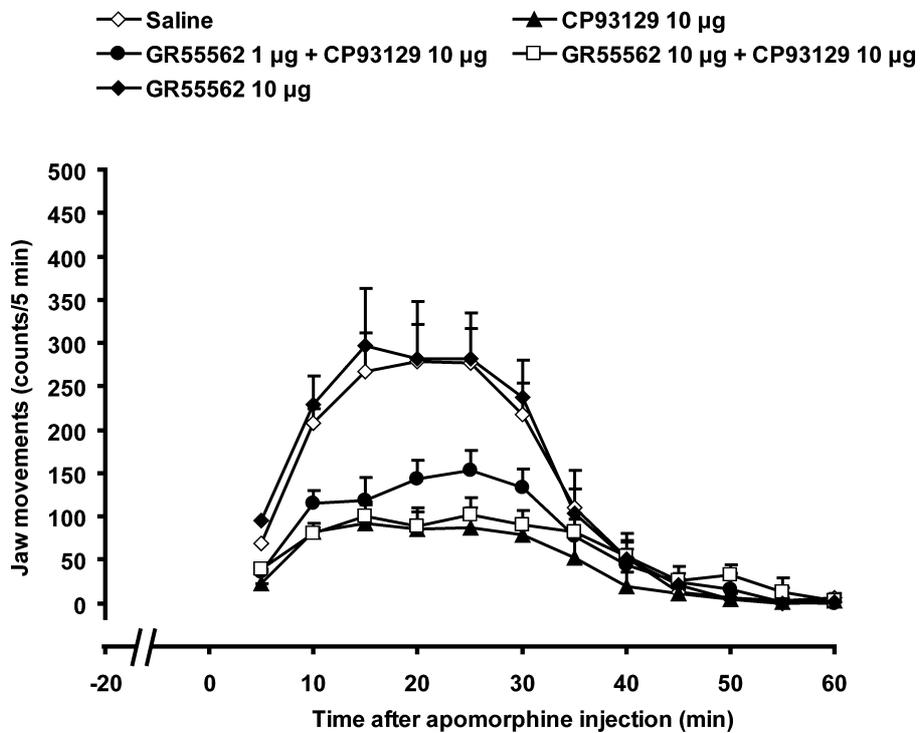


Fig. 6 Effects of bilateral injections into the ventrolateral striatum of GR55562 on CP93129-induced reduction in apomorphine (1 mg/kg i.v.)-induced repetitive jaw movements. The data are expressed as the mean number of jaw movements occurring in 5-min observation periods (n = 7). Vertical bars indicate S.E.M.

water injection into the same site (Fig. 5; see also Fig. 3). Bilateral injections of CP93129 (1 μ g, $n = 8$; 10 μ g, $n = 6$) into the ventrolateral striatum 20 min beforehand significantly reduced apomorphine-induced repetitive jaw movements ($F(2,240) = 26.36$, $P < 0.001$, two-way ANOVA; Fig. 5). Bilateral injections of GR55562 (10 μ g, $n = 6$) into the ventrolateral striatum 20 min beforehand did not affect apomorphine-induced repetitive jaw movements (Fig. 6). The reduction by CP93129 (10 μ g) of the apomorphine-induced repetitive jaw movements was slightly, but not dose-dependently (1 μ g, $n = 8$ but not 10 μ g, $n = 8$), antagonized by co-administration of the 5-HT_{1B} receptor antagonist GR55562 ($F(2,228) = 6.93$, $P < 0.01$, two-way ANOVA; Fig. 6).

Discussion

The goal of the present study was to analyze the roles of 5-HT_{1A} and 5-HT_{1B} receptors in the ventrolateral striatum in modulating dopamine receptor-mediated jaw movements, using a magnet-sensing system combined with an intracerebral drug microinjection technique in freely moving rats. In the first series of experiments, we studied whether repetitive jaw movement induced by dopamine D₁ and D₂ receptor stimulation with apomorphine can be under inhibitory control of 5-HT_{1A} receptors in the ventrolateral striatum. Subsequently, we studied whether 5-HT_{1B} receptors in the ventrolateral striatum have any modulatory role in the expression of dopamine receptor-mediated jaw movements.

Intravenous injection of apomorphine (1 mg/kg) in freely moving rats receiving bilateral distilled water injections into the ventrolateral striatum induced repetitive jaw movements which are similar in pattern and number to those reported previously (25,26). Bilateral injections of the 5-HT_{1A} receptor agonist 8-OH-DPAT modestly but significantly reduced apomorphine-induced jaw movements. This reduction by 8-OH-DPAT was fully antagonized by the 5-HT_{1A} receptor antagonist WAY-100635, which alone did not significantly affect apomorphine-induced jaw movements. These results suggest that reduction in apomorphine-induced jaw movements by 8-OH-DPAT was mediated *via* stimulation of 5-HT_{1A} receptors located in the ventrolateral striatum. Although these results essentially support in with our above-mentioned hypothesis, that repetitive jaw movements induced by dopamine D₁ and D₂ receptor stimulation can be under inhibitory control of 5-HT_{1A} receptors in the ventrolateral striatum (see also Introduction), the reduction induced by 8-OH-DPAT was small (28%) over the dose range studied. The reason for this partial inhibitory effect is not known. It may reflect dosage. However, it is attractive

to speculate that if the contribution of endogenous dopamine to elicit apomorphine-induced repetitive jaw movements is small, removal of such a small endogenous tone may not markedly reduce apomorphine's effect. Alternatively, the results may be partly related to the density of 5-HT_{1A} receptors since expression of this receptor and its mRNA is much lower in the striatum than in the dorsal raphe nucleus (33): therefore, it is possible that 5-HT_{1A} receptors in the striatum may not play a pivotal role in the control of dopaminergic functions.

Bilateral injections of the 5-HT_{1B} receptor agonist CP93129 reduced apomorphine-induced jaw movements. Although the reduction was slightly antagonized by a lower dose of the 5-HT_{1B} receptor antagonist GR55562, this effect was not dose-dependent, as can be seen in the negligible effects with a higher dose of GR55562 which alone did not significantly affect apomorphine-induced jaw movements. Therefore, it is unlikely that GR55562 pharmacologically antagonizes the inhibitory effects of CP93129 on apomorphine-induced jaw movements. The present results therefore suggest that the reduction of dopamine receptor-mediated jaw movements by CP93129 is not mediated through activation of 5-HT_{1B} receptors in the ventrolateral striatum. Possible mechanisms other than 5-HT_{1B} receptors involved in this effect of CP93129 need to be investigated.

In conclusion, the present study suggests that 5-HT_{1A}, but not 5-HT_{1B}, receptors in the ventrolateral striatum play a modulatory role in the production of dopamine receptor-mediated jaw movements.

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