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Ventral striatal vs. accumbal (shell) mechanisms and non-cyclase-coupled dopamine D_1-like receptors in jaw movements

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Abstract

This study compared the effects of intracerebral injections of the dopamine D_1-like receptor agents 3-methyl-6-chloro-7,8-dihydroxy-1-[3-methylphenyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SK&F 83959) and [*R*]-3-methyl-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH 23390) into the ventrolateral striatum or the shell of the nucleus accumbens on the synergistic induction of jaw movements by intravenous (i.v.) co-administration of [*R*]-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SK&F 38393) or SK&F 83959 with the dopamine D_2-like receptor agonist, quinpirole. In the ventrolateral striatum, SCH 23390 and SK&F 83959 each blocked jaw movements induced by i.v. SK&F 38393 with quinpirole, while only SCH 23390 blocked i.v. SK&F 83959 with quinpirole. SCH 23390 was less effective in the accumbens shell than in the ventrolateral striatum, and SK&F 83959 was ineffective to block i.v. SK&F 38393 with quinpirole, while neither SCH 23390 nor SK&F 83959 blocked i.v. SK&F 83959 with quinpirole. As SK&F 83959 inhibits the stimulation of adenylyl cyclase via dopamine D_{1A} receptors but acts as an agonist at a putative dopamine D_1-like receptor site not linked to cyclase, an important role is indicated for non-cyclase-coupled dopamine D_1-like receptor sites as well as dopamine D_{1A} receptors in the regulation of jaw movements via dopamine D_1-like/D_2-like receptor synergism, particularly in the ventrolateral striatum.

Keywords: Dopamine D_1-like receptor; Adenylyl cyclase; Dopamine D_1-like receptor, non-cyclase-coupled; Striatum, ventrolateral; Accumbens, shell; Dopamine D_1-like/D_2-like receptor synergism; Jaw movement; SK&F 83959; (Rat)

1. Introduction

In seeking functional roles for molecular biologically defined dopamine D_1-like (D_{1A}/D_1, $D_{1B}/D_{5)}$ and dopamine D_2-like ($D_{2L/S}$, D_3, D_4) receptor families (Missale et al., 1998; Waddington et al., 2001), there is now a considerable body of evidence for their important role in the regulation of orofacial movements. In this regard, particular attention focuses on the role of the dopamine D_1-like receptor family and its functional interactions with dopamine D_2-like counterparts (Rosengarten et al., 1986; Collins et al., 1991; Waddington et al., 1995, 1998; Niznik et al., 2001). However, this putative role may be more complex than envisaged originally. While dopamine D_1-like receptors have been defined conventionally in terms of their linkage to the stimulation of adenylyl cyclase, neurochemical, neurophysiological and behavioural evidence indicates the existence of a dopamine D_1-like receptor linked to a transduction system other than/additional to adenylyl cyclase, with phosphoinositide hydrolysis being the most widely favoured candidate (Mahan et al., 1990; Undie and Friedman, 1990; Undie et al., 1994, 2000; Waddington et al., 1995, 1998; Niznik et al., 2001).

Recently, we have reported the synergistic induction of characteristic jaw movements in rats by co-administration of the selective dopamine D_1-like receptor agent, SK&F 83959, with the selective dopamine D_2-like receptor agonist, quinpirole, in a manner similar to a combination of the classical selective dopamine D_1-like receptor agonist, SK&F 38393, with quinpirole (Adachi et al., 1999). Yet, unlike SK&F 38393, SK&F 83959 fails to stimulate

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adenylyl cyclase and inhibits the cyclase stimulation induced by dopamine, showing the defining neurochemical characteristics of a selective dopamine D_1-like receptor antagonist. However, SK&F 83959 shows a behavioural profile similar to that of selective but partial, adenylyl cyclase-stimulating dopamine D_1-like receptor agonists such as SK&F 38393 and full efficacy agonists such as A 68930. Thus, may the compound may also exert agonist activity at a non-cyclase-coupled dopamine D_1-like receptor (Arnt et al., 1992; Deveney and Waddington, 1995; Gnanalingham et al., 1995; Waddington et al., 1995, 1998; Andringa et al., 1999; Undie, 1999; Undie et al., 2000; Niznik et al., 2001).

A previous study (Adachi et al., 1999) compared the effects of intravenous co-administration of SK&F 83959 and quinpirole with those of SK&F 38393 and quinpirole, but the resultant jaw movements were evaluated pharmacologically using peripherally administered dopamine D_1-like receptor antagonists. Thus, this study could not serve to clarify the brain region(s) involved in these antagonistic actions or further illuminate the nature of dopamine D_1-like receptor antagonist effects. Evidence for any regional specificity of these effects would be important, as the site(s) of action of SK&F 83959 for mediating these responses is(are) poorly understood. In particular, SK&F 83959 appears to have at least two actions on dopaminergic function with differing affinities, i.e. antagonism at cyclase-coupled dopamine D_1-like receptors, like SCH 23390, and agonism at non-cyclase-coupled dopamine D_1-like receptors, like SK&F 38393. Thus, it would be important to examine the effects of SK&F 83959 given intracerebrally into individual brain regions, where one action might predominate, on synergistic responses to i.v. co-administration of SK&F 83959 with quinpirole.

Given that both ventrolateral striatum and the shell of the nucleus accumbens have been implicated in such processes to elicit jaw movements (Koshikawa et al., 1989, 1996; Delfs and Kelley, 1990; Cools et al., 1995), we have compared the effects of intracerebral injections of SK&F 83959 vs. SCH 23390 into these areas on responsiveness to i.v. co-administration of SK&F 83959 with quinpirole vs. SK&F 38393 with quinpirole; this was to identify differences or similarities (i) in the roles of these regions in mediating antagonism of each of these synergistic dopamine D_1-like/D_2-like receptor interactions, and (ii) in the profiles of these two antagonists of dopamine D_1-like receptors coupled to adenylyl cyclase as putative inhibitors of such synergism.

2. Materials and methods

2.1. Surgical procedures

Male Sprague–Dawley rats weighing 240–310 g were housed in cages ($27 \times 45 \times 20$ cm) that were held in a temperature-controlled (24 ± 2 °C) environment under a 12-h light/dark cycle (lights on at 07:00 h), with free access to food and water.

The rats were anaesthetised with halothane (0.5–4.0%) and supplemented with ketamine HCl (10.0 mg/kg, i.p.). The surgical and recording procedures were as described previously (Koshikawa et al., 1991, 1996). After cannulation of the right external jugular vein, a small light-emitting diode was fixed to the mandible. The animal was then placed in a stereotactic frame so that the head was kept in constant relation to a light-sensitive transducer, which detected the vertical and lateral movements of the diode. After surgery, the animals received ketamine (10.0 mg/h, i.p.) continuously; this dose is in the range that fails to influence either jaw movements elicited by co-activation of dopamine D_1-like and D_2-like receptors or dopamine metabolism in the striatum (Koshikawa et al., 1988). Lignocaine (2.0% gel) was applied to all incisions to ensure complete analgesia. Rectal temperature was maintained at 37.0 °C with a thermostatically controlled heating pad. Monitored concentrations of expired O_2 and CO_2 during experiments were 19–21% and 2.0–2.5%, respectively. Jaw movements were recorded on a tape recorder (RD-180T; TEAC) for off-line analysis. The recordings were analysed automatically, using a spike trigger that counted vertical jaw movements per 5 min.

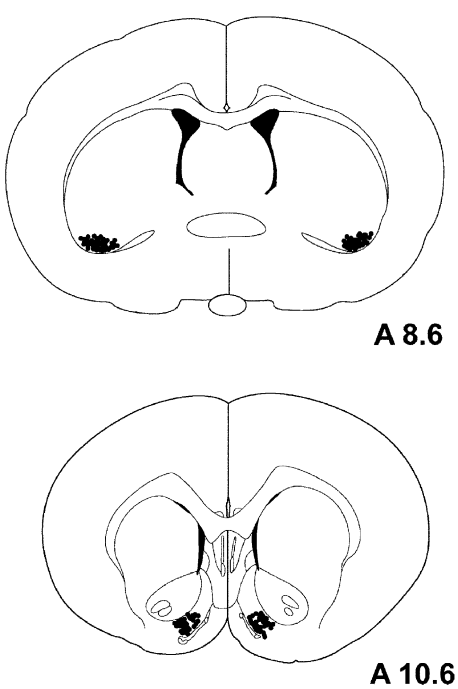

Fig. 1. Location of injection sites in ventrolateral striatum (upper) and accumbens shell (lower). Planes are modified from the atlas of Paxinos and Watson (1986); approximate coordinates indicated are mm anterior to the interaural line.

Guide cannulas (external diameter 0.5 mm, internal diameter 0.3 mm) were implanted bilaterally into the brain according to previously described procedures (Koshikawa et al., 1996). Coordinates based on the atlas of Paxinos and Watson (1986) were, for ventrolateral striatum: anterior = 8.6 mm from interaural line, vertical = 3.0 mm from interaural line, lateral = 4.0 mm from midline; for accumbens shell: anterior = 10.6 mm, vertical = 2.0 mm, lateral = 0.7 mm. Cannulas directed at the shell were angled 21° from the mid-sagittal plane to avoid the ventricular system. The injection volume was 0.2 μl per side, and was delivered over a 20-s period with the needle left in situ for an additional 20-s period after completion of the injection to allow diffusion. Damage to the target site was minimised by implanting the tips of guide cannulas 1.6 mm (ventrolateral striatum) or 2.0 mm (shell) above the desired injection site. Wire stylets were placed in the guide cannulas to prevent occlusion.

These 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 that were in compliance with the UK Animals Scientific Procedures Act 1986.

2.2. Histology

At the end of each experiment, the rats were deeply anaesthetised with pentobarbitone (80 mg/kg, i.p.) and perfused transcardially with 10% formalin. The brains were removed, sectioned at 50 μm and stained with Cresyl violet to visualise injection sites (Fig. 1); only data from animals in which the injections were correctly placed were included in subsequent analyses.

2.3. Drugs

The drugs used were: 3-methyl-6-chloro-7,8-dihydroxy-1-[3-methylphenyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SK&F 83959; Research Biochemicals International/

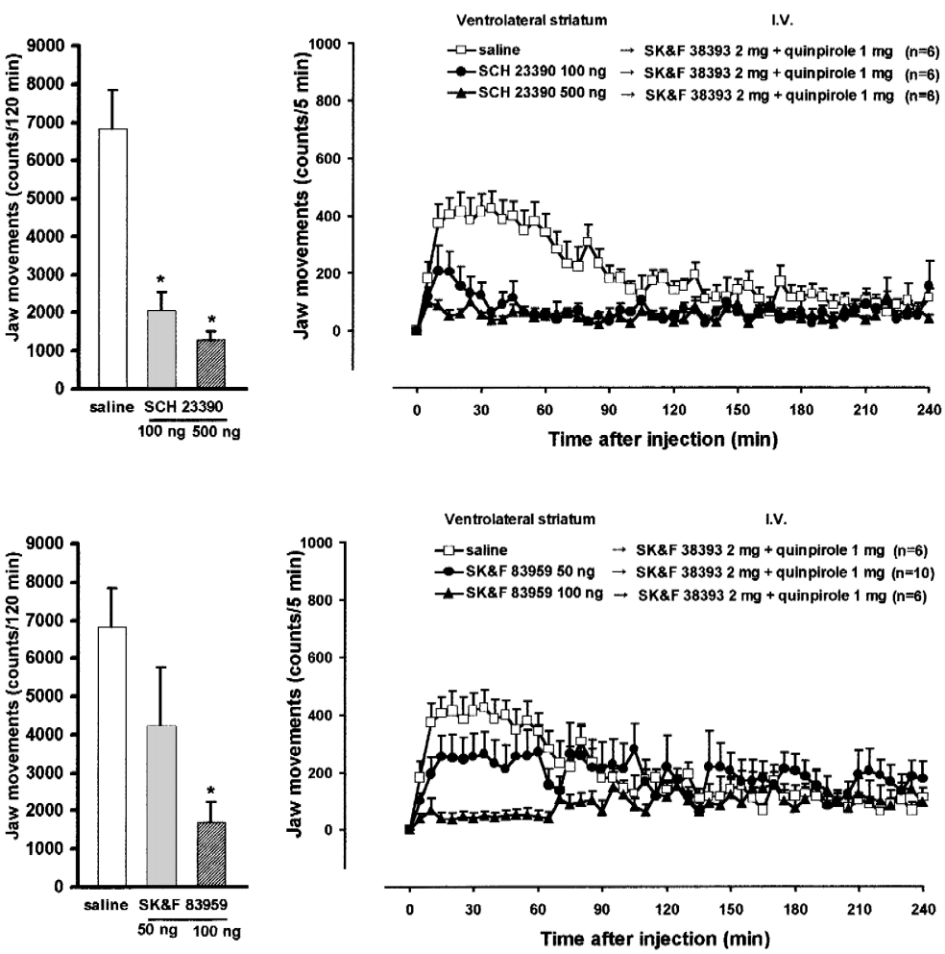

Fig. 2. Effect on jaw movement counts of pretreatment with vehicle, SCH 23390 (100–500 ng/0.2 μl; upper) or SK&F 83959 (50–100 ng/0.2 μl; lower) given into the ventrolateral striatum 30 min prior to i.v. co-administration of 2.0 mg/kg SK&F 38393 with 1.0 mg/kg quinpirole. Data are mean counts ± S.E.M. for $n = 6–10$ animals per group. $^{**}P < 0.01$ vs. vehicle pretreatment over initial 120 min.

NIMH Chemical Synthesis program, USA); [*R*]-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine ([*R*]-SK&F 38393; Research Biochemicals International); [*R*]-3-methyl-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH 23390; Research Biochemicals International); quinpirole (Research Biochemicals International). Drugs were dissolved in saline. SK&F 83959 and quinpirole, SK&F 38393 and quinpirole, or vehicle, were given i.v. via the jugular cannula, with putative antagonists or vehicle given intracerebrally 30 min prior to i.v. co-administration of agonists.

2.4. Data analysis

All data were expressed as means ± S.E.M. and analysed using one-way analysis of variance (ANOVA) or two-way ANOVA (group × time), followed by a post-hoc Student's *t*-test where appropriate. A probability value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Effect of SK&F 83959 vs. SCH 23390 into ventrolateral striatum on responsiveness to i.v. combination injections of SK&F 38393 with quinpirole

When given following intracerebral injections of vehicle, the i.v. combination of SK&F 38393 (2.0 mg/kg) with quinpirole (1.0 mg/kg) readily induced jaw movements which continued for approximately 120 min thereafter (Fig. 2). This effect was readily and dose-dependently blocked by prior injection of 100–500 ng SCH 23390 and of 50–100 ng SK&F 83959 into the ventrolateral striatum.

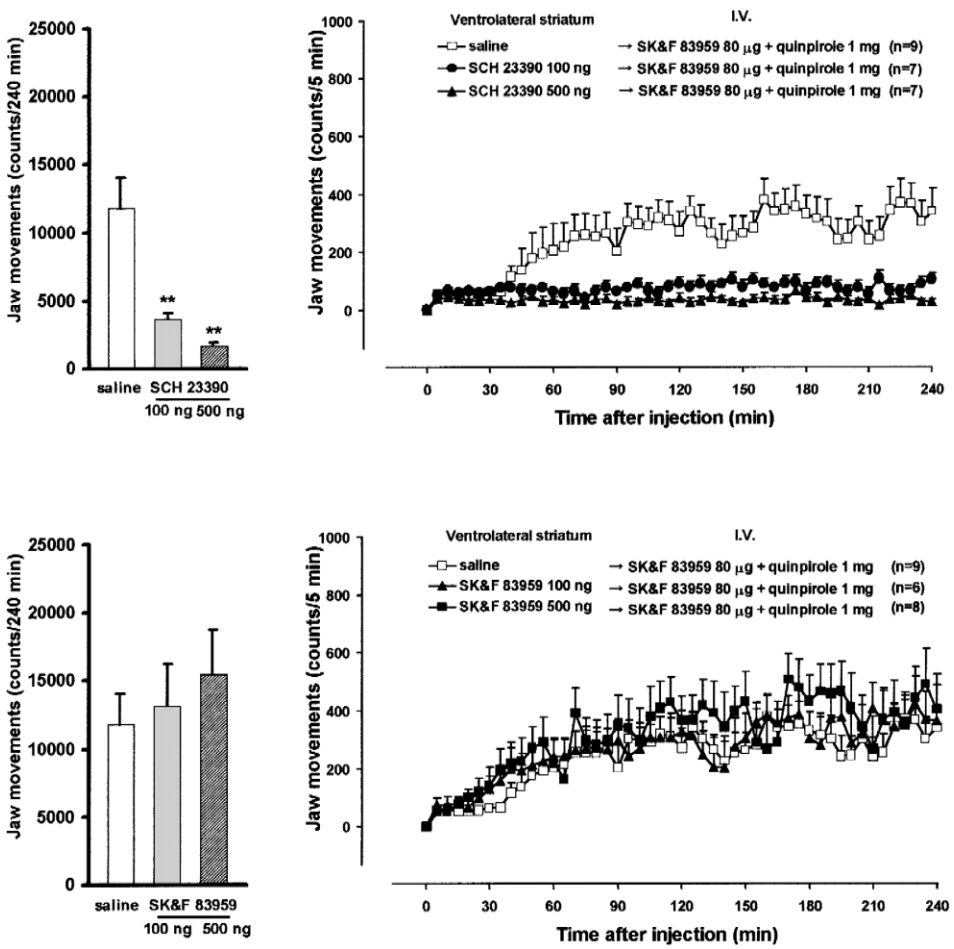

Fig. 3. Effect on jaw movement counts of pretreatment with vehicle, SCH 23390 (100–500 ng/0.2 μl; upper) or SK&F 83959 (100–500 ng/0.2 μl; lower) given into the ventrolateral striatum 30 min prior to i.v. co-administration of 80 μg/kg SK&F 83959 with 1.0 mg/kg quinpirole. Data are mean counts ± S.E.M. for $n = 6–9$ animals per group. $^{**}P < 0.01$ vs. vehicle pretreatment over 240 min.

3.2. Effect of SK&F 83959 vs. SCH 23390 into ventrolateral striatum on responsiveness to i.v. combination injections of SK&F 83959 with quinpirole

When given following intracerebral injections of vehicle, the i.v. combination of SK&F 83959 (80 μg/kg) with quinpirole (1.0 mg/kg) readily induced similar jaw movements after a modest latency of approximately 30 min, and these movements then persisted for more than 240 min (Fig. 3); as the onset of jaw movements had been rapid in our previous study but was modestly delayed here, there may have been some disruptive effect on the synergism between SK&F 83959 and quinpirole from vehicle injections given into the ventrolateral striatum, but why this should occur in this region only and only for this drug combination remains to be determined. This synergism between SK&F 83959 and quinpirole was readily and dose-dependently blocked by prior injection of 100–500 ng SCH 23390 into the ventrolateral striatum. However, prior injection of 100–500 ng SK&F 83959 was without significant effect on this response.

3.3. Effect of SK&F 83959 vs. SCH 23390 into accumbens shell on responsiveness to i.v. combination injections of SK&F 38393 with quinpirole

When given following intracerebral injections of vehicle, the i.v. combination of SK&F 38393 (2.0 mg/kg) with quinpirole (1.0 mg/kg) induced similar jaw movements which continued for approximately 120 min thereafter (Fig. 4). This effect was dose-dependently blocked by prior injection of 500–1000 ng SCH 23390 into the accumbens shell. However, prior injection of 100–500 ng SK&F 83959 was without significant effect on this response.

3.4. Effect of SK&F 83959 vs. SCH 23390 into accumbens shell on responsiveness to i.v. combination injections of SK&F 83959 with quinpirole

When given following intracerebral injections of vehicle, the i.v. combination of SK&F 83959 (80 μg/kg) with quinpirole (1.0 mg/kg) induced similar jaw movements,

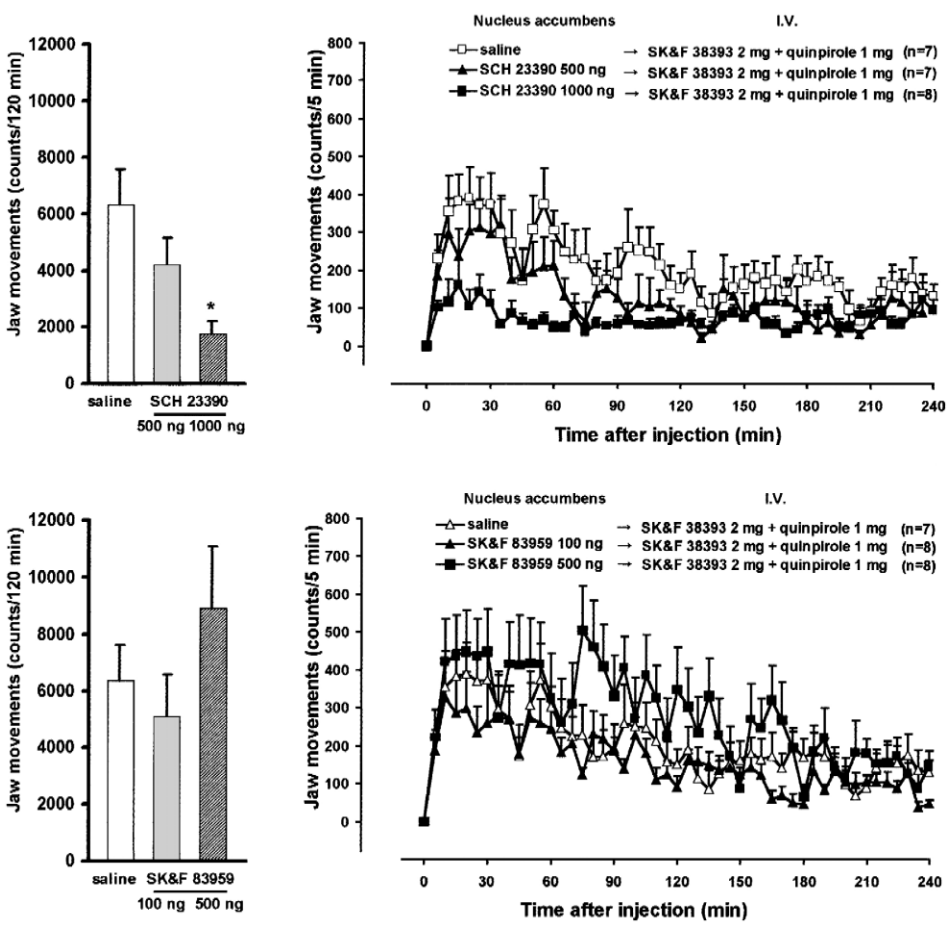

Fig. 4. Effect on jaw movement counts of pretreatment with vehicle, SCH 23390 (500–1000 ng/0.2 μl; upper) or SK&F 83959 (100–500 ng/0.2 μl; lower) given into the accumbens shell 30 min prior to i.v. co-administration of 2.0 mg/kg SK&F 38393 with 1.0 mg/kg quinpirole. Data are mean counts ± S.E.M. for $n = 6–8$ animals per group. $^{*}P < 0.05$ vs. vehicle pretreatment over initial 120 min.

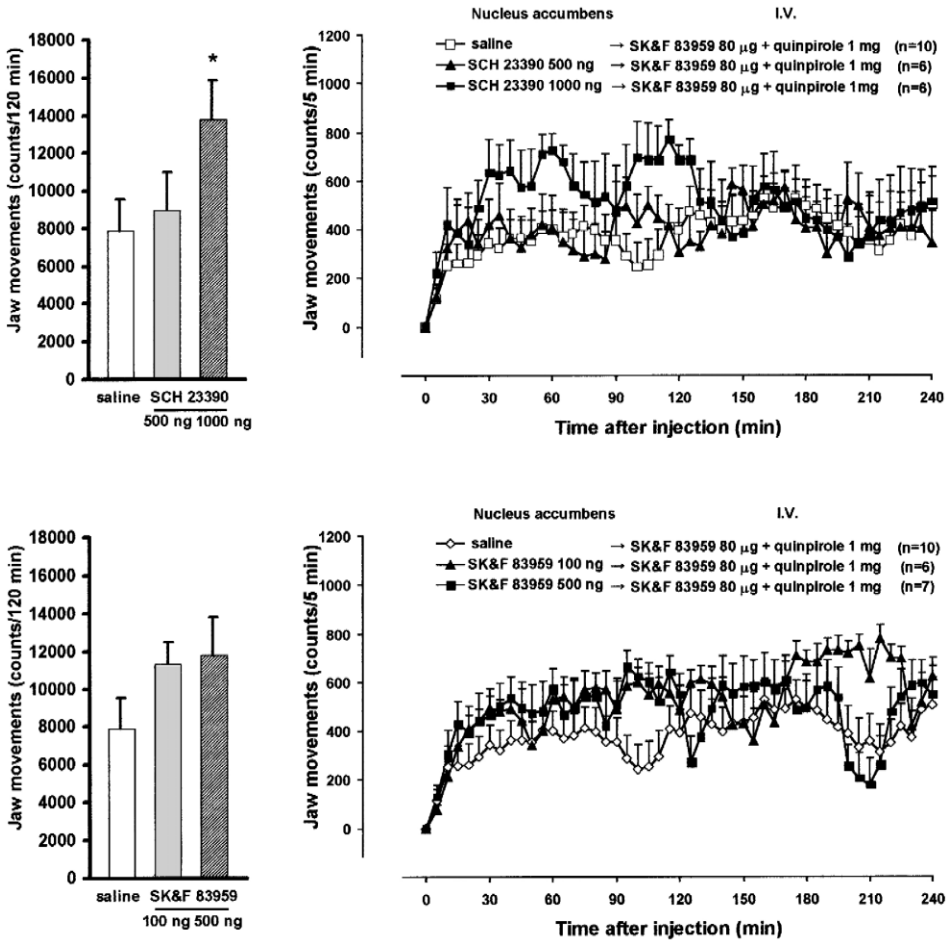

Fig 5. Effect on jaw movement counts of pretreatment with vehicle, SCH 23390 (500–1000 ng/0.2 μl; upper) or SK&F 83959 (100–500 ng/0.2 μl; lower) given into the accumbens shell 30 min prior to i.v. co-administration of 80 μg/kg SK&F 83959 with 1.0 mg/kg quinpirole. Data are mean counts ± S.E.M. for $n = 6–10$ animals per group. $^{*}P < 0.05$ vs. vehicle pretreatment over initial 120 min.

and these then persisted for more than 240 min (Fig. 5). Prior injection of 500–1000 ng SCH 23390 and of 100–500 ng SK&F 83959 into the accumbens shell each failed to block this response; instead, this response was potentiated by SCH 23390, particularly over the first 120 min, with a similar trend evident for SK&F 83959.

4. Discussion

Induction of jaw movements by i.v. co-administration of SK&F 38393 with quinpirole, via well-described co-operative/synergistic dopamine D_1-like/D_2-like receptor interactions (Waddington et al., 1994; Adachi et al., 1999), was readily blocked by injection of SCH 23390 into the ventrolateral striatum; this is consistent with previous evidence for a role of the ventrolateral striatum in mediating orofacial movements (Koshikawa et al., 1989; Delfs and Kelley, 1990). SK&F 83959 given into the ventrolateral striatum also blocked this response. Since SCH 23390 and SK&F 83959 share the property of inhibiting dopamine-sensitive adenylyl cyclase and thus act as antagonists at dopamine D_{1A} (and D_{1B}) receptors (see Introduction), their comparable effects in the ventrolateral striatum to block jaw movements induced via dopamine D_1-like/D_2-like receptor synergism would suggest the involvement of dopamine D_{1A} (or D_{1B}) receptors.

In accordance with our previous findings (Adachi et al., 1999), SK&F 83959 shared this action of SK&F 38393 to synergise with quinpirole on i.v. co-administration to induce jaw movements. Though SK&F 38393 and SK&F 83959 stimulate and block dopamine-sensitive adenylyl cyclase and thus act as agonists and antagonists at dopamine D_{1A} (and D_{1B}) receptors, respectively, they appear to share agonist activity at a putative non-cyclase-coupled dopamine D_1-like receptor (see Introduction). Their comparable synergism with dopamine D_2-like receptors would suggest at least two possible explanations. Firstly, SK&F 38393 and SK&F 83959 might each synergise with quinpirole via putative non-cyclase-coupled dopamine D_1-like receptors; this would imply no role in the synergism for cyclase-coupled dopamine D_{1A} (or D_{1B}) receptors. Secondly, SK&F 38393 might synergise via both cyclase-coupled dopamine D_{1A} (or D_{1B}) receptors *and* putative non-cyclase-coupled

dopamine D_1-like receptors, while SK&F 83959 might synergise only via a putative non-cyclase-coupled dopamine D_1-like site; this would imply that cyclase-coupled dopamine D_{1A} (or D_{1B}) receptors and putative non-cyclase-coupled dopamine D_1-like receptors synergise independently with their dopamine D_2-like counterparts for expressing jaw movements. This second possibility is supported by the present finding that SCH 23390 given into the ventrolateral striatum readily antagonised synergism involving SK&F 38393 *and* SK&F 83959 with quinpirole, while SK&F 83959 blocked the synergism involving SK&F 38393 but *not* SK&F 83959 with quinpirole.

In the accumbens shell, induction of jaw movements by i.v. co-administration of SK&F 38393 with quinpirole was readily blocked by local injection of the dopamine D_1-like receptor antagonist, SCH 23390, though with less potency than when the injection was given into the ventrolateral striatum; this is consistent with previous evidence for a role of the accumbens shell in mediating orofacial movements (Cools et al., 1995; Koshikawa et al., 1996). SK&F 83959 given into the accumbens shell failed to block this response, though it effected blockade when given into ventrolateral striatum. This would suggest that SK&F 83959 may be a less effective antagonist at dopamine D_{1A} (or D_{1B}) receptors in the accumbens shell, as appeared to be the case for SCH 23390; furthermore, its affinity to block dopamine-sensitive adenylyl cyclase is reported to be less than that of SCH 23390 (Arnt et al., 1992; Gnanalingham et al., 1995; Andringa et al., 1999).

Neither SCH 23390 nor SK&F 83959 given into the accumbens shell was able to block the induction of jaw movements by i.v. co-administration of SK&F 83959 with quinpirole. Therefore, it would appear that in the accumbens shell, blocking either dopamine-sensitive adenylyl cyclase (dopamine D_{1A} or D_{1B} receptors) or putative non-cyclase-coupled dopamine D_1-like receptors cannot attenuate such jaw movements when these involve synergism between non-cyclase-coupled dopamine D_1-like receptors and dopamine D_2-like receptors. The modest potentiation of synergism induced by SCH 23390 and SK&F 83959 given into the accumbens shell might thus reflect local additive effects of agonist actions of SK&F 83959 and putative partial agonist actions of SCH 23390 (Wachtel and White, 1995) at non-cyclase-coupled dopamine D_1-like sites (Undie, 1999; Undie et al., 2000) in a brain region where the influence of dopamine D_{1A} (or D_{1B}) receptors appears less prominent than in the ventrolateral striatum. More generally, it is not yet possible to relate specific behavioural effects to subtle, partial agonist activities in in vitro test systems whose relation to in vivo conditions is unknown.

These findings indicate that the effects of intracerebrally administered SCH 23390 and SK&F 83959 on jaw movements mediated by dopamine D_1-like/D_2-like receptor synergism depend upon: (i) the brain region involved, with effects appearing more pronounced in the ventrolateral striatum than in the accumbens shell; and (ii) the dopamine D_1-like receptor agent utilised, with effects appearing more pronounced for SCH 23390 than for SK&F 83959 given intracerebrally when synergism is induced by combining quinpirole with SK&F 83959 rather than with SK&F 38393. Thus, an important role for non-cyclase-coupled dopamine D_1-like sites as well as dopamine D_{1A} (or D_{1B}) receptors in the regulation of jaw movements via dopamine D_1-like/D_2-like receptor synergism is indicated, and this appears to be more evident in the ventrolateral striatum than in the accumbens shell.

Acknowledgements

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