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Topographical resolution of jaw movements mediated by cyclase- vs. non-cyclase-coupled dopamine D_1-like receptors: Studies with SK&F 83822

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Abstract

This study examined the effects on orofacial movement topography of SK&F 83822 ([*R*/*S*]-6-chloro-7,8-dihydroxy-3-allyl-1-[3-methylphenyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine), which stimulates dopamine D_1-like receptors coupled to stimulation of adenylyl cyclase (AC) but not phosphoinositide (PI) hydrolysis, in comparison with SK&F 83959 ([*R*/*S*]-3-methyl-6-chloro-7,8-dihydroxy-1-[3-methyl-phenyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine), which stimulates PI hydrolysis but not AC. SK&F 83822 alone induced chattering, while SK&F 83959 alone exerted little effect. SK&F 83822 and SK&F 83959 each in combination with the dopamine D_2-like agonist quinpirole resulted in synergistic induction of non-chattering movements with tongue protrusions. These effects were blocked by the dopamine D_1-like receptor antagonist SCH 23390 ([*R*]-3-methyl-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine). However, the dopamine D_2-like receptor antagonist YM 09151-2 (*cis*-*N*-[1-benzyl-2-methyl-pyrrolidin-3-yl]-5-chloro-2-methoxy-4-methylaminobenzamide) exerted a biphasic effect on synergism with SK&F 83822: chattering was initially released but antagonised thereafter. Only antagonism was seen for synergism with SK&F 83959. While both AC- and PI-coupled dopamine D_1-like receptors participate in synergistic dopamine D_1-like:D_2-like receptor interactions, topographically specific synergistic and oppositional dopamine D_1-like:D_2-like interactions evident with SK&F 83822 reflect the involvement primarily of D_1-like receptors coupled to AC rather than PI.

Keywords: Dopamine D_1-like receptor; Cyclase-coupled; Dopamine D_1-like receptor; Non-cyclase-coupled; Dopamine D_1-like:D_2-like receptor interaction; Jaw movement; Orofacial movement; SK&F 83822; SK&F 83959; (Rat)

1. Introduction

Orofacial movements are critically involved in consummatory behaviour, self-care, defensive and attack behaviours, vocalisation and, in higher mammals, non-verbal and verbal communication. It is well recognised that dopamine-mediated mechanisms in general and dopamine D_1-like [D_1, D_5] receptors in particular are part of the fundamental regulatory process involved in the genesis and expression of such movements (Waddington et al., 1995; Niznik et al., 2002). However, the mechanisms by which these processes are regulated by dopamine D_1-like receptors remain poorly understood. Such uncertainty is heightened by evidence for putative dopamine D_1-like receptors that are linked to a transduction system other than or additional to the defining linkage to adenylyl cyclase [AC],

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with stimulation of phospholipase C-mediated phosphoinositide [PI] hydrolysis being the most widely entertained candidate (Mahan et al., 1990; Undie and Friedman, 1990; Undie et al., 1994, 2000; Niznik et al., 2002).

Most dopamine D_1-like receptor agonists and antagonists are unable to distinguish between these putative AC- and PI-coupled entities. In previous studies (Adachi et al., 1999, 2003; Hasegawa et al., 2001), we have explored the actions of the dopamine D_1-like receptor agonist SK&F 83959, which stimulates PI hydrolysis but not AC (Panchalingam and Undie, 2001; Jin et al., 2003), to induce jaw movements which are an important element of orofacial movements. This involved comparisons with SK&F 38393, which stimulates both AC and PI hydrolysis (Niznik et al., 2002). However these findings, while informative, remain inconclusive in the absence of complementary studies using a selective agent which stimulates AC but not PI hydrolysis.

The present studies have been prompted by two recent developments. Firstly, SK&F 83822 has been identified as stimulating AC but not PI hydrolysis (Andersen and Jansen, 1990; Undie et al., 1994). While there was some latency before it received initial psychopharmacological examination in non-human primates (Peacock and Gerlach, 2001), we have studied its psychopharmacological profile in rodents using an ethologically based approach (O'Sullivan et al., 2004, 2005). Secondly, our automated technique for the overall quantification of jaw movements in rats in response to SK&F 83959 (Adachi et al., 1999, 2003; Hasegawa et al., 2001) has been shown to be capable of resolving distinct topographies of orofacial movement (Koshikawa et al., 1989, 1991; Lee et al., 2003), while our studies in mutant (Tomiyama et al., 2001, 2002, 2004) and intact (Makihara et al., 2004) mice indicate that such individual topographies of movement may be mechanistically distinct.

Additionally, dopamine D_1-like receptors are known to participate in critical cooperative/synergistic and oppositional interactions with their dopamine D_2-like [D_2, D_3, D_4] receptor counterparts in the regulation of distinct aspects of behaviour (Waddington et al., 1986, 1994; Niznik et al., 2002): dopamine D_1-like and D_2-like receptors interact in a cooperative/synergistic manner in the regulation of typical dopaminergic behaviours, such that dopamine D_1-like and D_2-like receptor agonists synergise to promote sniffing, locomotion, stereotyped behaviour and some measures of jaw movements. Conversely, dopamine D_1-like and D_2-like receptors interact in an apparently oppositional manner in the regulation of atypical behaviours that include other measures of orofacial movements (Murray and Waddington, 1989; Waddington et al., 1994; Adachi et al., 1999, 2003; Niznik et al., 2002).

We report here, using quantitative resolution, the effects of SK&F 83822 on jaw movements that contribute to orofacial movement topography, in comparison with the effects of SK&F 83959. Each drug was given alone and in combination with the dopamine D_2-like receptor agonist quinpirole. Additionally, the effects of the dopamine D_1-like receptor antagonist SCH 23390 and the dopamine D_2-like receptor antagonist YM 09151-2 were studied.

2. Materials and methods

2.1. Surgical procedures

Male Sprague–Dawley rats weighing 240–310 g were housed in cages (27×45×20 cm) that were held in a temperature (24±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.

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 (Adachi et al., 1999, 2003; Hasegawa et al., 2001). 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/kg/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 (Koshikawa et al., 1989) 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.

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. Jaw movement analysis

Jaw movements were recorded on a tape recorder (RD-180T; TEAC) for off-line analysis. Recordings were analysed automatically over successive, continuous 5 min periods, using a spike trigger that counted jaw movements greater than 1 mm, and from these recordings four topographies of orofacial movement were resolved (Koshikawa et al., 1989, 1991; Lee et al., 2003): (i) total jaw movements, involving any vertical jaw movement greater than 1 mm with or without tongue protrusions; (ii) chattering jaw movements, consisting of very rapid closing movements of the jaw, accompanied by sounds made by resultant rapid contacts between the teeth; (iii) non-chattering jaw movements, derived by subtracting (ii) from (i); (iv) tongue protrusions, consisting of a characteristic pattern of jaw openings accompanied by forward excursions of the tongue beyond the incisors.

2.3. Drugs

The drugs used were: SK&F 83822 ([*R*/*S*]-6-chloro-7,8-dihydroxy-3-allyl-1-[3-methylphenyl]-2,3,4,5-tetrahydro-1*H*-

3-benzazepine; GlaxoSmithKline, UK); SK&F 83959 ([*R*/*S*]-3-methyl-6-chloro-7,8-dihydroxy-1-[3-methyl-phenyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine; RBI/SRI/NIMH Chemical Synthesis Program, USA); quinpirole (Sigma, USA); SCH 23390 ([*R*]-3-methyl-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; RBI, USA); YM 09151-2 (*cis*-*N*-[1-benzyl-2-methyl-pyrrolidin-3-yl]-5-chloro-2-methoxy-4-methylaminobenzamide; Yamanouchi, Japan). SK&F 83822, SK&F 83959, quinpirole and SCH 23390 were dissolved in saline; YM 09151-2 was dissolved in 0.1 N HCl and made up to volume with saline. All drugs were given i.v. via the jugular cannula, with antagonists administered 30 min prior to 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 post-hoc Dunnett's multiple comparison test when appropriate. In addition, Student's *t*-test or Mann–Whitney *U*-test was used to analyse difference between two groups as appropriate. A probability value of $P \leq 0.05$ was considered statistically significant.

3. Results

3.1. Topography of responsivity to SK&F 83822 and SK&F 83959

When given alone at a dose that we have reported to stimulate general aspects of behaviour (O'Sullivan et al., 2004, 2005), SK&F 83822 [0.08 mg/kg i.v.] induced jaw movements, among which chattering was the primary topography together with some non-chattering jaw movements and a modest number of tongue protrusions (Fig. 1); these effects emerged rapidly over the first 5–10 min following drug administration but were of relatively short duration, declining over a period of approximately 60 min. Conversely, at the same dose, which we have reported to stimulate similar levels of general behaviours (O'Sullivan et al., 2004, 2005), SK&F 83959 [0.08 mg/kg i.v.] induced only low levels of jaw movements (see Section 3.3; also Adachi et al., 1999).

3.2. Effects of SCH 23390 and YM 09151-2 on the topography of responsivity to SK&F 83822 and SK&F 83959

Chattering, the primary topography of jaw movements induced by SK&F 83822 [0.08 mg/kg i.v.] given alone, was readily antagonised by SCH 23390 [0.01–0.1 mg/kg i.v.], with high variability obscuring a similar effect on total jaw movements (Fig. 1). However, SCH 23390 had no consistent effect on the low levels of non-chattering jaw movements or tongue protrusions induced by SK&F 83822. While the effects of YM 09151-2 [0.005–0.05 mg/kg i.v.] on topographies of jaw movements induced by SK&F 83822 appeared similar, high variability precluded statistical significance. The induction of only low levels of jaw movements by SK&F 83959 precluded similar studies with antagonists.

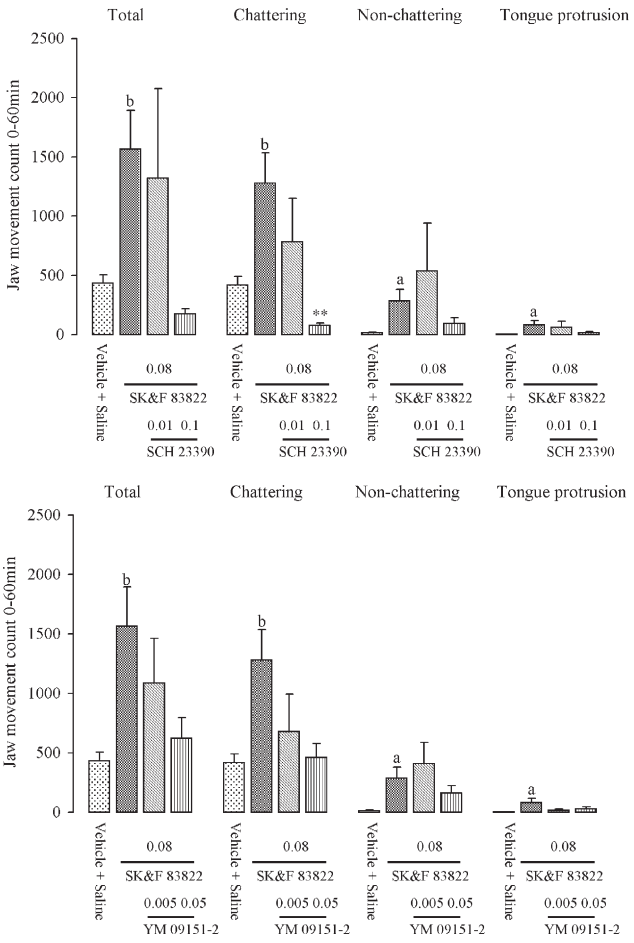

Fig. 1. Jaw movements following injection of vehicle or SK&F 83822 [0.08 mg/kg i.v] and the effects of 30 min pretreatments with SCH 23390 [0.01–0.1 mg/kg i.v.] or YM 09151-2 [0.005–0.05 mg/kg i.v.]. Data are mean counts ± S.E.M. of $n = 6$–9 animals per group over a period of 60 min for total jaw movements, chattering, non-chattering movements and tongue protrusions. $^{a}P \leq 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ vs. vehicle; $*P \leq 0.05$, $**P < 0.01$, $***P < 0.001$ vs. SK&F 83822 alone.

3.3. Topography of responsivity to SK&F 83822 and SK&F 83959 in combination with quinpirole

When given with quinpirole [1.0 mg/kg i.v.], SK&F 83822 [0.08 mg/kg i.v.] induced greatly intensified jaw movements [total jaw movements over 60 min: vehicle, 434 ± 72; SK&F 83822, 1565 ± 328; quinpirole, 492 ± 150; SK&F 83822 with quinpirole, 7560 ± 717, $P < 0.001$ vs. SK&F 83822, $P < 0.001$ vs. quinpirole]. Non-chattering movements were the primary topography, together with prominent tongue protrusions but little chattering (Figs. 2 and 3); these effects emerged rapidly over the first 5–10 min following drug administration, after which they were sustained for 60 min before declining over a total period of 120 min. When given with quinpirole [1.0 mg/kg i.v.], SK&F 83959 [0.08 mg/kg i.v.] now induced intense jaw movements [total jaw movements over 60 min: vehicle, 434 ± 72; SK&F 83959, 599 ± 155; quinpirole, 492 ± 150; SK&F 83959 with quinpirole, 5109 ± 1548, $P < 0.05$ vs. SK&F 83959, $P < 0.05$ vs. quinpirole]. Non-chattering movements were the primary topography, together with prominent

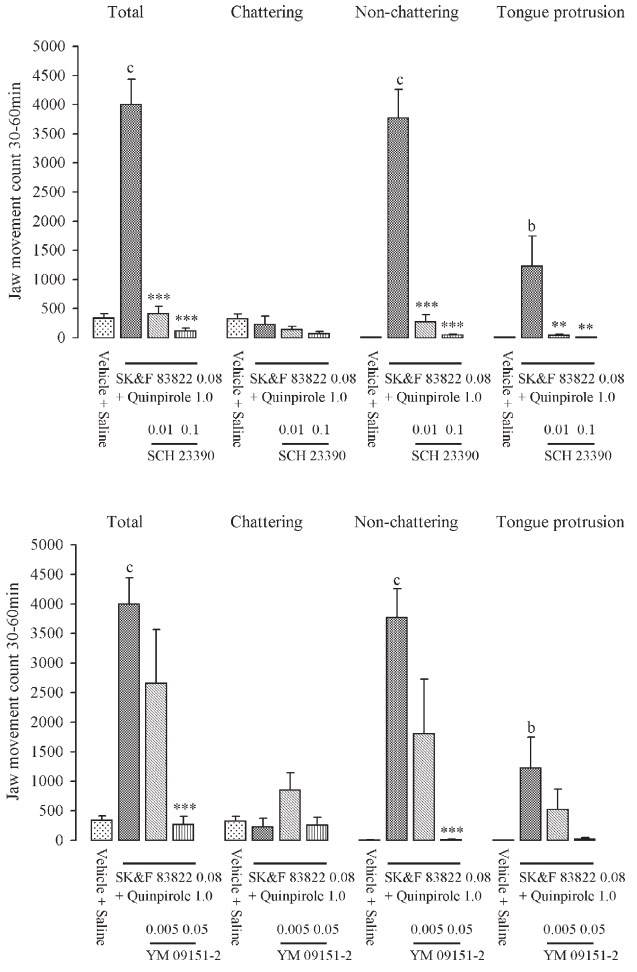

Fig. 2. Jaw movements following injection of vehicle or SK&F 83822 [0.08 mg/kg i.v.] in combination with quinpirole [1.0 mg/kg i.v.] and the effects of 30 min pretreatments with SCH 23390 [0.01–0.1 mg/kg i.v.] or YM 09151-2 [0.005–0.05 mg/kg i.v.]. Data are mean counts±S.E.M. of $n=6$–9 animals per group over a period of 30–60 min for total jaw movements, chattering, non-chattering movements and tongue protrusions (for data over 0–30 min, see text and Fig. 3). $^{a}P\leq0.05$, $^{b}P<0.01$, $^{c}P<0.001$ vs. vehicle; $*P\leq0.05$,$**P<0.01$, $***P<0.001$ vs. SK&F 83822 in combination with quinpirole.

tongue protrusions but little chattering (Fig. 4); these effects emerged rapidly over the first 5–10 min following drug administration, after which they increased further over 60 min and were then sustained through 120 min before declining over a total period of 240 min.

3.4. Effects of SCH 23390 and YM 09151-2 on the topography of responsivity to SK&F 83822 and SK&F 83959 in combination with quinpirole

Total jaw movements induced by SK&F 83822 [0.08 mg/kg i.v.] and SK&F 83959 [0.08 mg/kg i.v.] in combination with quinpirole [1.0 mg/kg i.v.], including its primary topographies of non-chattering movements with tongue protrusions, were each readily antagonised by SCH 23390 [0.01–0.1 mg/kg i.v.] over the duration of action of these agonist combinations (Figs. 2 and 4).

Responsivity to SK&F 83822 [0.08 mg/kg i.v.] in combination with quinpirole [1.0 mg/kg i.v.] was influenced by YM 09151-2 [0.005–0.05 mg/kg i.v.] in a time-dependent manner. At the lower dose, YM 09151-2 exerted a biphasic effect on total jaw movements [treatment×time interaction, $F(11,115)=3.72$, $P<0.001$]: these were enhanced over the initial 0–30 min following drug administration but antagonised over 30–60 min thereafter; topographically, this initial enhancement was due primarily to an increase in chattering, with only minor effects on non-chattering movements and tongue protrusions (Fig. 3). At the higher dose, YM 09151-2 exerted monophasic antagonism of all topographies of jaw movements across the duration of action of SK&F 83822 in combination with quinpirole. In contrast, YM 09151-2 [0.005–0.05 mg/kg i.v.] exerted only monophasic antagonism of all topographies of jaw movements induced by SK&F 83959 [0.08 mg/kg i.v.] in combination with

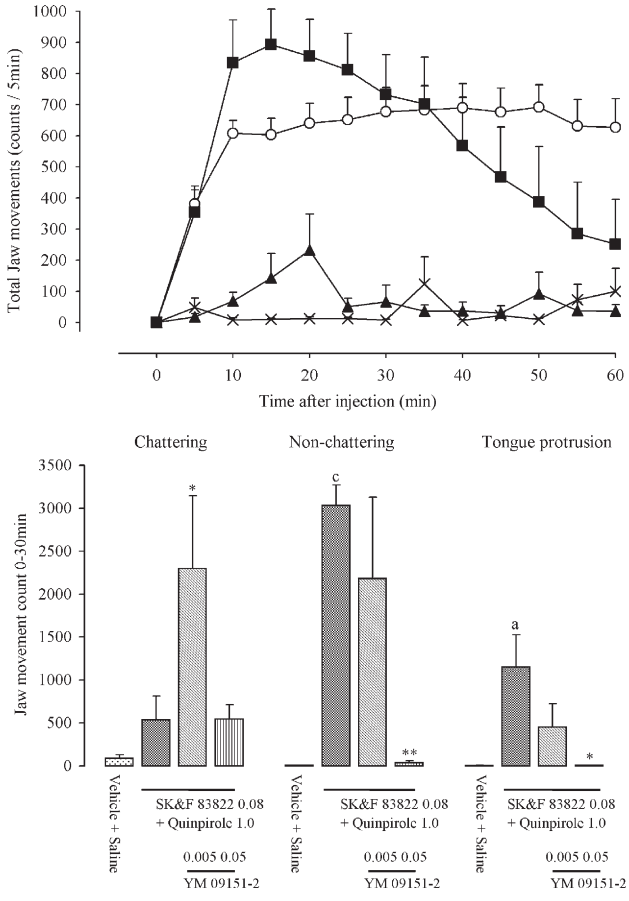

Fig. 3. Upper panel: total jaw movements following injection of vehicle (×) or SK&F 83822 [0.08 mg/kg i.v] given in combination with quinpirole [1.0 mg/kg i.v.] (○) and the effects of 30 min pretreatment with 0.005 mg/kg (■) and 0.05 mg/kg (▲)YM 09151-2; data are mean counts±S.E.M. of $n=6$ animals per group in successive 5 min periods over 60 min. Lower panel: jaw movements following injection of vehicle or SK&F 83822 [0.08 mg/kg i.v.] given in combination with quinpirole [1.0 mg/kg i.v.] and the effects of 30 min pretreatment with YM 09151-2 [0.005–0.05 mg/kg i.v.]; data are mean counts ±S.E.M. of $n=6$ animals per group over a period of 0–30 min for chattering, non-chattering movements and tongue protrusions (for data over 30–60 min, see text and Fig. 2). $^{a}P\leq0.05$, $^{b}P<0.01$, $^{c}P<0.001$ vs. vehicle; $*P\leq0.05$, $**P<0.01$, $***P<0.001$ vs. SK&F 83822 in combination with quinpirole.

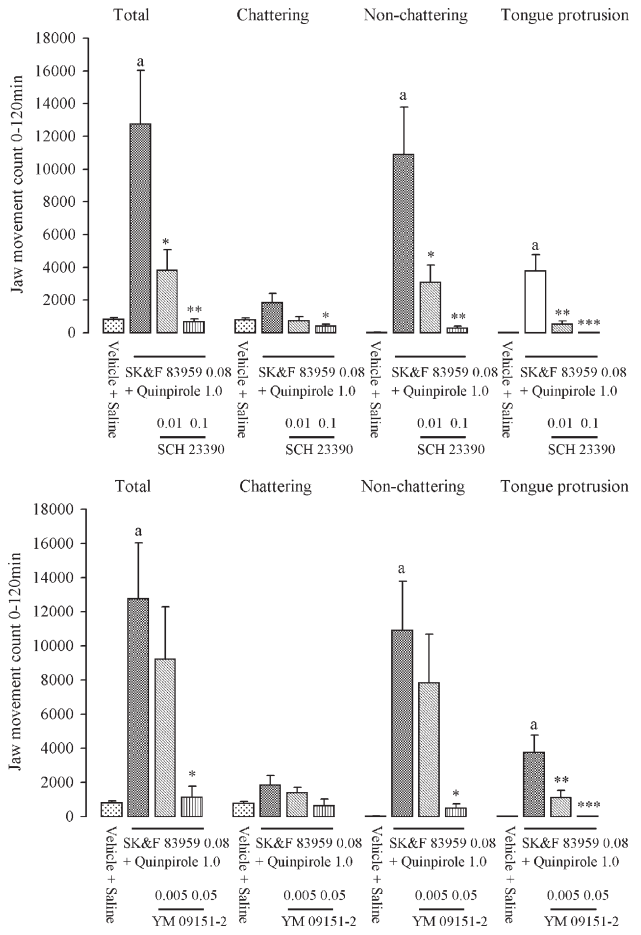

Fig. 4. Jaw movements following injection of vehicle or SK&F 83959 [0.08 mg/kg i.v.] in combination with quinpirole [1.0 mg/kg i.v.] and the effects of 30 min pretreatments with SCH 23390 [0.01–0.1 mg/kg i.v.] or YM 09151-2 [0.005-0.05 mg/kg i.v.]. Data are mean counts ± S.E.M. of $n = 6$–10 animals per group over a period of 0–120 min for total jaw movements, chattering, non-chattering movements and tongue protrusions. $^{a}P \leq 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ vs. vehicle; $*P \leq 0.05$, $**P < 0.01$, $***P < 0.001$ vs. SK&F 83959 in combination with quinpirole.

quinpirole [1.0 mg/kg i.v.] across the duration of action of this agonist combination (Fig. 4).

4. Discussion

SK&F 83822 and SK&F 83959 are selective dopamine D_1-like receptor agonists that we have reported to have very similar potencies for stimulating a wide range of general behaviours in rodents. More specifically, in the present study the dose utilised for each of these drugs has been shown to induce very similar levels of sniffing, locomotion, rearing and sifting, indicating equivalent potencies (O'Sullivan et al., 2004, 2005, 2006). Here, we find SK&F 83822, which stimulates AC but not PI hydrolysis (see Section 1), to induce orofacial movements, primarily jaw movements, with a characteristic topography: these involve essentially chattering, together with some non-chattering movements and a modest number of tongue protrusions. Conversely, in confirmation of our initial report (Adachi et al., 1999), we find SK&F 83959, which stimulates PI hydrolysis but not AC, to exert a small effect on jaw movements.

The primary effect of SK&F 83822 to induce chattering was blocked by the selective dopamine D_1-like receptor antagonist SCH 23390. This confirms the involvement of dopamine D_1-like receptors in these actions of SK&F 83822. The selective dopamine D_2-like receptor antagonist YM 09151-2, whose potency to inhibit a range of general behaviours in rodents is similar to that of SCH 23390 (McNamara et al., 2003; O'Sullivan et al., 2004), was without consistent effect. This indicates only minimal involvement of dopamine D_1-like:D_2-like receptor interactions in these processes in the rat. We have found that YM 09151-2 can cause some 'release' of *vacuous chewing* in response to SK&F 83822 in mice (O'Sullivan et al., 2004). This is consistent with (i) the participation of oppositional dopamine D_1-like:D_2-like receptor interactions that have been reported previously to regulate *vacuous chewing* in the rat (Murray and Waddington, 1989; Waddington et al., 1994; Niznik et al., 2002) and (ii) release of dopamine D_1-like receptor-mediated stimulation of AC from dopamine D_2-like receptor-mediated inhibition (Niznik et al., 2002). However, the relationship between *vacuous chewing*, a composite of orofacial movements assessed by direct visual observation, and topographically specific jaw movements, assessed quantitatively, remains to be determined. Individual topographies of orofacial movement, both in intact mice and in mutant mice with dopamine receptor subtype 'knockout', appear to involve different dopamine receptor mechanisms (Tomiyama et al., 2001, 2002, 2004; Waddington et al., 2001, 2005). The present study is the first to resolve quantitatively individual topographies of such movements in the rat.

Administration of SK&F 83822 in combination with the dopamine D_2-like receptor agonist quinpirole resulted in the synergistic induction of intense jaw movements. However, while SK&F 83822 alone induced essentially chattering together with some non-chattering movements and a modest number of tongue protrusions, SK&F 83822 in synergism with quinpirole now induced primarily non-chattering movements together with prominent tongue protrusions but little chattering. Thus, dopamine D_1-like:D_2-like receptor synergism involves a change in the qualitative as well as the quantitative expression of jaw movements. This synergistic shift from primarily chattering movements without tongue protrusions to primarily non-chattering movements with tongue protrusions illustrates the importance of topographical resolution. It indicates how assessing such behaviours using composite terms such as *vacuous chewing* or *total jaw movements* can obscure topographically specific effects. How these topographies of orofacial movement relate to stereotyped biting and gnawing in intact animals is not clear.

These topographical effects of SK&F 83822 in synergism with quinpirole were readily blocked by SCH 23390. This confirms the involvement of dopamine D_1-like receptors in these actions of SK&F 83822. In contrast, there was a biphasic effect of a low dose of YM 09151-2: chattering was initially enhanced but antagonised thereafter. This indicates the initial involvement of oppositional dopamine D_1-like:D_2-like receptor

interactions, which may again involve release of dopamine D_1-like receptor-mediated stimulation of AC from dopamine D_2-like receptor-mediated inhibition (Niznik et al., 2002).

However, two anomalies are apparent. Firstly, the induction of non-chattering movements and tongue protrusions by SK&F 83822 given together with quinpirole involves synergistic dopamine D_1-like:D_2-like receptor interactions. Conversely, induction of chattering appears to be at least partially regulated by oppositional dopamine D_1-like:D_2-like receptor interactions. This suggests that these distinct topographies of jaw movement are mechanistically distinct in terms of differential regulation by dopamine D_1-like:D_2-like receptor interactions.

Secondly, at least initially, YM 09151-2 appears to release chattering movements by blocking dopamine D_2-like receptors involved in oppositional dopamine D_1-like:D_2-like receptor interactions. Yet it does *not* block dopamine D_2-like receptors involved in synergistic dopamine D_1-like:D_2-like receptor interactions. This suggests that dopamine D_2-like receptors involved in oppositional dopamine D_1-like:D_2-like receptor interactions differ pharmacologically in some way from those involved in synergistic dopamine D_1-like:D_2-like receptor interactions. These differences may involve either differential sensitivity to antagonism at anatomically distinct sites, or differential involvement of dopamine D_2, D_3 or D_4 receptors. A higher dose of YM 09151-2 only blocked topographical jaw movement responses to SK&F 83822 given with quinpirole. This likely reflects overriding antagonism of the actions of quinpirole. However, some involvement of non-dopaminergic receptors cannot be excluded. For example, YM 09151-2 has some agonist activity at serotonergic 5-HT_{1A} receptors (Assié et al., 1997). As for most such studies, our current level of understanding means that it is not yet possible to account for all of the complex effects and interactions encountered.

SK&F 83959 exhibited both similarities to and differences from SK&F 83822 following coadministration with quinpirole. Both of these dopamine D_1-like receptor agonists shared a synergistic induction of non-chattering jaw movements with tongue protrusions that was readily blocked by SCH 23390. However, at no dose or time point did YM 09151-2 release chattering to SK&F 83959 in combination with quinpirole.

Interpretations are predicated on four factors. Firstly, the potency equivalence of SK&F 83822 and SK&F 83959, and of SCH 23390 and YM 09151-2, at the doses used. We have described above the evidence that these agents have similar potencies. Secondly, we cannot exclude incontrovertibly some pharmacokinetic interaction between the drugs or the anaesthetic used. These issues apply to all studies of this type. Thirdly, our understanding of the differential pharmacology of SK&F 83822 vis-à-vis SK&F 83959, particularly at a cellular level, is incomplete. SK&F 83822 stimulates AC but not PI hydrolysis, while SK&F 83959 stimulates PI hydrolysis but not AC. However, SK&F 83959 has some activity to inhibit AC and there may also be interactions between AC- and PI-coupled receptors (Undie and Freidman, 1990; Undie et al., 1994; Panchalingam and Undie, 2001; Cools et al., 2002; Niznik et al., 2002; Jin et al., 2003; O'Sullivan et al., 2004).

Finally, our understanding of dopamine D_1-like receptors coupling to AC vis-à-vis PI is incomplete. There may be distinct dopamine D_1-like receptors utilising different signalling cascades which demonstrate G-protein subunit-coupling specificity. Thus, $G\alpha_s$ and $G\alpha_q$ could be linked to activation of AC and PI hydrolysis, respectively (Panchalingam and Undie, 2001; Niznik et al., 2002; Jin et al., 2003). Alternatively, cloned dopamine D_1-like receptors identified to date may demonstrate autonomous coupling to diverse signalling cascades in a response-specific manner (Montague et al., 2001; Niznik et al., 2002). Recent studies (Lezcano et al., 2000) have isolated a dopamine D_1 receptor-interacting transmembrane protein, designated calcyon, that appears capable of regulating G-protein crosstalk. Thus, D_1 receptors may shift effector coupling between $G\alpha_s$ and $G\alpha_q$, and might function as a molecular switch enabling reciprocal signalling through AC or PI pathways at individual D_1 receptors.

Subject to these challenges, the present findings indicate that both AC- and PI-coupled dopamine D_1-like receptors can participate in synergistic dopamine D_1-like:D_2-like receptor interactions. However, there is a complex profile of concurrent, topographically specific synergistic and oppositional D_1-like:D_2-like interactions evident with SK&F 83822 in combination with quinpirole. This appears to reflect the involvement primarily of dopamine D_1-like receptors coupled to AC rather than PI. Thus, distinct topographies of jaw movement appear to be regulated differentially by AC- vs. PI-coupled dopamine D_1-like receptor mechanisms and their interactions with dopamine D_2-like receptors. These findings may be relevant for the pathogenesis and treatment of conditions characterised by orofacial movement disorder, such as tardive dyskinesia and Huntington's disease, where inter alia abnormalities of dopaminergic function are implicated.

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References

Adachi, K., Ikeda, H., Hasegawa, M., Nakamura, S., Waddington, J.L., Koshikawa, N., 1999. SK&F 83959 and non-cyclase-coupled dopamine D_1-like receptors in jaw movements via dopamine D_1-like/D_2-like receptor synergism. Eur. J. Pharmacol. 367, 143–149.

Adachi, K., Hasegawa, M., Fujita, S., Lee, J., Cools, A.R., Waddington, J.L., Koshikawa, N., 2003. Prefrontal, accumbal [shell] and ventral striatal

mechanisms in jaw movements and non-cyclase-coupled dopamine D_1-like receptors. Eur. J. Pharmacol. 473, 47–54.

Andersen, P.H., Jansen, J.A., 1990. Dopamine receptor agonists: selectivity and dopamine D_1 receptor efficacy. Eur. J. Pharmacol. 188, 335–347.

Assié, M.B., Cosi, C., Koek, W., 1997. 5-HT_{1A} receptor agonist properties of the antipsychotic, nemonapride: comparison with bromerguride and clozapine. Eur. J. Pharmacol. 334, 141–147.

Cools, A.R., Lubbers, L., van Oosten, R.V., Andringa, G., 2002. SKF 83959 is an antagonist of dopamine D_1-like receptors in the prefrontal cortex and nucleus accumbens: a key to its antiparkinsonian effect in animals? Neuropharmacology 42, 237–245.

Hasegawa, M., Adachi, K., Nakamura, S., Sato, M., Waddington, J.L., Koshikawa, N., 2001. Ventral striatal vs. accumbal (shell) mechanisms and non-cyclase-coupled dopamine D_1-like receptors in jaw movements. Eur. J. Pharmacol. 423, 171–178.

Jin, L.Q., Goswami, S., Cai, G., Zhen, X., Friedman, E., 2003. SKF83959 selectively regulates phosphatidylinositol-linked D_1 dopamine receptors in rat brain. J. Neurochem. 85, 378–386.

Koshikawa, N., Tomiyama, K., Omiya, K., Kobayashi, M., 1988. Ketamine anaesthesia has no effect on striatal dopamine metabolism in rats. Brain Res. 444, 394–396.

Koshikawa, N., Aoki, S., Hiruta, M., Tomiyama, K., Kobayashi, M., Tsuboi, Y., Iwata, K., Sumino, R., Stephenson, J.D., 1989. Effects of intrastriatal injections of selective dopamine D-1 and D-2 agonists and antagonists on jaw movements of rats. Eur. J. Pharmacol. 163, 227–236.

Koshikawa, N., Kikuchi de Beltrán, K., Tomiyama, K., Kobayashi, M., Cools, A.R., 1991. Functional interaction between dopamine D_1 and D_2 receptors in rat jaw movements. Eur. J. Pharmacol. 201, 47–51.

Lee, J., Adachi, K., Gionhaku, N., Fujita, S., Uchida, T., Koshikawa, N., 2003. Measurement of dopamine receptor-mediated jaw movements by a magnet-sensing system in freely moving rats. Methods Find. Exp. Clin. Pharmacol. 25, 525–530.

Lezcano, N., Mrzljak, L., Eubanks, S., Levenson, R., Goldman-Rakic, P., Bergson, C., 2000. Dual signaling regulated by calcyon, a D_1 dopamine receptor interacting protein. Science 287, 1660–1664.

Mahan, L.C., Burch, R.M., Monsma Jr., F.J., Sibley, D.R., 1990. Expression of striatal D_1 dopamine receptors coupled to inositol phosphate production and Ca^{2+} mobilization in *Xenopus* oocytes. Proc. Natl. Acad. Sci. U. S. A. 87, 2196–2200.

Makihara, Y., Yamamoto, H., Inoue, M., Tomiyama, K., Koshikawa, N., Waddington, J.L., 2004. Topographical effects of D_1-like dopamine receptor agonists on orofacial movements in mice and their differential regulation via oppositional versus synergistic D_1-like: D_2-like interactions: cautionary observations on SK&F 82958 as an anomalous agent. J. Psychopharmacol. 18, 484–495.

McNamara, F.N., Clifford, J.J., Tighe, O., Kinsella, A., Drago, J., Croke, D.T., Waddington, J.L., 2003. Congenic D_{1A} dopamine receptor mutants: ethologically based resolution of behavioural topography indicates genetic background as a determinant of knockout phenotype. Neuropsychopharmacology 28, 86–99.

Montague, D.M., Striplin, C.D., Overcash, J.S., Drago, J., Lawler, C.P., Mailman, R.B., 2001. Quantification of D_{1B}(D_5) receptors in dopamine D_{1A} receptor-deficient mice. Synapse 39, 319–322.

Murray, A.M., Waddington, J.L., 1989. The induction of grooming and vacuous chewing by a series of selective D-1 dopamine receptor agonists: two directions of D-1:D-2 interaction. Eur. J. Pharmacol. 160, 377–384.

Niznik, H.B., Sugamori, K.S., Clifford, J.J., Waddington, J.L., 2002. D_1-like dopamine receptors: molecular biology and pharmacology. In: Di Chiara, G. (Ed.), Handbook of Experimental Pharmacology: Dopamine in the CNS. Springer, Heidelberg, pp. 122–158.

O'Sullivan, G.J., Roth, B.L., Kinsella, A., Waddington, J.L., 2004. SK&F 83822 distinguishes adenylyl cyclase from phospholipase C-coupled dopamine D_1-like receptors: behavioural topography. Eur. J. Pharmacol. 486, 273–280.

O'Sullivan, G.J., Kinsella, A., Sibley, D.R., Tighe, O., Croke, D.T., Waddington, J.L., 2005. Ethological resolution of behavioural topography and D_1-like versus D_2-like agonist responses in congenic D_5 dopamine receptor mutants: identification of D_5:D_2-like interactions. Synapse 55, 201–211.

O'Sullivan, G.J., Kinsella, A., Grandy, D.K., Tighe, O., Croke, D.T., Waddington, J.L., 2006. Ethological resolution of behavioral topography and D_2-like versus D_1-like agonist responses in congenic D_4 dopamine receptor 'knockouts': identification of D_4:D_1-like interactions. Synapse 59, 107–118.

Panchalingam, S., Undie, A.S., 2001. SKF83959 exhibits biochemical agonism by stimulating [(^{35})S]GTP(S binding and phosphoinositide hydrolysis in rat and monkey brain. Neuropharmacology 40, 826–837.

Peacock, L., Gerlach, J., 2001. Aberrant behavioral effects of a dopamine D_1 receptor antagonist and agonist in monkeys: evidence of uncharted dopamine D_1 receptor actions. Biol. Psychiatry 50, 501–509.

Tomiyama, K., McNamara, F.N., Clifford, J.J., Kinsella, A., Koshikawa, N., Waddington, J.L., 2001. Topographical assessment and pharmacological characterization of orofacial movements in mice: dopamine D_1-like vs. D_2-like receptor regulation. Eur. J. Pharmacol. 418, 47–54.

Tomiyama, K., McNamara, F.N., Clifford, J.J., Kinsella, A., Drago, J., Tighe, O., Croke, D.T., Koshikawa, N., Waddington, J.L., 2002. Phenotypic resolution of spontaneous and D_1-like agonist-induced orofacial movement topographies in congenic dopamine D_{1A} receptor 'knockout' mice. Neuropharmacology 42, 644–652.

Tomiyama, K., McNamara, F.N., Clifford, J.J., Kinsella, A., Drago, J., Fuchs, S., Grandy, D.K., Low, M.J., Rubinstein, M., Tighe, O., Croke, D.T., Koshikawa, N., Waddington, J.L., 2004. Comparative phenotypic resolution of spontaneous, D_2-like and D_1-like agonist-induced orofacial movement topographies in congenic mutants with dopamine D_2 vs. D_3 receptor "knockout". Synapse 51, 71–81.

Undie, A.S., Friedman, E., 1990. Stimulation of a dopamine D_1 receptor enhances inositol phosphate formation in rat brain. J. Pharmacol. Exp. Ther. 253, 987–992.

Undie, A.S., Weinstock, J., Sarau, H.M., Friedman, E., 1994. Evidence for a distinct D_1-like dopamine receptor that couples to activation of phosphoinositide metabolism in brain. J. Neurochem. 62, 2045–2048.

Undie, A.S., Berki, A.C., Beardsley, K., 2000. Dopaminergic behaviors and signal transduction mediated through adenylate cyclase and phospholipase C pathways. Neuropharmacology 39, 75–87.

Waddington, J.L., Molloy, A.G., O'Boyle, K.M., Mashurano, M., 1986. Enantiomeric analogues of SCH 23390 as new probes for behavioral interactions between D_1 and D_2 dopaminergic function. Adv. Exp. Med. Biol. 204, 125–136.

Waddington, J.L., Daly, S.A., McCauley, P.G., O'Boyle, K.M., 1994. Levels of functional interaction between D_1-like and D_2-like dopamine receptor systems. In: Niznik, H.B. (Ed.), Dopamine Receptors and Transporters: Pharmacology, Structure and Function. Marcel-Dekker, New York, NY, pp. 511–537.

Waddington, J.L., Daly, S.A., Downes, R.P., Deveney, A.M., McCauley, P.G., O'Boyle, K.M., 1995. Behavioural pharmacology of "D_1-like" dopamine receptors: further subtyping, new pharmacological probes and interactions with "D_2-like" receptors. Prog. Neuro-psychopharmacol. Biol. Psychiatry 19, 811–831.

Waddington, J.L., Clifford, J.J., McNamara, F.N., Tomiyama, K., Koshikawa, N., Croke, D.T., 2001. The psychopharmacology–molecular biology interface: exploring the behavioural roles of dopamine receptor subtypes using targeted gene deletion ['knockout']. Prog. Neuro-psychopharmacol. Biol. Psychiatry 25, 925–964.

Waddington, J.L., O'tuathaigh, C., O'sullivan, G., Tomiyama, K., Koshikawa, N., Croke, D.T., 2005. Phenotypic studies on dopamine receptor subtype and associated signal transduction mutants: insights and challenges from 10 years at the psychopharmacology–molecular biology interface. Psychopharmacology 181, 611–638.