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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

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Abstract

This study compared the effects of the dopamine D_1-like receptor agents SK&F 83959 (3-methyl-6-chloro-7,8-dihydroxy-1-[3-methylphenyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine), which inhibits the stimulation of adenylyl cyclase, and A 68930 ([1*R*,3*S*]-1-aminomethyl-5,6-dihydroxy-3-phenylisochroman), a full efficacy agonist, in regulating jaw movements in the rat by synergism with dopamine D_2-like receptor agonism. When SK&F 83959 and A 68930 were given in combination with quinpirole, there was a synergistic induction of jaw movements. Responsivity to SK&F 83959 + quinpirole was antagonised by the dopamine D_1-like receptor antagonists SCH 23390 ([*R*]-3-methyl-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine) and BW 737C ([*S*]-6-chloro-1-[2,5-dimethoxy-4-propylbenzyl]-7-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline); synergism was antagonised also by 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). Responsivity to A 68930 + quinpirole was enhanced by low doses of SCH 23390, BW 737C and YM 09151-2, and antagonised by higher doses of SCH 23390 and YM 09151-2. These results implicate a novel, dopamine D_1-like receptor that is coupled to a transduction system other than/additional to adenylyl cyclase, and suggest that its functional role extends to the regulation of jaw movements by synergistic interactions with dopamine D_2-like receptors.

Keywords: Dopamine D_1-like receptor; Adenylyl cyclase; Dopamine D_1-like receptor, non-cyclase-coupled; Jaw movement; SK&F 83959; A 68930; SK&F 38393; Quinpirole; (Rat)

1. Introduction

Though the cellular biology of the dopamine D_1-like receptor family [$D_{1A/B/C/D}$] has been widely studied, many of the findings are related intimately to the molecular biological origins of such subtyping and to the criteria by which dopamine D_1-like receptors have been defined conventionally in terms of linkage to the stimulation of adenylyl cyclase (Jaber et al., 1996). Over the past several years an increasing body of classical, non-molecular evidence has emerged to indicate the existence of an additional dopamine D_1-like receptor that is coupled not to adenylyl cyclase but to an alternative or additional transduction system, with phosphoinositide hydrolysis being the most widely studied candidate (Mahan et al., 1990; Undie and Friedman, 1990; Undie et al., 1994). However, any role for such a site at other levels of function is poorly understood. At the levels of behaviour and electrophysiology, several responses to dopamine D_1-like receptor agonists appear unrelated to their varying efficacies to stimulate adenylyl cyclase (Murray and Waddington, 1989; Johansen et al., 1991; Waddington et al., 1995, 1998) but such data are far from conclusive in implicating a functional role for a dopamine D_1-like receptor having an alternative transduction system.

Recently, functional effects of the anomalous dopamine D_1-like receptor agent SK&F 83959 have been described. This agent shows high affinity and selectivity for dopamine D_1-like over D_2-like receptors, fails to stimulate adenylyl cyclase and inhibits the stimulation of adenylyl cyclase induced by dopamine, and thus shows all the defining characteristics of a dopamine D_1-like receptor antagonist (Arnt et al., 1992; Deveney and Waddington, 1995). Yet

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its behavioural profile is similar to that of a wide range of dopamine D_1-like receptor agonist analogues of SK&F 38393 having from low to high efficacies to stimulate adenylyl cyclase; more specifically, similar to the highly potent and selective full efficacy dopamine D_1-like receptor agonist A 68930, SK&F 83959 readily induces grooming and vacuous chewing, and therefore appears to induce these responses through a dopamine D_1-like receptor that is not associated with adenylyl cyclase (Deveney and Waddington, 1995; Waddington et al., 1998). In order to clarify further the actions of this agent, we have studied its effects in a well-characterised behavioural model for the regulation of jaw movements by synergism between dopamine D_1-like and D_2-like receptor activation such as can be induced with SK&F 38393 and quinpirole, respectively, on their co-administration (Koshikawa et al., 1991). The effects of SK&F 83959 were compared with those of A 68930, each in combination with quinpirole, and we examined their sensitivities to the dopamine D_1-like receptor antagonists SCH 23390 and BW 737C, and to the dopamine D_2-like receptor antagonist YM 09151-2. As this model is distinct both phenomenologically and physiologically from more naturalistic dopamine D_1-like receptor agonist-induced vacuous chewing (Koshikawa et al., 1991; Deveney and Waddington, 1995), it might identify effects involving a dopamine D_1-like receptor not linked to adenylyl cyclase in terms of alternative functional responses.

2. Materials and methods

2.1. Surgical procedures

Male Sprague–Dawley rats weighing 260–330 g were housed in cages (27 × 45 × 20 cm) that were placed in a temperature-controlled (24 ± 2°C) environment under a 12 h light/dark cycle (lights on at 0700 h), with free access to food and water.

Rats were anaesthetized 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). 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 mg/h i.p.) continuously, the dose is in a range that fails to influence the jaw movements elicited by co-activation of dopamine D_1-like and D_2-like receptors (Koshikawa et al., 1989) and dopamine metabolism in the striatum (Koshikawa et al., 1988). Lidocaine (2.0% gel) was applied to all incisions to ensure complete analgesia. The rectal temperature was maintained at 37.0°C with a thermostatically controlled heating pad. Monitored concentrations of expired O_2 and CO_2 during experiment 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 automatically analysed, using a spike trigger that counted the vertical jaw movements per 5 min. After each experiment, rats were deeply anaesthetized with pentobarbital (80 mg/kg i.p.) and sacrificed. The experiments were approved by the Animal Experimentation Committee at 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. Drugs

The drugs used were: SK&F 83959 (3-methyl-6-chloro-7,8-dihydroxy-1-[3-methylphenyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine; Research Biochemicals International/NIMH Chemical Synthesis Program, USA); A 68930 ([1*R*,3*S*]-1-aminomethyl-5,6-dihydroxy-3-phenylisochroman; Abbott, USA), [*R*]-SK&F 38393 (7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; Research Biochemicals International, USA); quinpirole (Research Biochemicals International, USA); SCH 23390 ([*R*]-3-methyl-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; Research Biochemicals International, USA); BW 737C ([*S*]-6-chloro-1-[2,5-dimethoxy-

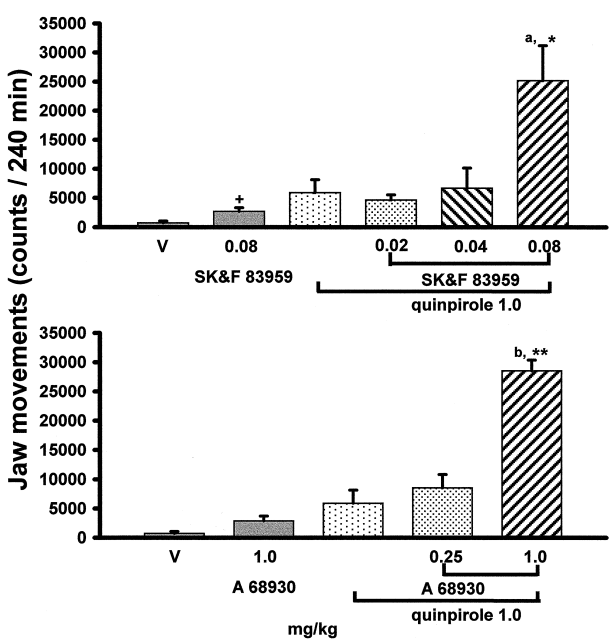

Fig. 1. Jaw movement counts over 240 min of quantification, following i.v. administration of vehicle (V), 0.08 mg/kg SK&F 83959, 1.0 mg/kg A 68930, 1.0 mg/kg quinpirole, 1.0 mg/kg quinpirole + 0.02–0.08 mg/kg SK&F 83959, and 1.0 mg/kg quinpirole + 0.25–1.0 mg/kg A 68930. Data are mean counts ± S.E.M. of $n = 6$–8 animals per group. $^{+}P < 0.05$ vs. vehicle; $^{a}P < 0.05$, $^{b}P < 0.01$ vs. SK&F 83959 or A 68930 alone; $*\ P < 0.05$, $**\ P < 0.01$ vs. quinpirole alone.

4-propylbenzyl]-7-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline; Glaxo-Wellcome, UK); YM 09151-2 (*cis*-*N*-[1-benzyl-2-methyl-pyrrolidin-3-yl]-5-chloro-2-methoxy-4-methylaminobenzamide; Yamanouchi, Japan). SK & F 83959, A 68930, SK&F 38393, SCH 23390 and BW 737C were dissolved in saline; YM 09151-2 was dissolved in dilute HCl and made up to volume with saline; all drugs were given i.v. via the jugular cannula, with antagonists given 30 min prior to agonists.

2.3. Data analysis

All values are expressed as means ± S.E.M. and analysed using one-way analysis of variance followed by a

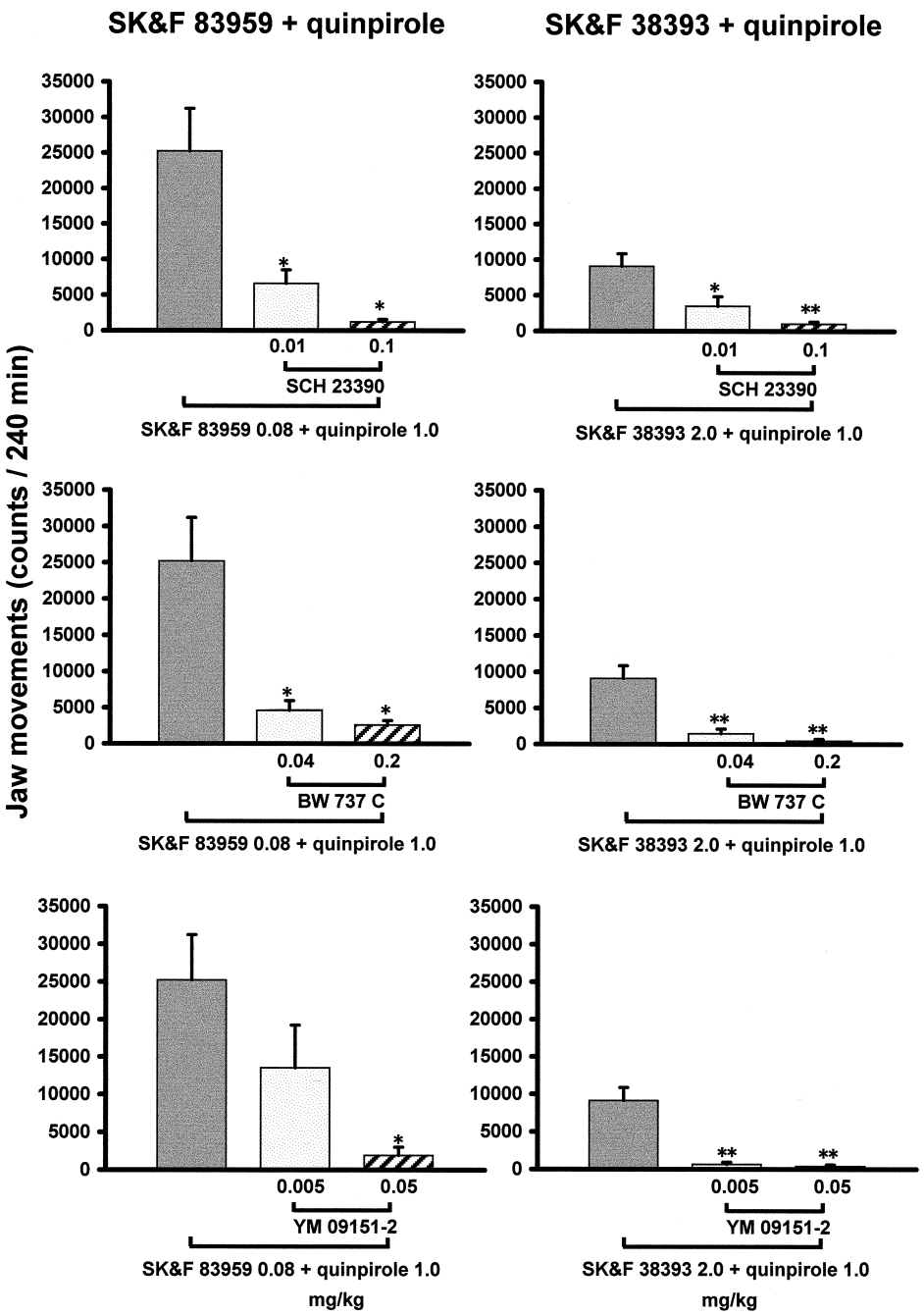

Fig. 2. Jaw movement counts over 240 min of quantification following i.v. co-administration of 0.08 mg/kg SK&F 83959 + 1.0 mg/kg quinpirole, and 2.0 mg/kg SK&F 38393 + 1.0 mg/kg quinpirole, with 0.01–0.1 mg/kg SCH 23390, 0.04–0.2 mg/kg BW 737C, or 0.005–0.05 mg/kg YM 09151-2 given 30 min before agonist co-administration. Data are mean counts ± S.E.M. of $n = 6$–10 animals per group. $*P < 0.05$, $**P < 0.01$ vs. agonist co-administration.

post-hoc Student's *t*-test where appropriate. A probability level of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Effects of SK&F 83959 and A 68930, alone and in combination with quinpirole

When given alone, SK&F 83959 (0.08 mg/kg) induced a modest level of jaw movements, while A 68930 (1.0 mg/kg) and quinpirole (1.0 mg/kg) each induced only a weak level of jaw movements ($P < 0.1$), relative to vehicle-treated controls. However, when SK&F 83959 (0.02–0.08 mg/kg) and A 68930 (0.25–1.0 mg/kg) were each given in combination with quinpirole (1.0 mg/kg) there was a synergistic induction of prominent jaw movements; effects were observed consistently over 240 min of quantification, hence cumulative measures over this period are given (Fig. 1). These jaw movement responses were qualitatively indistinguishable, and were similar to those

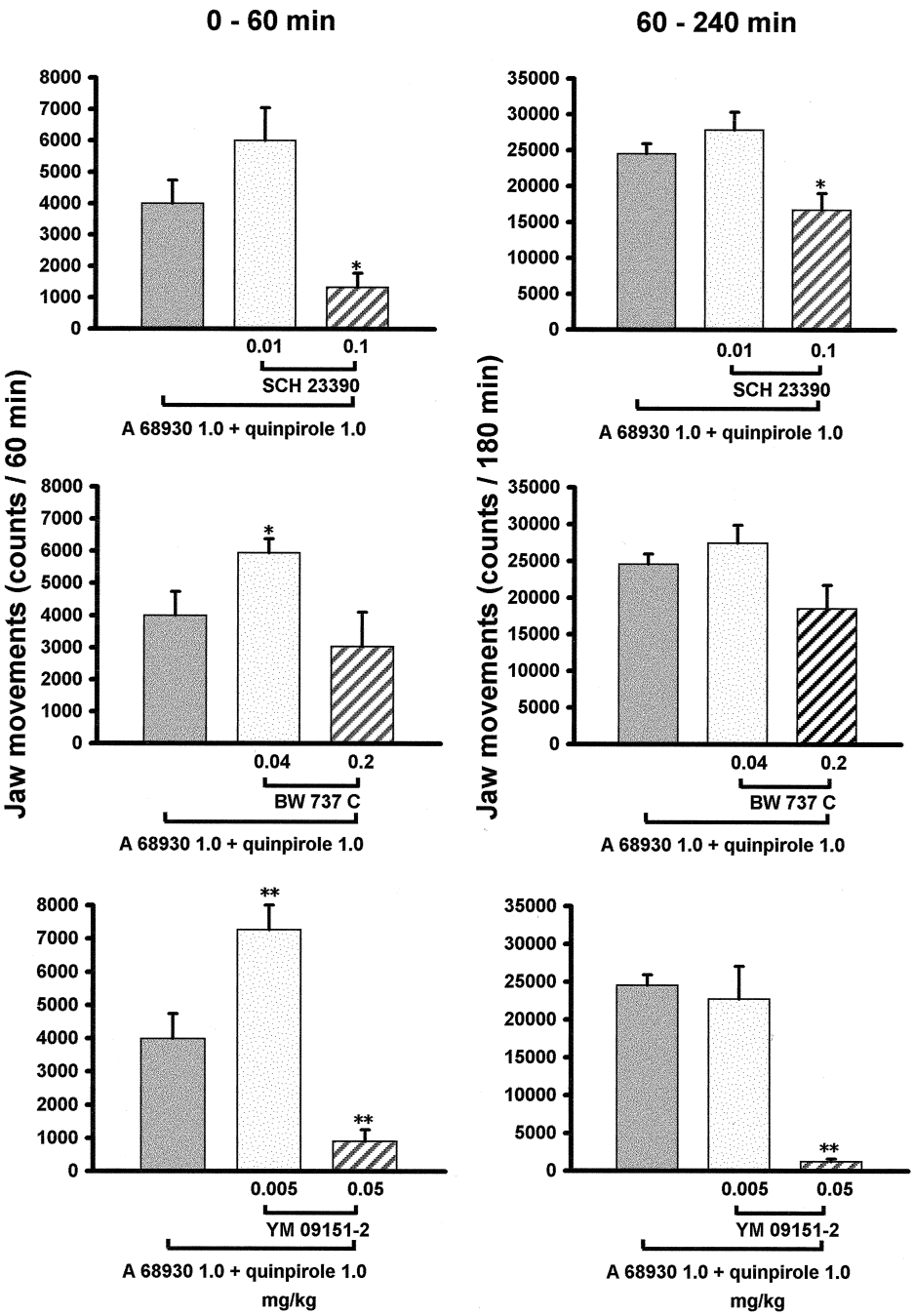

Fig. 3. Jaw movement counts following i.v. co-administration of 1.0 mg/kg A 68930 + 1.0 mg/kg quinpirole, with 0.01–0.1 mg/kg SCH 23390, 0.04–0.2 mg/kg BW 737C, or 0.005–0.05 mg/kg YM 09151-2 given 30 min before agonist co-administration. Data are mean counts ± S.E.M. of $n = 6–7$ animals per group, given separately for 0–60 min and 60–240 min of quantification. $*\ P < 0.05$, $**\ P < 0.01$ vs. agonist co-administration.

induced by SK&F 38393 (2.0 mg/kg) + quinpirole (1.0 mg/kg).

3.2. Effects of antagonists on responsivity to SK&F 83959 and A 68930 in combination with quinpirole

The jaw movement response to SK&F 83959 (0.08 mg/kg) + quinpirole (1.0 mg/kg) was readily and dose-dependently antagonised by 0.01–0.1 mg/kg SCH 23390 and by 0.04–0.2 mg/kg BW 737C; responsivity was also antagonised by 0.005–0.05 mg/kg YM 09151-2. These effects were observed consistently over the 240 min of quantification, hence cumulative measures over this period are given. A similar profile was seen for the effects of these same antagonist doses on responsivity to SK&F 38393 (2.0 mg/kg) + quinpirole (1.0 mg/kg) (Fig. 2).

In contrast, the effects of these same doses of antagonists on jaw movement responsivity to A 68930 (1.0 mg/kg) + quinpirole (1.0 mg/kg) were more complex. Responsivity tended to be enhanced by 0.01 mg/kg ($P = 0.1$), particularly over the first hour of quantification following agonist co-treatment, but was antagonised by 0.1 mg/kg SCH 23390. With BW 737C, responsivity was enhanced by a low dose of 0.04 mg/kg, particularly over the first hour, but little antagonised by 0.2 mg/kg. Responsivity was enhanced by 0.005 mg/kg YM 09151-2 over the first hour, but was blocked by 0.05 mg/kg YM 09151-2 throughout the period of quantification (Fig. 3).

4. Discussion

In the behavioural model utilised here, individual stimulation of dopamine D_1-like and of dopamine D_2-like receptors induces only weak jaw movements, while their co-activation produces an almost continuous pattern of jaw movements that differs both in topography and intensity from movements associated with stimulation of either receptor family alone; it was developed (Koshikawa et al., 1991) using SK&F 38393 and quinpirole as prototypical dopamine D_1-like and D_2-like receptor agonists, respectively, and has its basis in well-described co-operative/synergistic dopamine D_1-like:D_2-like receptor interactions that regulate multiple aspects of mammalian psychomotor behaviour (Waddington et al., 1995, 1998). We now describe the benzazepine dopamine D_1-like receptor agent SK&F 83959 to induce only a modest extent of jaw movements when given alone, similar to those produced by SK&F 38393 (Koshikawa et al., 1991); however, SK&F 83959 synergises prominently with quinpirole in a manner very similar not only to SK&F 38393 (Koshikawa et al., 1991) but also to the isochroman dopamine D_1-like receptor agonist A 68930.

This common action of SK&F 83959, A 68930 and SK&F 38393 is, however, in marked contrast to their radically different actions on dopamine-sensitive adenylyl cyclase. More specifically, SK&F 83959 shows high selectivity for dopamine D_1-like over D_2-like receptors, at which it fails to stimulate adenylyl cyclase and inhibits the stimulation of adenylyl cyclase induced by dopamine; it thus evidences all the classical defining characteristics of a dopamine D_1-like receptor antagonist such as SCH 23390 (Arnt et al., 1992; Deveney and Waddington, 1995). Thus, its common action with A 68930, a highly selective dopamine D_1-like receptor agonist with full efficacy to stimulate adenylyl cyclase (DeNinno et al., 1991; Daly and Waddington, 1993), and SK&F 38393, a partial agonist, would indicate these effects not to have their basis in any dopamine D_1-like receptor linked to cyclase stimulation, though an alternative explanation that several subtypes of dopamine D_1-like receptors including one linked to cyclase are involved in the dopamine D_1-like:D_2-like receptor synergism cannot be excluded. This conclusion is in accordance with our recent findings (Deveney and Waddington, 1995, 1996, 1997) that, when given alone, SK&F 83959 and A 68930 each induce both grooming, the most widely accepted behavioural index of dopamine D_1-like receptor activation (Molloy and Waddington, 1984; Wachtel et al., 1992; Waddington et al., 1995, 1998) and vacuous chewing, another putative behavioural index thereof that is both phenomenologically and physiologically different from the pattern of jaw movements studied here (Rosengarten et al., 1986; Murray and Waddington, 1989; Collins et al., 1991; Waddington et al., 1995, 1998).

It should be emphasised that the present responses to i.v. SK&F 83959, like those following s.c. administration, have a rapid onset that is inconsistent with the generation of an active metabolite of SK&F 83959 which might have fundamentally different pharmacological actions; this would be in accordance with known metabolic profiles and structure-activity relationships within the benzazepine series (Weinstock et al., 1985; Arnt et al., 1992; Deveney and Waddington, 1995). These effects did not appear to be idiosyncratic to benzazepines, as the SK&F 83959 component of synergism was antagonised also by the isoquinoline BW 737C which, like SCH 23390, selectively blocks the stimulation of adenylyl cyclase induced by dopamine (Riddall, 1992).

We also studied the pharmacological characteristics of the sites mediating the present responses using a series of dopamine receptor subtype antagonists. The synergistic interaction between SK&F 83959 and quinpirole was antagonised by SCH 23390; as SK&F 83959 and SCH 23390 share high, selective affinity for dopamine D_1-like over D_2-like receptors and similar actions to inhibit the stimulation of adenylyl cyclase induced by dopamine, but SCH 23390 antagonises the present action of SK&F 83959, this would emphasise further that the mediating dopamine D_1-like receptor does not appear to be coupled to cyclase stimulation. Blockade of synergism by the selective dopamine D_2-like receptor antagonist YM 09151-2 was as

expected, through the component of the synergistic interaction mediated by the selective dopamine D_2-like receptor agonist quinpirole.

However, the effects of these antagonists on synergism between A 68930 and quinpirole were unexpected and more complex. Some enhancement of responsivity to A 68930 + quinpirole, but not of SK&F 83959 + quinpirole, by low doses of SCH 23390 and particularly of BW 737C is likely to reflect pharmacological difference(s) between A 68930 and SK&F 83959. The principle difference between them is the powerful stimulation of adenylyl cyclase induced only by A 68930. This cyclase stimulation might have some inhibitory effect on non-cyclase-coupled dopamine D_1-like receptors involved in these jaw movements, as Undie and Friedman (1994) have reported stimulation of adenylyl cyclase to inhibit the dopaminergic activation of a non-cyclase-coupled dopamine D_1-like receptor at the level of phosphoinositide hydrolysis. When attenuated by a cyclase-inhibiting antagonist, this would give disinhibition of jaw movement as noted here with SCH 23390 and, particularly, with BW 737C; no such effect would be expected for SK&F 83959, which fails to stimulate cyclase, and none was observed. At a higher dose, SCH 23390 but less so BW 737C antagonised responsivity, perhaps because this particular disinhibiting action of BW 737C on jaw movements was able to overcome its direct antagonist action at non-cyclase-coupled dopamine D_1-like receptors.

Responsivity to A 68930 + quinpirole was enhanced by a low dose of YM 09151-2. This may reflect some disinhibition of perioral movement, as we have noted YM 09151-2 to slightly increase the vacuous chewing response to A 68930 when given alone (Daly and Waddington, 1993); such an effect would be in accordance with the regulation of dopamine D_1-like receptor agonist-induced perioral phenomena by oppositional dopamine D_1-like:D_2-like receptor interactions which are distinct from the synergistic interactions that regulate the present induction of jaw movements by co-administration of dopamine D_1-like and D_2-like receptor agonists (Murray and Waddington, 1989; Koshikawa et al., 1991; Waddington et al., 1994). The interplay between these differing regulatory processes may underlie some of the present complexities. At a higher dose, YM 09151-2 antagonised synergistic responsivity to A 68930 + quinpirole, presumably through a direct action on the component of dopamine D_1-like:D_2-like receptor synergism mediated by the selective dopamine D_2-like receptor agonist quinpirole. It should be emphasised, however, that systemic drug administration means that hypotheses as to particular receptor-mediated effects should be treated with caution. Moreover, it cannot be excluded that SK&F 83959 and A 68930 may have differing profiles of regional brain penetration, such that they might influence a common output system via a primary action in distinct brain areas that confers on them distinct antagonist profiles; further studies would be necessary to identify the specific brain regions mediating these effects of SK&F 83959 and A 68930.

Irrespective of these considerations, the present findings indicate that SK&F 83959 and A 68930 share with SK&F 38393 a common dopamine D_1-like receptor action to synergise with the dopamine D_2-like receptor agonist quinpirole in the promotion of characteristic jaw movements, but do so in a manner that appears incompatible with mediation via a dopamine D_1-like receptor coupled to the stimulation of adenylyl cyclase. There is an increasing body of evidence, primarily neurochemical in nature, for the existence of dopamine D_1-like receptors that are coupled to a transduction system other than/additional to adenylyl cyclase, with stimulation of phosphoinositide hydrolysis being the most widely studied candidate (Mahan et al., 1990; Undie and Friedman, 1990; Schoors et al., 1991; Laitinen, 1993; Giambalvo and Wagner, 1994). In particular, Undie et al. (1994) have indicated a dopamine D_1-like receptor mediating phosphoinositide hydrolysis that is pharmacologically distinct from the classical dopamine D_1 receptor (D_{1A}) coupled to the stimulation of adenylyl cyclase; recently, it has been reported that in transgenic mice with targeted gene deletion of the dopamine D_{1A} receptor, the action of dopamine to stimulate adenylyl cyclase is lost while its action to stimulate phosphoinositide hydrolysis remains intact (Friedman et al., 1997). Furthermore, SK&F 83959 evidences antiparkinsonian activity in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-lesioned non-human primate in a manner that suggests clinical relevance for these concepts (Gnanalingham et al., 1995). The results reported here are not only consistent with the existence of such a novel, non-cyclase-coupled dopamine D_1-like receptor; they indicate also that its functional role extends to the regulation of characteristic jaw movements by synergistic interactions with dopamine D_2-like receptors, and suggest that the classical, cyclase-coupled dopamine D_1 receptor may actually oppose such synergism.

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