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SK&F 83822 distinguishes adenylyl cyclase from phospholipase C-coupled dopamine D1-like receptors: behavioural topography

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Abstract

Effects of SK&F 83822 [3-allyl-6-chloro-7,8-dihydroxy-1-(3-methylphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine], an agonist at dopamine D1-like receptors which stimulate adenylyl cyclase but not phosphoinositide hydrolysis, were studied topographically so as to clarify differences between these receptors in the regulation of behaviour. Using cloned receptors, SK&F 83822 showed high, selective affinity for dopamine D1 and D5 over D2, D3, D4 and several non-dopamine receptors. SK&F 83822 induced little intense grooming, but readily induced sniffing, locomotion and rearing; seizures were evident at higher doses, characterised by tonic convulsions, forepaw myoclonus and explosive hyperlocomotion. The dopamine D1-like receptor antagonist SCH 23390 [*R*(+)-3-methyl-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine] readily antagonised these responses to SK&F 83822, particularly seizure activity. The dopamine D2-like receptor antagonist YM 09151-2 [*cis*-*N*-(1-benzyl-2-methyl-pyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide] did not alleviate seizures induced by SK&F 83822; YM 09151-02 did, however, attenuate SK&F 83822-induced sniffing, locomotion and rearing, and released vacuous chewing. These findings indicate that dopamine D1-like receptors linked to adenylyl cyclase can be differentiated from those not linked to adenylyl cyclase in terms of their roles in the topographical regulation of behaviour. For example, the seizure and vacuous chewing responses appear to involve dopamine D1-like receptors that stimulate adenylyl cyclase, while intense grooming involves those which do not.
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1. Introduction

Conventional nomenclature defines dopamine D1-like [D1/1A, D5/1B] receptors in terms of their linkage to the stimulation of adenylyl cyclase (Kebabian and Calne, 1979; Niznik et al., 2002). However, a controversy endures as to whether there exist additional dopamine D1-like receptors that might utilise alternative/additional transduction mechanisms and what their functional properties might be (Niznik et al., 2002; Waddington et al., 1995). In particular, there is a body of evidence for a dopamine D1-like receptor coupled to stimulation of phospholipase C-mediated phosphoinositide hydrolysis, with concomitant elevation of inositol triphosphate and diacylglycerol (Undie and Friedman, 1990; Undie et al., 1994, 2000). There may be distinct dopamine D1-like receptors utilising different signaling cascades which demonstrate G-protein subunit-coupling specificity, with $G\alpha_s$ and $G\alpha_q$ linked to activation of adenylyl cyclase and phosphoinositide hydrolysis, respectively (Jin et al., 2003; Niznik et al., 2002; Panchalingam and Undie, 2000). Alternatively, the cloned D1-like receptors identified to date may demonstrate autonomous coupling to diverse signaling cascades in a response-specific manner (Montague et al., 2001; Niznik et al., 2002). Recent studies (Lezcano et al., 2000) have isolated a dopamine D1 receptor-interacting transmembrane protein,

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designated calcyon, that appears capable of regulating G-protein cross talk such that dopamine D1 receptors may shift effector coupling between $G\alpha_s$ and $G\alpha_q$; thus, calcyon might function as a molecular switch enabling reciprocal signaling through adenylyl cyclase or phosphoinositide pathways at individual dopamine D1 receptors.

These arguments have important functional significance, as the behavioural effects of dopamine D1-like receptor agonists in intact and lesioned rodents and in a non-human primate model of Parkinson's disease (Gnanalingham et al., 1995a,b; Murray and Waddington, 1989; Niznik et al., 2002; Waddington et al., 1995) appear unrelated to their efficacies to stimulate adenylyl cyclase. More specifically, the benzazepine SK&F 83959, which fails to stimulate adenylyl cyclase (Andringa et al., 1999a; Arnt et al., 1992; Gnanalingham et al., 1995b), but which stimulates phosphoinositide hydrolysis (Jin et al., 2003; Panchalingam and Undie, 2001), induces typical dopamine D1-like receptor-mediated behavioural effects such as grooming (Adachi et al., 1999, 2003; Arnt et al., 1992; Deveney and Waddington, 1995; Hasegawa et al., 2001), including antiparkinsonian activity in a non-human primate model (Andringa et al., 1999b; Gnanalingham et al., 1995a).

While the behavioural properties of SK&F 83959 are substantially similar to those of typical dopamine D1-like receptor agonists which stimulate both adenylyl cyclase *and* phosphoinositide hydrolysis, including most other members of the benzazepine series typified by SK&F 38393 (Niznik et al., 2002; Undie et al., 1994; Waddington et al., 1995) and the isochroman A 68930 (Daly and Waddington, 1993; DeNinno et al., 1991; Rosengarten and Friedhoff, 1998), clarification of these issues would be greatly facilitated by the availability of a dopamine D1-like receptor agonist which stimulates adenylyl cyclase without stimulating phosphoinositide hydrolysis. SK&F 83822 is a benzazepine with selective affinity for dopamine D1-like over D2-like [D2, D3, D4] receptors (Andersen and Jansen, 1990) which stimulates adenylyl cyclase but not phosphoinositide hydrolysis (Undie et al., 1994) and has been reported recently to exhibit unusual psychopharmacological properties in non-human primates (Peacock and Gerlach, 2001). We describe here the first systematic examination of the behavioural profile of SK&F 83822 in rodents, including differential antagonism by the dopamine D1-like receptor antagonist SCH 23390 vs. the dopamine D2-like receptor antagonist YM 09151-2, and report its affinity for cloned dopamine and non-dopamine receptor subtypes in comparison with SK&F 83959.

2. Materials and methods

2.1. Animals

Young adult male C57BL/6J mice (23 ± 1 g; Harlan, UK) were housed in groups of five with standard laboratory chow and water available ad libitum. They were maintained at 21 ± 1 °C on a 12/12-h (0800 on; 2000 off) light/dark schedule. These studies were conducted under license from the Department of Health and Children in accordance with Irish legislation and the European Communities Council Directive 86/609/EEC for the care and use of experimental animals.

2.2. Behavioural assessment

For evaluation of the *ethogram* of SK&F 83822, mice were removed from their home cage, and placed individually in clear glass observation cages (36 × 20 × 20 cm) with wood shavings as bedding material. They were then left undisturbed for a 3-h habituation period to reduce initially high levels of exploratory activity and hence facilitate detection of stimulatory drug effects.

Immediately following treatment with drug or vehicle, behavioural assessments were carried out in a manner similar to that described previously (Clifford et al., 2000, 2001; McNamara et al., 2002, 2003). For this procedure, each of 10 randomly allocated mice was observed individually for 5-s periods at 1-min intervals over 15 consecutive minutes, using an extensive, ethologically based behavioural checklist to resolve all topographies of behaviour within the natural repertoire. This allowed the presence or absence of the following individual behaviours (occurring alone or in any combination) to be determined in each 5-s period: sniffing (flaring of nostrils with movement of vibrissae); locomotion (coordinated movement of all four limbs producing a change in location); total rearing (rearing of any form); rearing seated (front paws reaching upwards with hind limbs on floor in sitting position); rearing to wall (front paws reaching upwards onto or towards a cage wall while standing on hind limbs); rearing free (front paws reaching upwards away from any cage wall while standing on hind limbs); sifting (characteristic sifting movements of the front paws through bedding material on cage floor); total grooming (any form of grooming; paws or snout applied to any body region in any manner); intense grooming (a specific component of the above characteristised by innately programmed syntax of sequential grooming of the snout and then the face with the forepaws, followed by vigorous grooming of the hind flank/anogenital region with the snout); vacuous chewing (chewing movements not directed onto any physical material); seizures (tonic convulsions, progressing to forepaw myoclonus, and periodically culminating in explosive hyperlocomotion).

After each 15-min assessment using the checklist, each animal was evaluated over a 30-s period using a conventional 0–6 point stereotypy scale: 0 = asleep or inactive; 1 = episodes of normal activity; 2 = discontinuous activity with bursts of prominent sniffing or rearing; 3 = continuous stereotyped activity such as sniffing or

rearing along a fixed path; 4 = stereotyped sniffing or rearing fixated in one location; 5 = stereotyped behaviour with bursts of licking or gnawing; 6 = continuous licking or gnawing.

This cycle of assessment by behavioural checklist (0–15 min) followed by stereotypy scale (15–20 min) was repeated twice (20–40 and 40–60 min) over a total period of 1 h. Mice were used on two occasions only, separated by a drug-free interval of at least 1 week; on each occasion, mice were allocated randomly to one of the various treatment groups. All assessments were made between 1400 and 1700 h to minimise circadian effects on behaviour, by an observer who was unaware of the treatment status of each animal.

2.3. Radioligand binding studies

Binding profiles of drugs to cloned biogenic amine receptors were performed by the National Institute of Mental Health Psychoactive Drug Screening Program; K_i determinations were obtained from competition binding studies in which six to eight concentrations of unlabelled ligand (0.1–10,000 nM) were analysed using GraphPad Prizm, as described previously (Roth et al., 2002).

2.4. Drugs

The following drugs were used: SK&F 83822 [3-allyl-6-chloro-7,8-dihydroxy-1-(3-methylphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine; GlaxoSmithKline]; SK&F 83959 [3-methyl-6-chloro-7,8-dihydroxy-1-(3-methylphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine; RBI/SRI/NIMH Chemical Synthesis Program]; SCH 23390 [*R*(+)-3-methyl-7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; Sigma RBI]; YM 09151-2 [*cis*-*N*-(1-benzyl-2-methyl-pyrrolidin-3-yl)-5-chloro-2-methoxy-4-methylaminobenzamide; Yamanouchi]. For behavioural studies, SK&F 83822 (0.016–2.0 mg/kg) was dissolved in distilled water and administered subcutaneously into the flank in a volume of 4.0 ml/kg; SCH 23390 (0.025–0.625 mg/kg) was dissolved and injected similarly in a volume of 2.0 ml/kg; YM 09151-2 (0.025–0.625 mg/kg) was dissolved in a minimum of 0.1 M HCl, made up to volume with distilled water and administered subcutaneously into the flank in a volume of 2.0 ml/kg. Antagonists or respective vehicles were administered 30 min prior to challenge with agonist or vehicle.

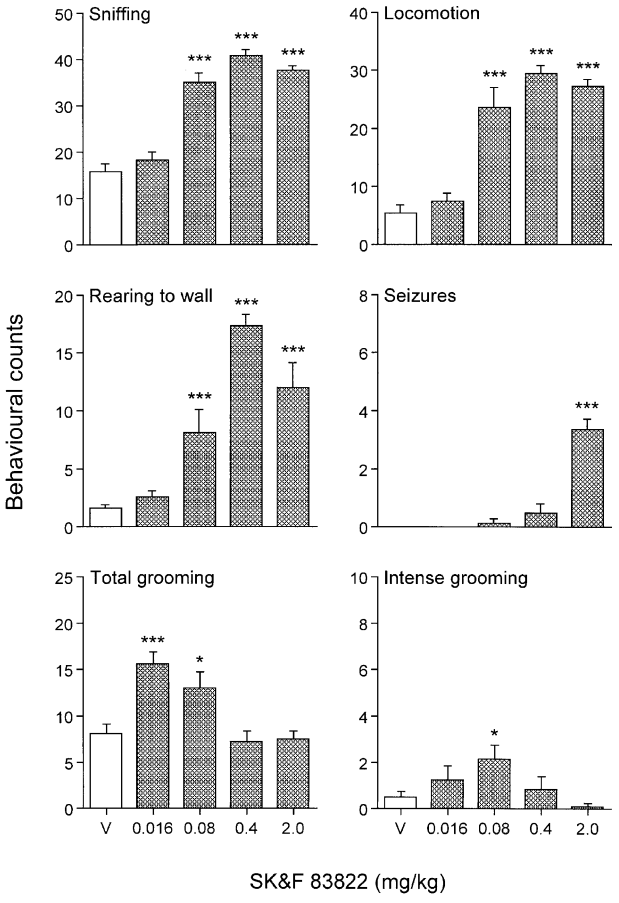

Fig. 1. Behavioural responses to 0.016–2.0 mg/kg SK&F 83822 over a 1-h period for sniffing [$F(1,4)=44.57$, $P<0.001$], locomotion [$F(1,4)=42.86$, $P<0.001$], rearing-to-wall [$F(1,4)=29.99$, $P<0.001$], seizures [$F(1,4)=35.90$, $P<0.001$], total grooming [$F(1,4)=8.79$, $P<0.001$], and intense grooming [$F(1,4)=2.65$, $P=0.05$]. Seizures were tonic convulsions, progressing to forepaw myoclonus, periodically culminating in explosive hyperlocomotion, and were scored as for other behaviours. Data are mean counts ± S.E.M. for $n=7–8$ per group. *$P<0.05$, ***$P<0.001$ vs. vehicle (V).

2.5. Data analysis

To quantify *ethograms* of drug-induced behavioural topography (Clifford et al., 2000, 2001; McNamara et al., 2002, 2003), total counts for each individual behaviour were determined as the number of 5-s observation windows in which a given behaviour was evident, summed over the 3 × 15 min (0–15, 20–35, 40–55) cycle periods and expressed as means ± S.E.M. Counts for individual behav-

Table 1
Affinities of SK&F 83822 and SK&F 83959 for cloned dopamine and non-dopamine receptor subtypes

	K_i (nM)							
	D1	D2	D3	D4	D5	5-HT_{2A}	α_{1A}	α_{1B}
SK&F 83822	3.2 ± 1.0	186 ± 42	66 ± 19	335 ± 34	3.1 ± 1.1	1167 ± 429	1251 ± 94	1385 ± 260
SK&F 83959	0.5 ± 0.1	879 ± 173	637 ± 99	1523 ± 211	2.1 ± 0.7	164 ± 26	654 ± 47	688 ± 47

Data are mean K_i values ± S.E.M.

iours were subjected to square-root transformation and analysed using analysis of variance [ANOVA] followed by Student's *t*-test. Stereotypy scores were averaged over the 1-h period, expressed similarly and analysed using the Kruskal–Wallis nonparametric ANOVA followed by Mann–Whitney *U*-test.

3. Results

3.1. Receptor binding profiles

SK&F 83822 showed indistinguishably high affinity for dopamine D1 and D5 receptors [K_i values 3.2 and 3.1 nM, respectively], 60-fold selectivity over D2, 20-fold selectivity over D3 and 105-fold selectivity over D4 receptors, together with 365-fold selectivity over 5-HT_{2A} receptors, 390-fold selectivity over adrenergic α_{1A} and 430-fold selectivity over α_{1B} receptors (Table 1).

SK&F 83959 showed high affinity for dopamine D1 and D5 receptors [K_i values 0.5 and 2.1 nM, respectively], 670-fold selectivity over D2, 490-fold selectivity over D3 and 1170-fold selectivity over D4 receptors, together with 120-fold selectivity over 5-HT_{2A} receptors, 500-fold selectivity over adrenergic α_{1A} and 520-fold selectivity over α_{1B} receptors (Table 1).

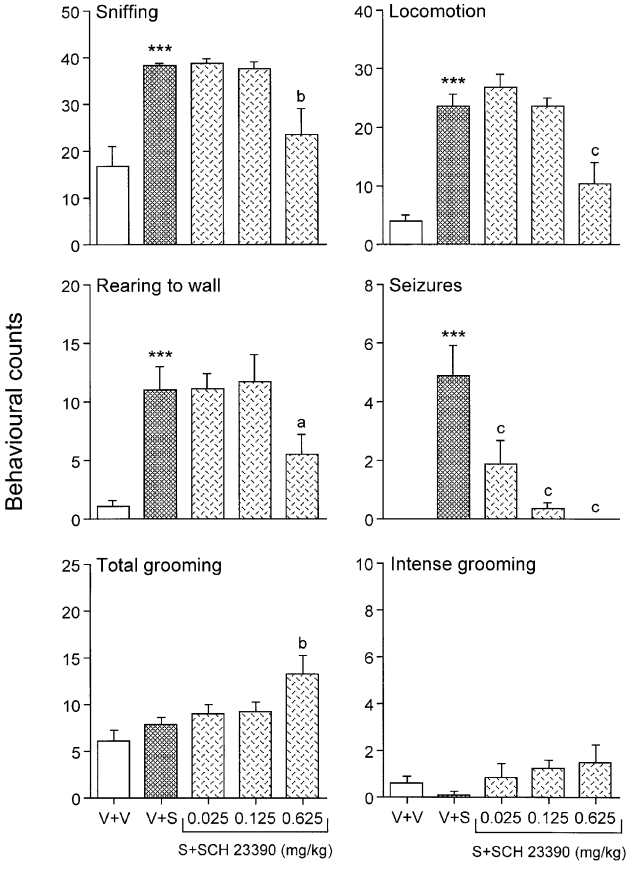

Fig. 2. Effect of 30-min pretreatment with 0.025–0.625 mg/kg SCH 23390 on behavioural responses to 2.0 mg/kg SK&F 83822 over a 1-h period for sniffing [$F(1,4)=11.61$, $P<0.001$], locomotion [$F(1,4)=20.37$, $P<0.001$], rearing-to-wall [$F(1,4)=11.01$, $P<0.001$], seizures [$F(1,4)=15.71$, $P<0.001$], total grooming [$F(1,4)=4.50$, $P<0.01$] and intense grooming. Data are mean counts ± S.E.M. for $n=6–8$ per group. ***$P<0.001$ vs. vehicle (V); [a]$P<0.05$, [b]$P<0.01$, [c]$P<0.001$ vs. SK&F 83822 (S).

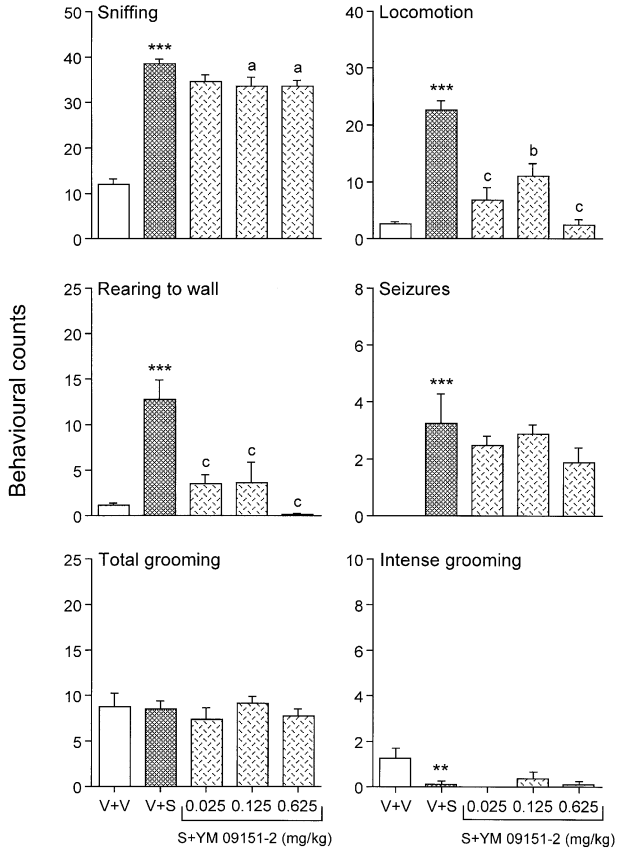

Fig. 3. Effect of 30-min pretreatment with 0.025–0.625 mg/kg YM 09151-2 on behavioural responses to 2.0 mg/kg SK&F 83822 over a 1-h period for sniffing [$F(1,4)=64.82$, $P<0.001$], locomotion [$F(1,4)=16.25$, $P<0.001$], rearing-to-wall [$F(1,4)=16.41$, $P<0.001$], seizures, total grooming and intense grooming. Data are mean counts ± S.E.M. for $n=8$ per group. **$P<0.01$, ***$P<0.001$ vs. vehicle (V); [a]$P<0.05$, [b]$P<0.01$, [c]$P<0.001$ vs. SK&F 83822 (S).

3.2. Topographical responsiveness to SK&F 83822

As a deliberate consequence of the habituation period, vehicle-treated animals displayed relatively low levels of exploratory and other topographies of behaviour.

Administration of SK&F 83822 (0.016–2.0 mg/kg; Fig. 1) readily and dose-dependently induced sniffing, locomotion and rearing, with rearing to wall being the primary component among individual topographies contributing to total rearing. Lower doses of SK&F 83822 also induced grooming, which declined as dosage was increased; this is likely to reflect response incompatibility with other behaviours stimulated at these higher doses. A similar profile was apparent for the induction of sifting by lower doses of SK&F 83822 [$F(1,4)=7.90$, $P<0.001$; data not shown].

There was little induction of intense grooming syntax by SK&F 83822, with a residual effect only at an intermediate dose of 0.08 mg/kg. Levels of vacuous chewing were too low for meaningful assessment. Stereotypy scores were very low, indicating that these behaviours were manifested in a non-stereotyped manner [Mean scores ± S.E.M. on the 0–6 stereotypy scale over the 1-h period were as follows: vehicle: 0.4 ± 0.1; SK&F 83822, 0.016 mg/kg: 0.5 ± 0.1; SK&F 83822, 0.08 mg/kg: 1.5 ± 0.1, $P<0.001$; SK&F 83822, 0.4 mg/kg: 1.8 ± 0.1, $P<0.001$; SK&F 83822, 2.0 mg/kg: 1.8 ± 0.1, $P<0.001$]. However, a primary response to SK&F 83822 was the emergence of seizure activity at higher doses (Fig. 1); this varied in intensity and duration, initially presenting as tonic convulsions, progressing to forepaw myoclonus, and periodically culminating in explosive hyperlocomotion.

3.3. Effect of the dopamine D1-like receptor antagonist SCH 23390 on topographical responsiveness to SK&F 83822

A dose of 2.0 mg/kg SK&F 83822 was selected for antagonist studies, to allow optimal pharmacological characterisation of its characteristic convulsant activity; for other behaviours, a dose of 0.4 mg/kg SK&F 83822 produced a maximal response. Pretreatment with SCH 23390 (0.025–0.625 mg/kg; Fig. 2) readily and dose-dependently antagonised seizures induced by 2.0 mg/kg SK&F 83822. Locomotion, sniffing and rearing, primarily rearing to wall, were also antagonised. While this dose of SK&F 83822 did not induce grooming (Fig. 1), pretreatment with higher doses of SCH 23390 was associated with release of a low level of grooming. Levels of vacuous chewing were too low for meaningful assessment.

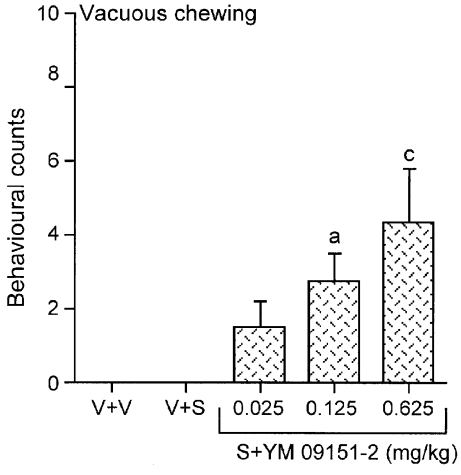

Fig. 4. Effect of 30-min pretreatment with 0.025–0.625 mg/kg YM 09151-2 to release vacuous chewing [$F(1,4)=7.09$, $P<0.001$] in response to 2.0 mg/kg SK&F 83822 over a 1-h period. Data are mean counts ± S.E.M. for $n=8$ per group. $^{a}P<0.05$, $^{c}P<0.001$ vs. SK&F 83822 (S) and vehicle (V).

3.4. Effect of the dopamine D2-like receptor antagonist YM 09151-2 on topographical responsiveness to SK&F 83822

Pretreatment with YM 09151-2 (0.025–0.625 mg/kg; Fig. 3) was without effect on seizures induced by 2.0 mg/kg SK&F 83822. Conversely, locomotion, sniffing and rearing, primarily rearing to wall, were antagonised. While pretreatment with YM 09151-2 failed to release grooming or intense grooming in response to SK&F 83822, there was prominent release of vacuous chewing (Fig. 4) that was not evident in response to any dose of SK&F 83822 given alone or following pretreatment with SCH 23390.

4. Discussion

This is the first systematic study in the rodent of the behavioural effects of SK&F 83822, a dopamine D1-like receptor agonist shown previously (Undie et al., 1994) to stimulate adenylyl cyclase but not phosphoinositide hydrolysis. It is a counterpart of the more widely studied congener SK&F 83959 which stimulates phosphoinositide hydrolysis but fails to stimulate adenylyl cyclase (Jin et al., 2003; Niznik et al., 2002; Panchalingam and Undie, 2001). Using cloned receptors, SK&F 83822 showed high, selective affinity for dopamine D1 and D5 over D2, D3, D4 and several non-dopamine receptors; SK&F 83822 was characterised by slightly lower selectivity for dopamine D1 and D5 over D2, D3 and D4 receptors but slightly greater selectivity over non-dopamine receptors, relative to SK&F 83959. These findings elaborate a previous report which noted a 40-fold selectivity of SK&F 83822 for otherwise undifferentiated dopamine D1-like over D2-like receptors (Andersen and Jansen, 1990).

Three major behavioural findings were apparent. Firstly, SK&F 83822 had little ability to induce intense grooming. Induction of such innately programmed grooming syntax, as a specific component of diverse elements of general grooming induced at lower doses, constitutes the most consistent and widely adopted behavioural index of dopamine D1-like receptor activation (Berridge and Aldridge, 2000; Molloy and Waddington, 1984; Murray and Waddington, 1989; Niznik et al., 2002; Waddington et al., 1995); it is readily induced by all dopamine D1-like receptor agonists examined to date, which stimulate adenylyl cyclase and phosphoinositide hydrolysis. On the basis that SK&F 83822 fails to induce a material syntactic grooming response with stimulation of adenylyl cyclase but not phosphoinositide hydrolysis, while we have consistently shown SK&F 83959 under the same experimental conditions to induce such grooming with stimulation of phosphoinositide hydrolysis but not adenylyl cyclase (Clifford et al., 1999; McNamara et al., 2002, 2003), it would appear that this behaviour may be mediated primarily through dopamine D1-like receptors linked to phosphoi-

nositide hydrolysis rather than those linked to adenylyl cyclase. Conversely, SK&F 83822 also induced less specific behaviours such as sniffing, locomotion and topographies of rearing, and we have consistently shown SK&F 83959 under the same experimental conditions to induce these same behaviours (Clifford et al., 1999; McNamara et al., 2002, 2003); these effects evidenced a biphasic dose–response relationship and their neuronal basis may differ, at least in part, from that of intense grooming.

Secondly, while SK&F 83822 has little ability to induce syntactic grooming, it induced in a dose-dependent manner its own characteristic response, namely tonic convulsions progressing to forepaw myoclonus and periodically culminating in explosive hyperlocomotion; these seizure responses to SK&F 83822 are more prominent than we have encountered using other dopamine D1-like receptor agonists when given alone. There is a body of evidence that dopamine D1-like receptor stimulation reduces while dopamine D2-like receptor stimulation increases convulsive threshold; also, dopamine D1-like receptor agonists stimulating adenylyl cyclase and phosphoinositide hydrolysis, such as A 68930, can sometimes induce convulsions in rodents when given alone (DeNinno et al., 1991; Starr and Starr, 1993; Starr, 1996) while SK&F 83959, which stimulates phosphoinositide hydrolysis but not adenylyl cyclase, does not (Arnt et al., 1992; Clifford et al., 1999; Deveney and Waddington, 1995; McNamara et al., 2003). Recently, it has been reported in non-human primates (Peacock and Gerlach, 2001) that SK&F 83822 induces extreme arousal and violent locomotor activation that may overlap with the episodes of explosive, hyperlocomotive seizures reported here. Thus, the present findings in mice suggest that, in contrast to induction of grooming syntax, induction of seizures may be mediated primarily through dopamine D1-like receptors linked to adenylyl cyclase rather than those linked to phosphoinositide hydrolysis.

The action of SK&F 83959 to stimulate phosphoinositide hydrolysis but not adenylyl cyclase is accompanied by inhibition of the stimulation of adenylyl cyclase induced by dopamine (Andringa et al., 1999a; Arnt et al., 1992; Gnanalingham et al., 1995b). Conversely, whether the action of SK&F 83822 to stimulate adenylyl cyclase but not phosphoinositide hydrolysis is accompanied by inhibition of the stimulation of phosphoinositide hydrolysis induced by dopamine is not yet clear. As stimulation of adenylyl cyclase has been shown to inhibit dopamine agonist-induced phosphoinositide hydrolysis (Undie and Friedman, 1994), some involvement of cross-talk between these two dopamine D1-like receptor transduction pathways cannot be excluded.

Seizures induced by SK&F 83822 were readily blocked by low doses of SCH 23390 which failed to attenuate spontaneous locomotion and rearing, but were not blocked by YM 09151-2. This indicates regulation via dopamine D1-like receptor mechanisms. However, alleviation of seizures by SCH 23390 was accompanied by release of a low level of grooming to a high dose of SK&F 83822. This may reflect the shifting of the dose–response curve for grooming to the right by dopamine D1-like receptor antagonism, as the grooming response to SK&F 83822 occurred only at low doses in the absence of pretreatment and only at a high dose following pretreatment with SCH 23390; alleviation of incompatible seizure activity may have facilitated this effect. At higher doses, SCH 23390 antagonised sniffing, locomotion and topographies of rearing induced by SK&F 83822. As these doses of SCH 23390 can also attenuate spontaneous behaviours under the same experimental conditions (McNamara et al., 2003), it cannot be excluded that these responses to SK&F 83822 involve other, possibly non-dopaminergic mechanisms. These matters might be clarified by dose–occupancy studies across different receptors.

Thirdly, while pretreatment with the dopamine D2-like receptor antagonist YM 09151-2 failed to attenuate seizure activity, it attenuated sniffing, locomotion and rearing topographies induced by SK&F 83822. For locomotion and rearing, this effect occurred even at the lowest dose of YM 09151-2, which failed to attenuate spontaneous locomotion and rearing under the same experimental conditions (McNamara et al., 2003). This would be consistent with attenuation of these responses to other dopamine D1-like receptor agonists by dopamine D2-like receptor antagonists, in accordance with the regulation of typical dopamine-mediated behaviours by cooperative/synergistic dopamine D1-like: D2-like receptor interactions (Molloy and Waddington, 1984; Niznik et al., 2002; Waddington et al., 1994, 1995); thus, SK&F 83822-induced seizure activity appears to be a 'pure' dopamine D1-like receptor-mediated effect that is not regulated materially by such interactions.

In particular, pretreatment with YM 09151-2 released a prominent vacuous chewing response to SK&F 83822 that was not seen when this agent was given alone or following pretreatment with SCH 23390. Pretreatment with dopamine D2-like receptor antagonists releases vacuous chewing in response to other dopamine D1-like receptor agonists, in accordance with the regulation of this atypical dopamine-mediated behaviour by oppositional dopamine D1-like: D2-like receptor interactions (Murray and Waddington, 1989; Niznik et al., 2002; Waddington et al., 1994, 1995); thus, dopamine D1-like receptors linked to adenylyl cyclase appear to participate in these interactions. However, release of vacuous chewing by pretreatment with a dopamine D2-like receptor antagonist occurs also for SK&F 83959 (Deveney and Waddington, 1995), and inactivation of dopamine D1-like receptors coupled to adenylyl cyclase spares dopamine D1-like receptor agonist-induced jaw movements (Rosengarten and Friedhoff, 1998; Undie et al., 2000). Thus, subject to evidence (Tomiyama et al., 2002) that orofacial movement topographies appear both neurobiologically and pharmacologically distinct rather than a unitary phenomenon, dopamine D1-like receptors linked

to phosphoinositide hydrolysis may also participate in oppositional dopamine D1-like/D2-like receptor interactions in the regulation thereof.

As the first available dopamine D1-like receptor agonist which stimulates adenylyl cyclase but not phosphoinositide hydrolysis, SK&F 83822 completes an armamentarium of pharmacological tools which can be applied to elucidate the behavioural roles of dopamine D1-like receptor subtypes. However, as for the great majority of such studies, we cannot exclude incontrovertibly some influence from as yet unknown properties of this agent at the level of receptor or transduction. Importantly, SK&F 83822 complements SK&F 83959, which stimulates phosphoinositide hydrolysis but not adenylyl cyclase, and the majority of other benzazepines such as SK&F 38393 and isochromans such as A 68930 which stimulate both adenylyl cyclase and phosphoinositide hydrolysis. However, while there is still a need to identify also antagonists with selectivity to block adenylyl cyclase-linked vs. phosphoinositide-linked dopamine D1-like receptors, such pharmacological approaches have yet to resolve dopamine D1 vs. D5 receptors; to date, these issues depend on the application of antisense and, particularly, gene targeting ['knockout'] techniques (Hollon et al., 2002; McNamara et al., 2003; Sibley, 1999; Tomiyama et al., 2002; Waddington et al., 2001). Studies with SK&F 83822 in dopamine D1 vs. D5 receptor 'knockouts' may be further informative on these processes.

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