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Evidence for dopamine 'D_1-like' receptor subtypes in the behavioural effects of two new selective antagonists, LY 270411 and BW 737C

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Abstract

A new, chemically distinct antagonist at dopamine 'D_1-like' receptors, the thienoazepine LY 270411, ([+]-2(3-chloro-6-methyl-8-phenyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3*d*]azepin-2-yl)propan-2-ol) was compared with the isoquinoline BW 737C ([*S*]-6-chloro-1-[2,5-dimethoxy-4-propylbenzyl]-7-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline) and the benzazepine SCH 23390 ([*R*]-7-chloro-8-hydroxy-2,3,4,5-tetrahydro-3-methyl-1-phenyl-1*H*-3-benzazepine) for effects on behavioural responses to the isochroman full efficacy dopamine 'D_1-like' receptor agonist A 68930 ([1*R*,3*S*]-1-aminomethyl-5,6-dihydroxy-3-phenylisochroman) vs. the dopamine 'D_2-like' receptor agonist RU 24213 (*N*-n-propyl-*N*-phenylethyl-*p*-3-hydroxyphenylethylamine). Grooming responses to A 68930 were readily blocked by each of LY 270411, BW 737C and SCH 23390; however, the vacuous chewing response was blocked only by BW 737C. Sniffing and locomotor responses to RU 24213 were attenuated by BW 737C and SCH 23390 but *not* by LY 270411; furthermore, myoclonic jerking to RU 24213 was released by BW 737C and SCH 23390 but *not* by LY 270411. These findings indicate that grooming induced by dopamine 'D_1-like' receptor agonism is blocked by all chemical classes of dopamine 'D_1-like' receptor antagonist while vacuous chewing is blocked only by isoquinoline dopamine 'D_1-like' receptor antagonism; this suggests that these behaviours may be mediated via functionally and pharmacologically distinct subtypes of dopamine 'D_1-like' receptor. Furthermore, LY 270411 appears unique in its activity to readily block 'D_1-like' receptor agonist-induced grooming without influencing behavioural responses to dopamine 'D_2-like' receptor agonism; thus, the site mediating prototypical dopamine 'D_1-like' receptor agonist-induced behaviours may be dissociable pharmacologically from dopamine 'D_1-like' site(s) participating in functional interactions with dopamine 'D_2-like' receptors.

Keywords: Dopamine 'D_1-like' receptor; Dopamine 'D_2-like' receptor; D_1/D_2 interaction; LY 270411; BW 737C; SCH 23390; Grooming behavior; Vacuous chewing; Myoclonic jerking; (Rat)

1. Introduction

It is well recognised from the application of molecular biological techniques that there exists a broad family of dopamine 'D_1-like' receptor subtypes (D_{1A}/D_1, D_{1B}/D_5, D_{1C}, D_{1D}) (Civelli et al., 1993; Gingrich and Caron, 1993; Sibley et al., 1993; Sugamori et al., 1994; Demchyshyn et al., 1995). The dopamine 'D_1-like' family of receptors plays an important role in the regulation of behaviour, often by way of both cooperative/synergistic and oppositional interactions with their dopamine 'D_2-like' receptor counterparts ($D_{2L/S}$, D_3, D_4) (Waddington et al., 1994, 1995), but similarities or differences in the role(s) of each individual member of the family are poorly understood. Furthermore, there is an expanding body of functional evidence that additional dopamine 'D_1-like' receptor subtypes may exist (Mailman et al., 1986; Murray and Waddington, 1989a; Mahan et al., 1990; Johansen et al., 1991; Arnt et al., 1992; Undie et al., 1994; Deveney and Waddington, 1995; Waddington et al., 1995).

We have previously described (Daly and Waddington, 1993) the isochroman full efficacy selective dopamine 'D_1-like' receptor agonist A 68930 to share with the prototypical benzazepine analogues of SK&F 38393 an action to induce prominent grooming, the most widely accepted behavioural model of dopamine 'D_1-like' receptor stimulation (Molloy and Waddington, 1984; Waddington et al., 1995) but to be much more active than the benzazepines in inducing vacuous chewing, a more controversial model thereof (Rosengarten et al., 1983; Murray and Waddington, 1989a; Collins et al., 1991; Waddington et al., 1995). Furthermore, while the benzazepine dopamine

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'D_1-like' receptor antagonist SCH 23390 and its isoquinoline counterpart BW 737C (Riddall, 1992) each readily blocked these grooming responses, only BW 737C but not SCH 23390 blocked the vacuous chewing response to A 68930; on classical pharmacological grounds, these findings would suggest that grooming is mediated by a dopamine 'D_1-like' receptor that recognises all known chemical classes of dopamine 'D_1-like' receptor ligands while vacuous chewing is mediated by a subtype of dopamine 'D_1-like' receptor that recognises preferentially the isochromans and the isoquinolines (Daly and Waddington, 1993; Waddington et al., 1995).

In order to clarify further these issues, it would be critical to establish the profile of any new, chemically distinct selective dopamine 'D_1-like' receptor antagonist in the same behavioural paradigms. Recently, the novel thienoazepine dopamine 'D_1-like' receptor antagonist LY 270411 has been described (Clark and Tupper, 1989; Bowman et al., 1990), and we have therefore undertaken a systematic examination of its effects not only on behavioural responses to A 68930 but also on those to the selective dopamine 'D_2-like' receptor agonist RU 24213 (Euvrard et al., 1980), in comparison with BW 737C and SCH 23390.

2. Materials and methods

2.1. Behavioural studies

Young adult male Sprague-Dawley rats (215–375 g; UCD, Dublin, Ireland) were housed in groups of five per cage with food and water available ad libitum, and were maintained at 21 ± 1°C on a 12/12 h (06:00 h on; 18:00 h off) light/dark schedule. On experimental days they were placed individually in clear glass observation cages ($36 \times 20 \times 20$ cm) and left undisturbed for a habituation period of 2.5 h.

Behavioural assessments were carried out in a manner similar to that described previously (Deveney and Waddington, 1995, 1996). Immediately before and at intervals after injection of drug or vehicle, animals were assessed using a rapid time-sampling behavioural check list technique. For this procedure, each rat was observed individually for 5 s periods at 1 min intervals over 15 consecutive minutes, using an extended behavioural check list. 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: stillness (motionless with no behaviour evident); sniffing; locomotion; rearing; grooming (of any form); intense grooming (a characteristic pattern of grooming of the face with the forepaws followed by vigorous grooming of the hind flank with the snout); vacuous chewing (not directed on to any physical material); chewing (directed on to any physical material); jerking (myoclonic movements of the limbs or whole body); the presence of any other unusual behaviour was also noted. After this 15 min assessment using the behavioural check list, animals were evaluated for 30 s each using a conventional 0–6 point stereotypy scale: 0 = asleep or inactive; 1 = episodes of normal activities; 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 check list followed by stereotypy scale was repeated on two further occasions over a total observation period of 1 h. Rats were used on two occasions only, separated by a drug-free interval of at least one week; on each occasion rats were allocated randomly to one of the various treatment groups. All assessments were made by an observer unaware of the treatment given to each animal.

2.2. Radioligand binding studies

Using methods similar to those described previously (Deveney and Waddington, 1995, 1996), striata from similar male Sprague-Dawley rats were homogenised in 30 vols. 50 mM Tris-HCl buffer, pH 7.6 at 25°C, and centrifuged at $10\,000 \times g$ at 4°C for 5 min. The pellet was twice resuspended, diluted and centrifuged as above. The membrane preparation was finally resuspended at 4–8 mg original wet weight/ml in Tris-HCl buffer containing: 120 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$, 0.2 mM $Na_2S_2O_5$ (as antioxidant) and 10 μM pargyline (as monoamine oxidase inhibitor).

The binding of [^{3}H]SCH 23390 (75 Ci/mmol, Amersham) to dopamine 'D_1-like' receptors was determined by incubating 0.5 ml membrane suspension (approximately 4 mg/ml) with 0.5 nM ligand plus unlabelled drugs at 37°C for 20 min in a total volume of 1 ml; specific binding was defined as that displaced by 100 nM piflutixol (Lundbeck) and typically represented $> 90\%$ of total binding. Incubations were stopped by filtration through GF/B filters, followed by two 8 ml washes with ice-cold buffer. Radioactivity trapped on the filters was quantified by liquid scintillation spectroscopy after addition of 5 ml Ecoscint A (Medlabs) using a LKB 1214 Rackbeta counter with 45–51% counting efficiency for tritium.

The binding of [^{3}H]spiperone (24 Ci/mmol, Amersham) to dopamine 'D_2-like' receptors was determined using membranes prepared as above. Incubations contained 0.5 ml membrane suspension (approximately 8 mg/ml) with 0.2 nM ligand plus unlabelled drugs in a total volume of 5 ml; specific binding was defined as that displaced by 1 μM domperidone (Janssen) and typically represented $> 75\%$ of total binding. Incubation and filtration were as described above.

2.3. Drugs

The following investigational drugs were used: LY 270411 ([+]-2(3-chloro-6-methyl-8-phenyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3*d*]azepin-2-yl)propan-2-ol; Lilly, UK); BW 737C ([*S*]-6-chloro-1-[2,5-dimethoxy-4-propylbenzyl]-7-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline; Wellcome Foundation, UK); SCH 23390 ([*R*]-7-chloro-8-hydroxy-2,3,4,5-tetrahydro-3-methyl-1-phenyl-1*H*-3-benzazepine; Schering-Plough, USA); A 68930 ([1*R*,3*S*]-1-aminomethyl-5,6-dihydroxy-3-phenylisochroman; Abbott, USA); RU 24213 (*N*-*n*-propyl-*N*-phenylethyl-*p*-3-hydroxyphenylethylamine; Roussel-UCLAF, France). RU 24213, BW 737C and SCH 23390 were dissolved in distilled water; A 68930 was dissolved in acetic acid and made up to volume with distilled water; LY 270411 was dissolved in a minimum of glacial acetic acid and made up to volume with distilled water. All drugs were injected subcutaneously into the flank in a volume of 2 ml/kg, with antagonists or respective vehicles given 30 min prior to agonist challenge.

2.4. Data analysis

From application of the behavioural check list, the total 'counts' for each individual behaviour was determined as the number of 5 s observation windows in which a given behaviour was evident, summed over the 1 h period, and expressed as means ± S.E.M.; stereotypy scores were averaged over the 1 h period and expressed similarly. These data were then analysed using analysis of variance (ANOVA) or the Kruskal-Wallis non-parametric ANOVA, followed by Student's *t*-test or Mann-Whitney *U*-test, respectively.

For radioligand binding studies, data were analysed using an iterative curve-fitting procedure (Barlow, 1983) to

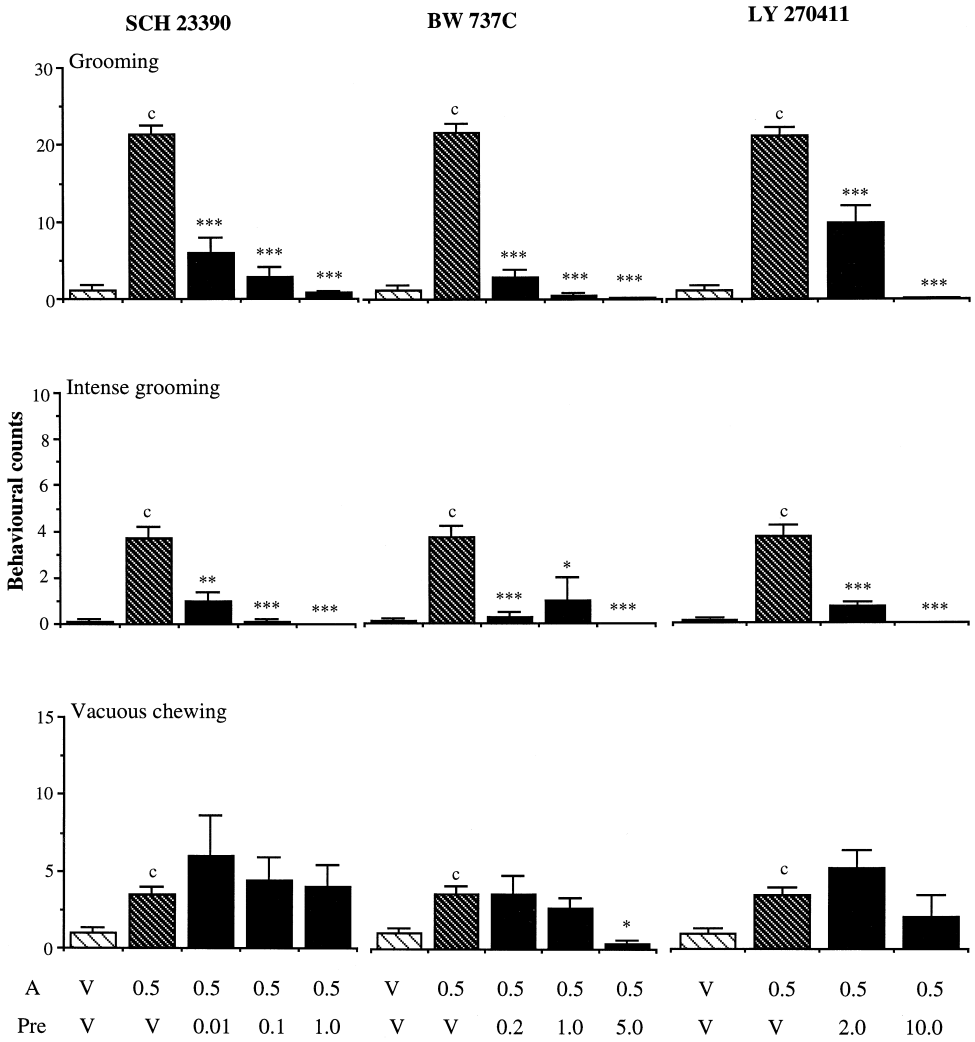

Fig. 1. Behavioural counts for grooming, intense grooming and vacuous chewing responses to challenge with A 68930 (A, 0.5 mg/kg; stippled columns) or its vehicle (V; hatched columns) following pretreatment (Pre) with vehicle (V), 0.01–1.0 mg/kg SCH 23390, 0.2–5.0 mg/kg BW 737C or 2.0–10.0 mg/kg LY 270411 (solid columns). Data are means ± S.E.M. of $n = 8$–26 animals per group. ^{c} $P < 0.001$ vs. vehicle challenge; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. A 68930 challenge.

derive IC_{50} values; these were converted to K_i values using the Cheng-Prusoff equation: $K_i = IC_{50}(1 + C/K_d)$ where C is ligand concentration and K_d is the apparent dissociation constant (Deveney and Waddington, 1995).

3. Results

3.1. Behavioural studies

The principal behavioural responses to A 68930 (0.5 mg/kg) were confirmed to be the ready induction of episodes of grooming, which encompassed a prominence of intense grooming, together with vacuous chewing; low scores on the stereotypy scale confirmed these behaviours to be emitted in an episodic, interpolated manner in the absence of classical stereotyped behaviour. As noted previously (Deveney and Waddington, 1996), the grooming and intense grooming responses to A 68930 were readily and dose-dependently blocked by 0.01–1.0 mg/kg SCH 23390, while the vacuous chewing response was *not* influenced significantly by any dose of SCH 23390 administered. In contrast, 0.2–5.0 mg/kg BW 737C dose-dependently blocked the grooming, intense grooming *and* vacuous chewing responses to A 68930. LY 270411, 2.0–10.0 mg/kg, readily and dose-dependently blocked A 68930-induced grooming and intense grooming, but exerted no significant effect on vacuous chewing (Fig. 1). When given alone at 10.0 mg/kg, LY 270411 failed to exert any stimulatory effect on spontaneous behaviour.

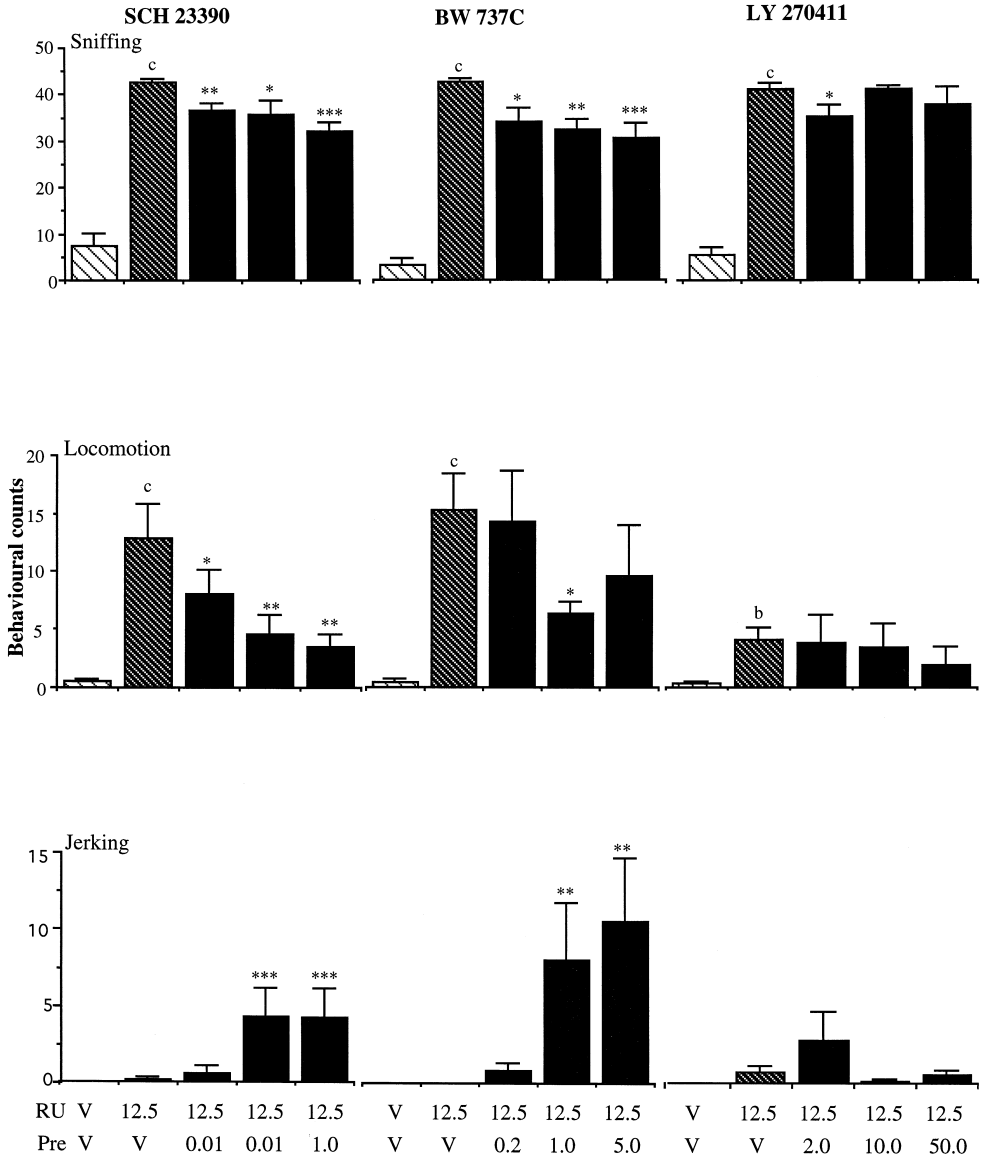

Fig. 2. Behavioural counts for sniffing, locomotor and jerking responses to challenge with RU 24213 (RU, 12.5 mg/kg; stippled columns) or its vehicle (V; hatched columns) following pretreatment (Pre) with vehicle (V), 0.01–1.0 mg/kg SCH 23390, 0.2–5.0 mg/kg BW 737C or 2.0–50.0 mg/kg LY 270411 (solid columns). Data are means ± S.E.M. of $n = 8$–72 animals per group. $^{b}P < 0.01$, $^{c}P < 0.001$ vs. vehicle challenge; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. RU 24213 challenge.

Table 1
Displacement of [^{3}H]SCH 23390 and of [^{3}H]spiperone from striatal 'D_1-like' and 'D_2-like' receptors, respectively, by investigatory and reference agents

Drug	K_i (nM)		'D_1-like'/'D_2-like' selectivity
	[^{3}H]SCH 23390 ('D_1-like')	[^{3}H]spiperone ('D_2-like')	
LY 270411	8.5	959	0.009
BW 737C	5.8	58	0.1
SCH 23390	0.18	189	0.001
A 68930	6.8	464	0.015
RU 24213	9482	87	109

Values are geometric means of at least three independent determinations, each performed in duplicate.

The principal behavioural responses to RU 24213 (12.5 mg/kg) were confirmed to be the ready induction of episodes of sniffing and locomotion; modest scores on the stereotypy scale confirmed these behaviours to be emitted in a discontinuous manner, in the absence of compulsive stereotypy. As noted previously (Deveney and Waddington, 1996), the sniffing response to RU 24213 was modestly attenuated and the locomotor response more prominently attenuated, but not blocked, by 0.01–1.0 mg/kg SCH 23390; these effects of SCH 23390 were accompanied by the release of episodes of myoclonic jerking to RU 24213. Similarly, 0.2–5.0 mg/kg BW 737C modestly attenuated the sniffing response to RU 24213, while an intermediate dose of BW 737C exerted significant attenuation of the locomotor response; these effects of BW 737C were accompanied by the prominent release of episodes of myoclonic jerking to RU 24213. Conversely, 2.0–50.0 mg/kg LY 270411 weakly attenuated the sniffing response to RU 24213 only at a low dose, and failed to influence significantly the locomotor response even in the face of a relatively modest, though still statistically significant, induction of locomotion in this instance; there was no significant release of myoclonic jerking to RU 24213 by any dose of LY 270411 administered (Fig. 2).

3.2. Radioligand binding studies

LY 270411 demonstrated high affinity and >100-fold selectivity for dopamine 'D_1-like' over 'D_2-like' receptors; BW 737C showed comparable high affinity but less (≈ 10-fold) selectivity (Table 1). The reference compounds SCH 23390, A 68930 and RU 24213 were confirmed to demonstrate high affinities and selectivities for dopamine 'D_1-like' and 'D_2-like' receptors, as appropriate (Deveney and Waddington, 1996).

4. Discussion

LY 270411 is a chemically novel thienoazepine selective dopamine 'D_1-like' receptor antagonist; it shows high, selective affinity for dopamine 'D_1-like' over 'D_2-like' receptors and inhibits the stimulation of adenylyl cyclase induced by dopamine but fails to elevate prolactin levels (Bowman et al., 1990, present data). In this study we found LY 270411 to demonstrate an action indistinguishable from that of the isoquinoline BW 737C (Riddall, 1992; Daly and Waddington, 1993) and the prototypical benzazepine SCH 23390 (Iorio et al., 1983; Waddington and O'Boyle, 1989) dopamine 'D_1-like' receptor antagonists to readily block grooming responses to the new isochroman, full efficacy selective dopamine 'D_1-like' agonist A 68930 (De Ninno et al., 1991; Daly and Waddington, 1993); grooming constitutes the most widely accepted behavioural index of dopamine 'D_1-like' receptor stimulation that is induced by all dopamine 'D_1-like' receptor agonists and blocked by all dopamine 'D_1-like' receptor antagonists examined to date (Waddington et al., 1995).

This generality of dopamine 'D_1-like' receptor drug action in relation to grooming does not extend to vacuous chewing, a more controversial behavioural index of dopamine 'D_1-like' receptor stimulation (Rosengarten et al., 1983; Collins et al., 1991; Waddington et al., 1995). We have reported the benzazepine dopamine 'D_1-like' receptor agonist series typified by SK&F 38393 not to induce vacuous chewing, though such chewing was induced by A 68930; furthermore, vacuous chewing to A 68930 was insensitive to SCH 23390 but was blocked by BW 737C (Molloy and Waddington, 1987; Murray and Waddington, 1989a; Daly and Waddington, 1992a,1993). On classical pharmacological grounds, we proposed that grooming appears to be mediated via a dopamine 'D_1-like' receptor that recognises all known dopamine 'D_1-like' receptor agonists and antagonists, while vacuous chewing might be mediated via a distinct dopamine 'D_1-like' receptor that recognises preferentially the isochromans/isoquinolines (Daly and Waddington, 1993).

Here, we replicate our heuristic finding that vacuous chewing to A 68930 is insensitive to SCH 23390 but is blocked by BW 737C. In a manner similar to SCH 23390, LY 270411 also failed to influence vacuous chewing to A 68930 even at a dose which completely blocked grooming responses thereto; however, while SCH 23390 induced vacuous chewing when given alone (Collins et al., 1991; Daly and Waddington, 1993; Deveney and Waddington, 1995), LY 270411 failed to stimulate this behaviour. Given the weight of evidence that the vacuous chewing response to selective dopamine 'D_1-like' receptor agonists is not an artefact of residual, non-selective affinity for serotonergic, muscarinic or other non-dopaminergic processes (Rosengarten et al., 1983, 1986; Collins et al., 1991; Daly and Waddington, 1993; Deveney and Waddington, 1995), it would appear that this response may indeed be mediated via a dopamine 'D_1-like' receptor that recognises preferentially the isochroman/isoquinoline agonist/antagonist compounds, and at which SCH 23390 may exert some agonist rather than antagonist activity; there is complemen-

tary neurochemical (Martin et al., 1995) and electrophysiological (Wachtel and White, 1995) evidence that SCH 23390 can exert agonist-like effects, though such an action does not appear to generalise to the benzofuranyl-benzazepine NNC 756 (Daly and Waddington, 1993), to BW 737C or to the novel thienoazepine LY 270411.

In terms of behavioural responses to stimulation of dopamine 'D_2-like' receptors, there is an extensive body of evidence that dopamine 'D_1-like' receptor antagonists attenuate typical sniffing and locomotor responses and release an atypical myoclonic jerking response to established selective dopamine 'D_2-like' receptor agonists such as RU 24213 and quinelorane (LY 163502) through well-described cooperative/synergistic and oppositional dopamine 'D_1-like' : 'D_2-like' receptor interactions, respectively (Waddington et al., 1994); this profile appears generic to benzazepine (SCH 23390 and SK&F 83566), benzonaphthazepine (SCH 39166), benzofuranylbenzazepine (NNC 756) and isoquinoline (A 69024 and BW 737C) dopamine 'D_1-like' receptor antagonists (Murray and Waddington, 1989b; Daly and Waddington, 1992b). However, we find that LY 270411 exerts little or no such action, even at a dose 25-fold greater than required to antagonise A 68930-induced grooming. Thus, LY 270411 is anomalous relative to other selective dopamine 'D_1-like' receptor antagonists identified to date by virtue of acting at a dopamine 'D_1-like' receptor that appears *not* to participate either in cooperative/synergistic or oppositional dopamine 'D_1-like' : 'D_2-like' receptor interactions.

In conclusion, LY 270411 appears to be a novel thienoazepine selective dopamine 'D_1-like' receptor antagonist with a unique functional profile of readily blocking typical dopamine 'D_1-like' receptor-mediated behaviours without influencing either atypical dopamine 'D_1-like' or any 'D_2-like' receptor-mediated behaviours; however, studies with dopamine 'D_1-like' and 'D_2-like' receptor agonists additional to A 68930 and RU 24213 would be necessary to establish such an effect. These data are challenging and heuristic, as they suggest for the first time that the site mediating prototypical dopamine 'D_1-like' receptor antagonist blockade of dopamine 'D_1-like' receptor agonist-induced behaviour may be dissociable pharmacologically from site(s) participating in functional interactions with dopamine 'D_2-like' receptors; they thus indicate further the existence of behaviourally relevant dopamine 'D_1-like' receptor subtypes, whose relationship, if any, to those identified by molecular/gene cloning approaches remains to be determined.

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