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New Putative Selective Agonists at the D-1 Dopamine Receptor: Behavioural and Neurochemical Comparison of CY 208-243 With SK&F 101384 and SK&F 103243

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MURRAY, A. M. AND J. L. WADDINGTON. *New putative selective agonists at the D-1 dopamine receptor: Behavioural and neurochemical comparison of CY 208-243 with SK&F 101384 and SK&F 103243.* PHARMACOL BIOCHEM BEHAV **35**(1) 105–110, 1990.—Three putative D-1 agonists with nonbenzazepine structures were compared with the prototype benzazepine D-1 partial agonist SK&F 38393 for their behavioural effects in the intact adult rat, and for their relative affinities for D-1 and D-2 dopamine receptors in vitro. SK&F 103243, a restricted conformation analogue of SK&F 38393, and SK&F 101384 (8-Cl-ADTN) showed low affinity for D-1 and D-2 receptors in in vitro binding studies, and failed to induce any behavioural effects on peripheral administration. CY 208-243, an indolophenanthridine derivative, showed appreciable affinity not only for D-1 receptors, but also for D-2 receptors, while in behavioural studies it showed some of the characteristics of a partial D-1 dopamine receptor agonist; thus, it failed to promote stereotyped behaviour, but induced episodes of intense grooming which were sensitive to blockade by the D-1 antagonist SCH 23390. No such effect was induced by the selective D-2 agonist RU 24213. CY 208-243 is the first nonbenzazepine which shows *some* of the properties of a D-1 agonist in the intact adult animal. However, the differences between its in vitro binding characteristics and its functional properties remain enigmatic.

CY 208-243 Dopamine D-1 and D-2 receptors Intense grooming

DOPAMINE receptors have been subdivided into D-1 and D-2 subtypes: D-1, stimulating dopamine-sensitive adenylate cyclase and D-2, inhibiting adenylate cyclase or else unassociated with this enzyme (11,32). Until recently, the majority of the central effects of dopamine were thought to be mediated through the D-2 dopamine receptor, with D-1 receptors deemed of unknown functional relevance (26). More recently, this view of the prepotent role of the D-2 receptor has been challenged through the introduction of the first selective D-1 antagonists SCH 23390 and SK&F 83566 (29). These exhibited prominent neuroleptic-like behavioural effects which have focussed attention on functional interactions between D-1 and D-2 dopamine receptor systems (5, 29–31). It would appear that D-1 receptor activation is necessary for the manifestation of common D-2-stimulated behaviours and that concurrent stimulation of both receptors is necessary for the full expression of typical dopamine-mediated responses (1, 3, 5, 14, 18, 23, 29–31). Despite the profound behavioural effects of D-1 antagonists, there remains a fundamental question in how D-1 agonists might influence unconditioned motor behaviour in the whole animal. In searching for behavioural correlates of central D-1 dopamine receptor activity, SK&F 38393, a 1-phenyl-1H-3-benzazepine partial D-1 agonist (27) with relatively poor penetration into the brain, was seen to induce episodes of prominent grooming in the intact adult rat, these occurring in the absence of typical stereotyped behaviour (15, 16, 19); similar effects have also been observed in mice (28). Additionally, SK&F 38393 has been noted to induce a syndrome of perioral dyskinesia, and this response may be most robust during concurrent suppression of D-2 tone (10, 19, 24, 25). We have recently reported these behaviours to be induced by a range of D-1 agonists within the same general chemical class (19), indicating that they are not an idiosyncratic response to SK&F 38393. However, almost all of the work on D-1 agonist effects still centres on the 1-phenyl-1H-3-benzazepines. Therefore, most of the conclusions derived from

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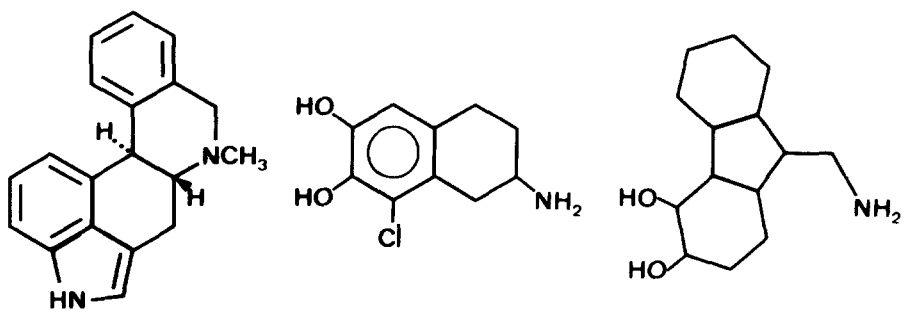

CY 208-243 SK&F 101384 SK&F 103243

FIG. 1. New putative selective agonists at the D-1 dopamine receptor.

studies to date await confirmation from work with structurally dissimilar agonists which act selectively at the D-1 receptor. To address this issue, we have studied the behavioural pharmacology of 3 putative D-1 agonists (Fig. 1): CY 208-243 (13), SK&F 101384 (34) and SK&F 103243 (12). They were evaluated using direct visual observation techniques sensitive to a wide range of typical and atypical behaviours, and radioligand binding measures, in comparison with SK&F 38393 and the selective D-2 agonist RU 24213 (7,23).

METHOD

Animals

Young adult male Sprague-Dawley rats (Biolabs, Ballina) weighing between 200–376 g were used in all experiments. The rats were housed in groups of 5 per cage, with food and water available ad lib, and were maintained on a 12/12-hour (6 a.m. on; 6 p.m. off) light/dark cycle.

Behavioural Studies

Animals were removed from their home cage, placed individually in perspex cages measuring $52 \times 39 \times 18$ cm, and left undisturbed for a habituation period of 2.5 hr.

Behavioural assessments were carried out in a manner similar to that previously described (19,20). Immediately before and at intervals after subcutaneous injections of drug or vehicle, animals were assessed using a rapid time-sampling behavioural checklist technique. For this procedure, each rat was observed individually for 5-sec periods at 1-min intervals over 5 consecutive minutes, using an extended behavioural checklist. This allowed the presence or absence of the following individual behaviours (occurring alone or in combination) to be determined in each 5-sec period: sniffing (Sn); locomotion (L); rearing (R); grooming (Gr; of any form); intense grooming (Gr_i; a characteristic pattern of grooming of the face with the forepaws followed by vigorous grooming of the hind flank with the snout); chewing (Ch; directed onto any physical material); vacuous chewing (VCh; not directed onto any physical material); stillness (St; motionless, with no behaviour evident). After assessment using the behavioural checklist, animals were assessed using a conventional 0–6 point stereotypy rating 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 was repeated at 10-min intervals. Rats were used on two occasions only, separated by a drug-free interval of one week. On each occasion rats were randomly allocated to one of the various treatment groups. All assessments were made by an observer unaware of the treatment given to each animal.

Radioligand Binding Studies

Using methods similar to those previously described (19,20), striata from similar male Sprague-Dawley rats were homogenised in 30 volumes of 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 (83 Ci/mmol, Amersham) to D-1 receptors was determined by incubating 0.5 ml of membrane suspension with 0.3 nM ligand and 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 represented 90–95% of total binding. Incubations were stopped by filtration through GF/B filters followed by three 5 ml washes with ice-cold buffer. Radioactivity trapped on the filters was quantified by liquid scintillation spectroscopy after addition of 5 ml of liquiscint (Med. Labs) using a Searle model Delta 300 counter with 23% counting efficiency for tritium.

The binding of ^{3}H-spiperone (15 Ci/mmol, Amersham) to D-2 receptors was determined using membranes prepared as above. Incubations contained 1 ml of membrane suspension with 0.18 nM ligand and unlabelled drugs in a total volume of 5 ml. Specific binding was defined as that displaced by 1 μM domperidone (Janssen) and represented 65–85% of total binding. Incubation and filtration were as described above.

Drugs

The following investigational drugs were used: SK&F 38393 (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine; Smith Kline & French, Philadelphia); CY 208-243 ([−]-4,6,6a, 7,8,12b-hexahydro-7-methylindolo[4,3-ab]phenanthridine; Sandoz, Basel); SK&F 101384 (2-amino-8-chloro-6,7-dihydroxytetralin[8-Cl-ADTN]; Smith Kline & French, Philadelphia); SK&F 103243 (3,4-dihydroxy-9H-fluorene-9-methanamine; Smith Kline & French, Philadelphia); RU 24213 (N-n-propyl-N-phenylethyl-p-[3-hydroxyphenyl]ethylamine; Roussel-UCLAF, Romainville).

TABLE 1

BEHAVIOURAL RESPONSES TO CY 208-243 IN COMPARISON WITH SK&F 38393 AND RU 24213

Drug	mg/kg	Sn	L	R	Gr	Gr_i	VCh	Ch	St	Stereotypy Score
Vehicle		16.4±2.9	2.6±0.9	2.9±0.9	1.1±0.7	1.0±0.7	0.0±0.0	0.8±0.4	20.5±2.4	0.9±0.2
SK&F 38393[a]	2.0	19.3±2.2	2.5±1.2	4.6±2.8	3.8±1.5	1.3±0.5	0.3±0.2	0.3±0.2	18.9±2.4	1.4±0.1
	8.0	15.1±2.5	3.5±1.2	2.4±0.8	4.8±1.6	4.0±1.4	0.0±0.0	0.0±0.0	17.4±3.0	1.3±0.2
	32.0	21.1±1.4	1.5±0.5	1.5±0.8	6.5±1.6*	5.6±1.8*	0.1±0.1	0.1±0.1	15.1±2.0	1.7±0.1*
Vehicle		8.1±3.0	2.7±0.7	1.4±0.5	2.9±0.6	0.1±0.1	0.4±0.2	0.4±0.2	27.2±0.8	0.7±0.2
CY 208-243	0.1	11.7±2.0	3.2±0.6	2.6±0.7	5.0±1.6	1.0±0.4	0.2±0.2	0.4±0.3	25.0±0.9	0.7±0.2
	1.0	12.9±2.8	5.5±3.0	3.0±1.6	7.6±1.3*	1.9±0.6*	0.2±0.2	0.6±0.4	21.4±3.3	1.1±0.2*
	10.0	23.4±2.5*	9.5±3.8	0.6±0.4	1.2±0.1	0.1±0.1	0.2±0.2	0.0±0.0	28.6±0.6	1.3±0.2*
Vehicle		10.1±2.6	0.9±0.6	0.9±0.5	1.1±0.5	0.4±0.2	0.1±0.1	0.2±0.2	27.2±0.8	0.4±0.1
RU 24213	1.25	8.4±2.9	0.9±0.6	0.6±0.4	0.2±0.2	0.0±0.0	0.2±0.2	1.6±1.0	27.5±1.0	0.5±0.2
	6.25	26.1±2.6*	7.6±2.7*	2.4±1.0	0.6±0.3	0.0±0.0	1.2±0.5*	2.2±0.4*	17.5±2.0*	1.9±0.1*
	25.0	28.0±0.8*	16.5±2.5*	2.1±1.3	0.2±0.2	0.0±0.0	0.6±0.4	1.2±0.9	16.6±2.5*	2.0±0.1*

Data are means ± SEM of behavioural counts for n = 8 animals per group. *$p<0.05$ vs. vehicle.
[a]Reference data from (19).

The selective D-1 antagonist SCH 23390 (*R*-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine; Schering, NJ), the selective D-2 antagonist *R*-piquindone (Roche, NJ) or vehicle were given 30 min prior to agonist challenge. CY 208-243 was dissolved in 0.1 N HCl and made up to volume with distilled water; other agents were dissolved in distilled water. In behavioural studies, drugs were given subcutaneously into the flank with control animals receiving similar injections of the respective vehicle alone.

Data Analysis

From the application of the behavioural checklist, the total 'counts' for each individual behaviour was determined as the number of 5-sec observation windows in which a given behaviour was evident, summed over a 1-hr period. These behavioural counts were expressed as means ± SEM and analysed using analysis of variance and Student's *t*-test. Stereotypy scores from the application of the rating scale were averaged over the 1-hr period. They were expressed as means ± SEM, and were analysed using the Kruskal-Wallis nonparametric analysis of variance and the Mann-Whitney U-test.

Data from radioligand displacement experiments were analysed by a computer-assisted nonlinear iterative curve fitting procedure (2). The resulting IC_{50} was converted to a K_i value 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.

RESULTS

Behavioural Studies

SK&F 38393 [2–32 mg/kg (19)] increased behavioural counts for grooming and intense grooming without inducing stereotyped behaviour. Low scores on the stereotypy rating scale, and the continuing presence of interpolated episodes of stillness indicated a discontinuous, fragmented activation of these particular elements of behaviour. CY 208-243 (0.1–10 mg/kg) likewise did not induce typical stereotyped behaviour. Behavioural counts for both grooming and intense grooming were increased over the dose range 0.1–1.0 mg/kg; however, the higher dose of 10.0 mg/kg was associated with a diminished response. Episodes of nonstereotyped sniffing were significantly increased only at the highest dose (Table 1). SK&F 101384 and SK&F 103243 (0.1–10.0 mg/kg; data not shown), did not induce statistically significant increases in counts for any of these behaviours. Neither vacuous chewing nor chewing directed onto any form of physical material was induced by any of the above agents.

Conversely, RU 24213 (1.25–25 mg/kg), induced a modest, dose-dependent increase in stereotypy scores, but mean scores rarely exceeded 2 on the 0–6 scale even at the highest dose. The behavioural check list revealed that counts for sniffing and locomotion were increased by RU 24213. At the intermediate dose only, there was some modest increase in behavioural counts for the behaviours of chewing and vacuous chewing, while higher doses were associated with a diminished response. No dose of RU 24213 had any significant effect on counts for either grooming or intense grooming.

CY 208-243 (1.0 mg/kg) was also administered after 30 min pretreatments with the selective D-1 antagonist SCH 23390 or the selective D-2 antagonist piquindone. As shown in Fig. 2, SCH 23390 (50–250 μg/kg) dose-dependently antagonised CY 208-243-induced intense grooming. This response was also attenuated by *R*-piquindone (100–750 μg/kg; $p<0.06$). No atypical behaviours emerged in animals given either pretreatment and then challenged with CY 208-243.

Radioligand Binding

As described in detail elsewhere (19), saturation studies with 0.1–3.0 nM ^{3}H-SCH 23390 yielded a B_{max} of 47.0 pmol/g and a K_D of 0.58 nM. Comparable studies with 0.05–2.5 nM ^{3}H-spiperone yielded a B_{max} of 21.1 pmol/g and a K_D of 0.09 nM (n = 11–16). SK&F 38393 showed high affinity and selectivity for ^{3}H-SCH 23390-labelled D-1 receptors. Conversely, RU 24213 showed high affinity and selectivity for the ^{3}H-spiperone-labelled D-2 receptor (Table 2). CY 208-243 showed high affinity for D-1 receptors, but also exhibited comparably high affinity for D-2 receptors. SK&F 101384 and SK&F 103243 showed low affinity and selectivity for both D-1 and D-2 receptors.

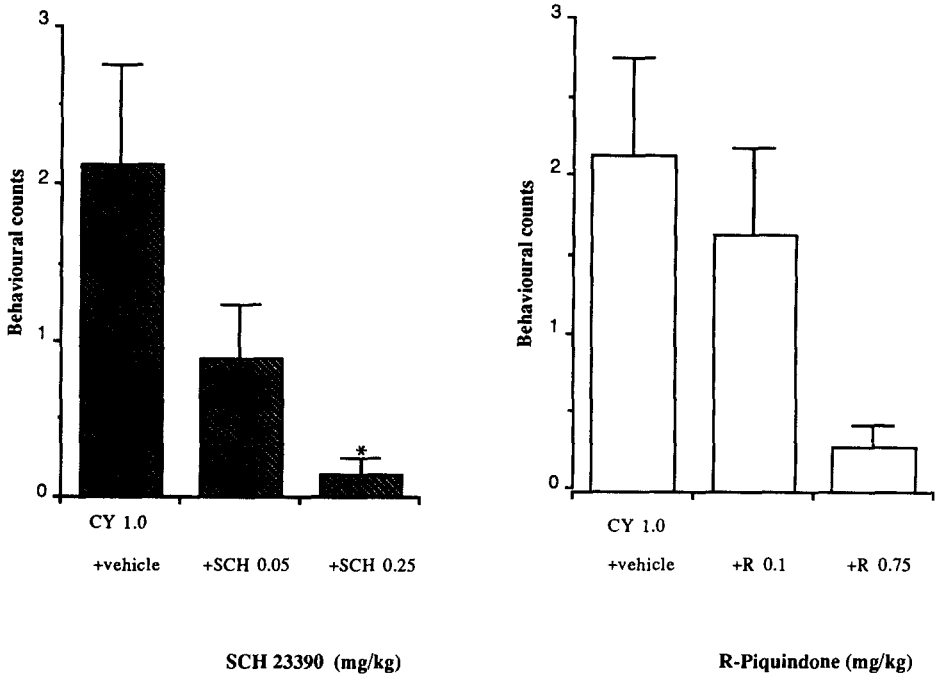

FIG. 2. Behavioural counts for intense grooming in animals given 1.0 mg/kg CY 208-243 after pretreatment with vehicle, or (left; hatched columns) 0.05–0.25 mg/kg SCH 23390, or (right; open columns) 0.1–0.75 mg/kg *R*-piquindone. Data are means ± sem; n = 8. *$p<0.05$ vs. vehicle pretreatment.

DISCUSSION

Because of the need to identify selective D-1 dopamine receptor agonists from chemical classes other than the 1-phenyl-1H-3-benzazepines, we have studied three new agents purported to show such properties.

SK&F 101384, an 8-chloro-analogue of ADTN, and SK&F 103243, a rigid aminomethylfluorene analogue of the benzazepine D-1 agonists, have each been recently reported to show considerably greater affinity for D-1 than for D-2 receptors (12,34); we were unable to replicate these findings. However, in these previous studies, selective affinity for D-1 receptors was reported on the basis of comparing K_i values for the displacement of the D-1 *agonist* ^{3}H-fenoldopam with those for the D-2 *antagonist* ^{3}H-spiperone; as dopaminergic agonists are reliably more potent in displacing ^{3}H-agonist than ^{3}H-antagonist ligands (26), such a procedure might lead to an inappropriate conclusion of selective affinity for D-1 receptors. On comparing relative affinities to displace D-1 and D-2 antagonist ligands, which readily reveal the D-1 selectivity of SK&F 38393 and the D-2 selectivity of RU 24213, we find no evidence that either SK&F 101384 or SK&F 103243 show selective D-1 receptor affinity; SK&F 101384 showed some affinity for both receptor subtypes, while SK&F 103243 was only weakly active. Following peripheral administration, no behavioural responses to either agonist were evident; on the basis of its structural relationship to ADTN, which does not cross the blood-brain barrier (4), SK&F 101384 might be predicted to exhibit poor penetration into the brain.

TABLE 2

DISPLACEMENT OF ^{3}H-SCH 23390 (^{3}H-SCH) AND OF ^{3}H-SPIPERONE (^{3}H-SPIP) FROM STRIATAL D-1 AND D-2 RECEPTORS BY INVESTIGATIONAL AGENTS

	K_i (nM)		
	^{3}H-SCH (D-1)	^{3}H-SPIP (D-2)	D-1/D-2
SK&F 38393*	296	14060	0.02
RU 24213	11520	75	153.0
SK&F 101384	1358	804	1.69
SK&F 103243	4089	12270	0.33
CY 208-243	161	285	0.57

Values are geometric means of at least 3 independent determinations, each performed in duplicate.

*Reference data from (19).

CY 208-243 is a phenanthridine derivative recently shown to have affinity for the ^{3}H-SCH 23390-labelled D-1 receptor and to stimulate DA-sensitive adenylate cyclase in the manner of a partial agonist; however, while in in vitro binding studies this agent also showed appreciable affinity for the ^{3}H-spiperone-labelled D-2 receptor (and for some nondopaminergic sites), no functional correlates of that apparent affinity for D-2 receptors were evident (13). Thus, CY 208-243, like SK&F 38393, had no effect either on plasma prolactin levels in rats or to induce emesis in dogs, two sensitive indices of D-2 activity; in the unilateral 6-hydroxydopamine-lesioned rat, CY 208-243 and SK&F 38393 induced rotational behaviour that was antagonised by SCH 23390, but not by the selective D-2 antagonist sulpiride (13). In the present studies in the intact adult animal, CY 208-243 failed to induce stereotyped behaviour, but variably promoted episodes of general grooming and of intense grooming; these were indistinguishable from those induced by SK&F 38393 and a range of related benzazepine D-1 agonists (15, 16, 19). This response to CY 208-243 was dose-related only over the range of 0.1–1.0 mg/kg. The higher dose of 10.0 mg/kg was associated with a reduction in

these grooming responses and the emergence of episodes of sniffing, with some locomotion, but this did not appear to have a basis in response competition through induction of stereotypy; scores on the 0–6 scale remained well below '2' and interpolated episodes of stillness were not reduced. These responses to CY 208-243 were clearly different from those induced by the selective D-2 agonist RU 24213, which failed to promote either general or intense grooming, readily induced prominent sniffing and locomotion at threshold levels of stereotypy and markedly reduced (but did not abolish) interpolated episodes of stillness. Whether the diminished grooming response to CY 208-243 at high doses has some basis in its partial agonist activity at the D-1 receptor, and/or in other as yet unspecified aspects of its pharmacology, remains to be determined.

The intense grooming induced by CY 208-243 was readily blocked by the selective D-1 antagonist SCH 23390. Its attenuation by the selective D-2 antagonist *R*-piquindone (6,21) is consistent with the view that tonic activity through one DA receptor subtype is required for the expression of typical behaviour initiated by stimulation of its counterpart, in accordance with prevailing schema for D-1:D-2 interactions (5, 29–31); this mirrors the antagonism of grooming responses to the benzazepine D-1 agonists SK&F 38393 and SK&F 77434 by a range of selective D-2 antagonists (8,17).

However, while the benzazepine D-1 agonists can induce atypical vacuous chewing when tonic activity through D-2 receptors is concurrently blocked (19,25), no such effect was seen with CY 208-243 following pretreatment with *R*-piquindone. This suggests some differences between the D-1 agonist-like effects of CY 208-243 and of the 1-phenyl-1H-3-benzazepines, the nature of which is not yet clear. Also, while agents with D-2 agonist activity can induce episodic jerking of the limbs or whole body when tonic activity through D-1 receptors is concurrently blocked (20,33), no such atypical effect was seen with CY 208-243 following pretreatment with SCH 23390. Such behavioural data would be consistent with evidence from previous physiological studies (9,13) that for some as yet unexplained reason it has not proved possible to detect a functional correlate of the affinity of CY 208-243 for D-2 receptors. In the present study we confirm that in in vitro radioligand binding studies CY 208-243 shows appreciable affinity for both D-1 and D-2 receptors in rat striatum; a similar profile is evident in the putamen of human postmortem brain, where our preliminary kinetic studies suggest that CY 208-243 shows similar affinities for, but different modes of interaction with D-1 and D-2 receptors (22).

In summary, our results indicate that CY 208-243 is the first nonbenzazepine agent to show some, but not all, of the properties of a behaviourally active D-1 agonist on peripheral administration to intact adult animals. Additionally, these results generalise, to outside the realm of the 1-phenyl-1H-3-benzazepines, the notion that the induction of intense grooming may be a characteristic behavioural response to D-1 receptor stimulation. However, the relationship of the spectrum of behavioural effects of CY 208-243 to its in vitro binding characteristics remains enigmatic, and will require further study.

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REFERENCES

1. Arnt, J.; Hyttel, J.; Perregaard, J. Dopamine D-1 receptor agonists combined with the selective D-2 agonist quinpirole facilitate the expression of oral stereotyped behaviour in rats. Eur. J. Pharmacol. 133:137–145; 1987.
2. Barlow, R. B. Biodata handling with microcomputers. Elsevier: Amsterdam: 1983.
3. Braun, A. R.; Chase, T. N. Obligatory D-1/D-2 receptor interaction in the generation of dopamine agonist related behaviours. Eur. J. Pharmacol. 131:301–306; 1986.
4. Cannon, J. G.; Costall, B.; Laduron, P. M.; Leysen, J. E.; Naylor, R. J. Effects of some derivatives of 2-aminotetralin on dopamine-sensitive adenylate cyclase and on the binding of ^{3}H-haloperidol to neuroleptic receptors in the rat striatum. Biochem. Pharmacol. 27: 1417–1420; 1978.
5. Clarke, D.; White, F. J. D-1 dopamine receptor—the search for a function: a critical evaluation of the D-1/D-2 dopamine receptor classification and its functional implications. Synapse 1:347–388; 1987.
6. Davidson, A. B.; Boff, E.; MacNeil, D. A.; Wanger, J.; Cook, L. Pharmacological effects of Ro22-1319: a new antipsychotic agent. Psychopharmacology (Berlin) 79:32–39; 1983.
7. Euvrard, C.; Ferland, L.; Di Paolo, T.; Beaulieu, M.; Labrie, F.; Oberlander, C.; Raynaud, J. P.; Boissier, J. R. Activity of two new potent dopaminergic agonists at the striatal and anterior pituitary levels. Neuropharmacology 19:379–386; 1980.
8. Gandolfi, O.; Dall'Olio, R.; Vaccheri, A.; Roncada, P.; Montanaro, N. Responses to selective D-1 and D-2 agonists after repeated treatment with selective D-1 and D-2 antagonists. Pharmacol. Biochem. Behav. 30:463–469; 1988.
9. Imperato, A.; Di Chiara, G. CY 208-243, a novel dopamine D-1 receptor agonist, fails to modify dopamine release in freely moving rats. Eur. J. Pharmacol. 160:155–158; 1989.
10. Johansson, P.; Levin, E.; Gunne, L.; Ellison, G. Opposite effects of a D-1 and a D-2 agonist on oral movements in rats. Eur. J. Pharmacol. 134:83–88; 1987.
11. Kebabian, J. W.; Calne, D. B. Multiple receptors for dopamine. Nature 277:93–96; 1979.
12. Ladd, D. L.; Weinstock, J.; Wise, M.; Gessner, G. W.; Sawyer, J. L.; Flaim, K. E. Synthesis and dopaminergic binding of 2-aryldopamine analogues: phenethylamines, 3-benzazepines, and 9-(aminomethyl)fluorenes. J. Med. Chem. 29:1904–1912; 1986.
13. Markstein, R.; Seiler, M. P.; Vigouret, J. M.; Urwyler, S.; Eng, A.; Dixon, K. Pharmacological properties of CY 208-243, a novel D-1 agonist. In: Sandler, M.; Dahlstrom, A.; Belmaker, R., eds. Progress in catecholamine research. Part B: Central aspects. New York: Alan R. Liss Inc.; 1988:59–64.
14. Mashurano, M.; Waddington, J. L. Stereotyped behaviour in response to the selective D-2 dopamine receptor agonist RU 24213 is enhanced by pretreatment with the selective D-1 agonist SK&F 38393. Neuropharmacology 25:947–949; 1986.
15. Molloy, A. G.; Waddington, J. L. Dopaminergic behaviour stereospecifically promoted by the D-1 agonist *R*-SK&F 38393 and selectively blocked by the D-1 antagonist SCH 23390. Psychopharmacology (Berlin) 82:409–410; 1984.
16. Molloy, A. G.; Waddington, J. L. Assessment of grooming and other behavioural responses to the D-1 dopamine receptor agonist SK&F 38393 and its *R* and *S*-enantiomers in the intact adult rat. Psychopharmacology (Berlin) 92:164–168; 1987.
17. Molloy, A. G.; Waddington, J. L. Pharmacological characterisation in the rat of grooming and other behavioural responses to the D-1 dopamine receptor agonist *R*-SK&F 38393. J. Psychopharmacol. 1:177–183; 1987.
18. Molloy, A. G.; O'Boyle, K. M.; Pugh, M. T.; Waddington, J. L. Locomotor behaviours in response to new selective D-1 and D-2 dopamine receptor agonists. Pharmacol. Biochem. Behav. 25:249–253; 1986.
19. Murray, A. M.; Waddington, J. L. 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; 1989.

20. Murray, A. M.; Waddington, J. L. Further evidence for two directions of D-1:D-2 dopamine receptor interaction revealed concurrently in distinct elements of typical and atypical behaviour: studies with the new enantioselective D-2 agonist LY 163502. Psychopharmacology (Berlin) 98:245–250; 1989.
21. O'Boyle, K. M.; Waddington, J. L. Identification of the enantiomers of SK&F 83566 as specific and stereoselective antagonists at the striatal D-1 dopamine receptor: comparisons with the D-2 enantioselectivity of Ro22-1319. Eur. J. Pharmacol. 106:219–220; 1984.
22. O'Boyle, K. M.; Waddington, J. L. CY 208-243: kinetics of binding to D-1 and D-2 dopamine receptors. Br. J. Pharmacol. 95:560P; 1988.
23. Pugh, M. T.; O'Boyle, K. M.; Molloy, A. G.; Waddington, J. L. Effects of the putative D-1 antagonist SCH 23390 on stereotyped behaviour induced by the D-2 agonist RU 24213. Psychopharmacology (Berlin) 87:308–312; 1985.
24. Rosengarten, H.; Schweitzer, J. W.; Friedhoff, A. J. Induction of oral dyskinesias in naive rats by D-1 stimulation. Life Sci. 33:2479–2482; 1983.
25. Rosengarten, H.; Schweitzer, J. W.; Friedhoff, A. J. Selective dopamine D-2 receptor reduction enhances a D-1 mediated oral dyskinesia in rats. Life Sci. 39:29–35; 1986.
26. Seeman, P. Brain dopamine receptors. Pharmacol. Rev. 32:229–313; 1980.
27. Setler, P. E.; Sarau, H. M.; Zirkle, C. L.; Saunders, H. L. The central effects of a novel dopamine agonist. Eur. J. Pharmacol. 50:419–430; 1978.
28. Starr, B. S.; Starr, M. S. Differential effects of dopamine D-1 and D-2 agonists and antagonists on velocity of movement, rearing and grooming in the mouse. Neuropharmacology 25:445–453; 1986.
29. Waddington, J. L. Behavioural correlates of the action of selective D-1 dopamine receptor antagonists: impact of SCH 23390 and SK&F 83566, and functionally interactive D-1: D-2 receptor systems. Biochem. Pharmacol. 35:3661–3667; 1986.
30. Waddington, J. L. Functional interactions between D-1 and D-2 dopamine receptor systems: their role in the regulation of psychomotor behaviour, putative mechanisms and clinical relevance. J. Psychopharmacol.; in press.
31. Waddington, J. L.; O'Boyle, K. M. The D-1 dopamine receptor and the search for its functional role: from neurochemistry to behaviour. Rev. Neurosci. 1:157–184; 1987.
32. Waddington, J. L.; O'Boyle, K. M. Drugs acting on brain dopamine receptors: a conceptual re-evaluation five years after the first selective D-1 antagonist. Pharmacol. Ther. 43:1–52; 1989.
33. Waddington, J. L.; Molloy, A. G.; O'Boyle, K. M. Motor consequences of D-1 dopamine receptor blockade. Clin. Neuropharmacol. 9(Suppl. 4):20–22; 1986.
34. Weinstock, J.; Gaitanopoulos, D. E.; Oh, H.-J.; Pfeiffer, F. R.; Karash, C. B.; Venslavsky, J. W.; Sarau, H. M.; Flaim, K. E.; Hieble, J. P.; Kaiser, C. Synthesis and dopaminergic activity of some halogenated mono- and dihydroxylated 2-aminotetralins. J. Med. Chem. 29:1615–1627; 1986.