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CY 208-243 Behaves as a Typical D-1 Agonist in the Reserpine-Treated Mouse

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ABBOTT, B , B S STARR AND M S STARR *CY 208-243 behaves as a typical D-1 agonist in the reserpine-treated mouse* PHARMACOL BIOCHEM BEHAV **38**(2) 259–263, 1991 —The object of this study was to determine if the newly developed phenanthridine derivative, CY 208-243, retains its apparent in vivo preference for dopamine D-1 receptors under conditions of dopamine depletion, as a starting point to understanding why CY 208-243 possesses antiparkinson activity and the selective D-1 agonist SKF 38393 does not Three hours after receiving reserpine (5 mg/kg), mice were strongly sedated and completely unresponsive to the motor stimulant effects of CY 208-243 (0 1–10 mg/kg) or the selective D-2 agonist RU 24213 (0 5–5 mg/kg) administered alone After 24 h reserpine, the akinesia was partially and dose-dependently reversed by both CY 208-243 (0 1–10 mg/kg) and RU 24213 (0 5–5 mg/kg) alone CY 208-243 also stimulated rearing and grooming, while RU 24213 gave rise to strong head-down sniffing The response to 1 mg/kg CY 208-243 was practically abolished by pretreatment with the D-1 antagonist SCH 23390 (0 2 mg/kg) On the other hand, blocking D-2 receptors with metoclopramide (0 25 mg/kg) unexpectedly facilitated CY 208-243-induced locomotion and rearing, but suppressed grooming When CY 208-243 (1 mg/kg) was injected together with RU 24213 (0 5–5 mg/kg), the two drugs interacted synergistically to stimulate locomotion at all times after reserpine These animals also exhibited a greater preponderance of grooming, sniffing, gnawing and oral dyskinesia Apart from the potentiation of some elements of CY 208-243-stimulated motor behaviour by D-2 blockade, these results are qualitatively indistinguishable from those previously obtained with the prototype D-1 agonist SKF 38393 The differences between the antiparkinson efficacies of these two drugs are discussed in terms of multiple D-1 receptors, and as yet undisclosed receptor actions of CY 208-243

CY 208-243 D-1 receptors Motor behaviour Reserpine Mouse

BEHAVIOURAL studies in rats and mice have consistently shown that the most effective way of increasing the motor activity of normal animals (5, 7, 10, 33, 35), and of ameliorating the motor deficits caused by a loss of brain dopamine (3, 13, 15, 24, 25, 29, 30), is to stimulate dopamine D-1 and D-2 receptors in the brain simultaneously. From these experiments in rodents, it was predicted that the selective D-1 agonist SKF 38393 (26) should also alleviate the symptoms of Parkinson's disease in man This promise was not fulfilled in the clinic, however, where it was found that SKF 38393 caused no discernible improvement in the poverty of movement of a group of parkinsonian volunteers (8)

This failure of SKF 38393 has far-reaching implications, for it calls into question (a) the reliability of rodent models as predictors of the efficacy of D-1 agonists in man, (b) the relevance of D-1 receptors to the human condition of parkinsonism; and (c) why SKF 38393 binds to D-1 receptor sites in homogenates of human brain (23), yet is ineffective in the treatment of Parkinson's disease (8).

Recently, a new chemical class of D-1 agonists has been synthesised, of which CY 208-243 is one example (18) Unlike SKF 38393, this compound is not only behaviourally active in rodents (9, 18, 20), but also exhibits antiparkinson activity in MPTP-treated marmosets (21, 22, 31, 32) and squirrel monkeys (18), and has been reported to switch 5/8 parkinsonian patients from "off" to "on" to a degree that matched the response to L-DOPA (32). Is this beneficial action of CY 208-243 due to D-1 receptor stimulation, or is it mediated by one or more of a range of other receptors for which CY 208-243 has a demonstrable affinity in vitro (12, 18, 20)?

In attempting to shed further light on this question, we have reverted to the reserpine-treated mouse as a test-bed for distinguishing drugs which activate D-1 receptors from those which are active at D-2 and other transmitter receptors (3,29) In this model, the prototype D-1 agonist SKF 38393 exhibits a distinct behavioural profile, which includes a SCH 23390-sensitive reversal of immobility at 24 h (but not 3 h) after reserpine, and a synergistic facilitation of the motor stimulant action of D-2 agonists (3, 29, 30). If it can be shown that CY 208-243 has similar behavioural properties to SKF 38393 in this test system, then we must entertain the notion that CY 208-243's effectiveness in primates is also related to the activation of D-1 receptors, though possibly a discrete subclass from those engaged by SKF 38393

METHOD

Behavioural Testing

Wistar albino mice (A. R. Tuck Ltd.) of either sex and weigh-

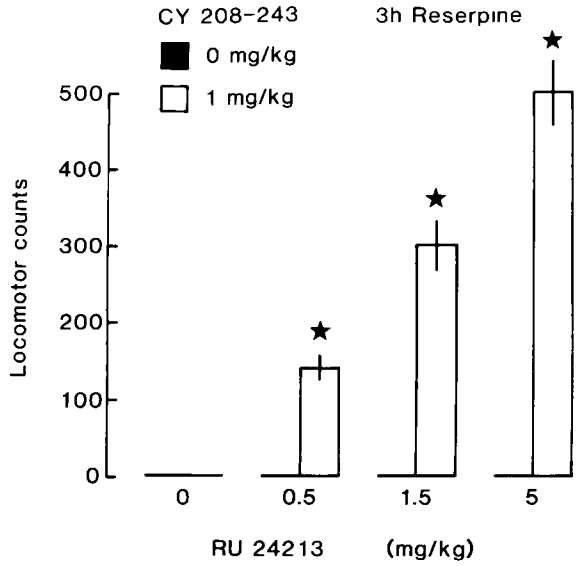

FIG 1 Dose-related effects of CY 208-243 and the selective D-2 agonist RU 24213, administered alone and in combination, on the locomotor activity of mice treated 3 h earlier with reserpine (5 mg/kg) Each column is the mean ± S E of 6–10 experiments Stars indicate $p<0$ 05 versus RU 24213 or CY 208-243 alone by ANOVA

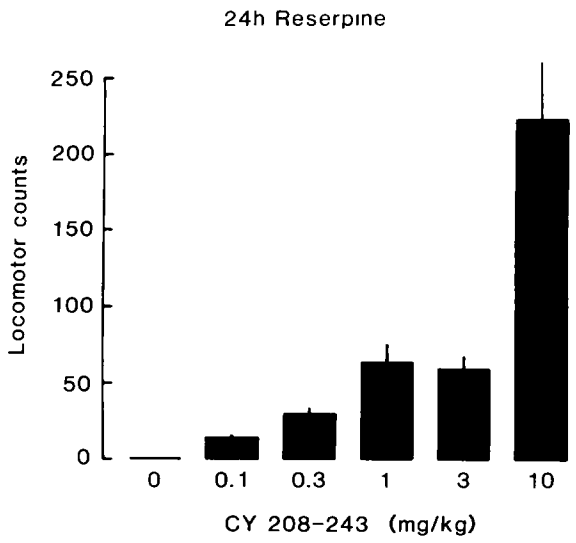

FIG 2 Dose-related increase in locomotor activity produced by CY 208-243 in mice treated 24 h beforehand with reserpine (5 mg/kg) Each column is the mean ± S E of 6–10 experiments

ing 20–35 g were used in this study. They were normally housed in groups of twenty, at 22 ± 1°C, under fluorescent lighting from 07.00–17.00 h and allowed free access to food and water. Experimental testing was conducted between 10.00 and 17.00 h.

Mice were injected intraperitoneally (IP) with saline (controls) or reserpine (5 mg/kg IP) and the effects of drugs or vehicle on their motor behaviour studied 3 h or 24 h later The animals were placed singly onto the floor of a Perspex container (30 × 26 × 20 cm high), situated on a Panlab 0603 proximity sensor unit. Horizontal movements were recorded for 10 min at maximum sensitivity (setting 7) Rearing, in which both forepaws were lifted off the ground, and episodes of grooming, were also quantified by an experienced observer with the aid of hand-held counters connected to digital printers (Malden Electronics) The occurrence of other activities, such as sniffing, gnawing and oral dyskinesia, were noted but not quantified.

Drugs

CY 208-243 (Sandoz), the D-1 antagonist SCH 23390 (Schering), the D-2 antagonist metoclopramide (Beechams) and reserpine (Sigma) were injected IP, while the selective D-2 agonist RU 24213 (Roussel) was delivered subcutaneously in the neck region. All drugs were administered in a volume of 5 ml/kg, agonists 30 min and antagonists 60 min prior to testing. CY 208-243 and reserpine were first dissolved in one drop glacial acetic acid and then diluted with saline

Statistical Analysis

Locomotor and grooming scores of drug-treated animals were compared with appropriate controls by one- or two-factor analysis of variance (ANOVA)

RESULTS

Motor Activity of Nonreserpine-Treated Mice

A group of ten mice injected with reserpine vehicle (t = 0 min), and later with saline (5 ml/kg IP, t = 150 min), registered an average of 541 ± 31.7 locomotor counts, 35 5 ± 4.3 rears and 107.0 ± 14.7 s grooming, when tested over the period 180–190 min.

Behavioural Effects of CY 208-243 and RU 24213 in 3-h Reserpine-Treated Mice

The sedative action of the Rauwolfia alkaloid was evident after only 20–30 min. By 3 h, the animals were completely immobile (Fig. 1) and all species-typical behaviours had ceased Administration of saline or CY 208-243 (0.1–10 mg/kg) to mice at this stage had no visible effect whatsoever on their akinetic state (not shown) The D-2 agonist RU 24213 was similarly ineffective when tested over the dose range 0.5–5 mg/kg (Fig. 1)

Behavioural Effects of CY 208-243 and RU 24213 in 24-h Reserpine-Treated Mice

Although mice were completely unmoving and prostrate 24 h after the reserpine injection, they nevertheless responded to CY 208-243 (0 1–10 mg/kg) with a clear-cut increase in motor activity, as can be seen in Fig. 2. Locomotion was stimulated dose-dependently over the range 0 1–1 mg/kg, and appeared to reach a plateau at 3 mg/kg. At the lower doses (0 1 and 0 3 mg/kg), the animals walked slowly and unsteadily about the test arena Locomotion appeared to be most fluid and coordinated at 1 mg/kg CY 208-243, though signs of ataxia were still present and the mice clearly did not have the full mobility on nonreserpine-treated controls. Rearing also reappeared with 1 mg/kg CY 208-243 (6.5 ± 1 2 rears, n = 10, $p<0.05$ vs controls) and the animals made frequent (though often abortive) attempts to groom (93.0 ± 17 2 s, n = 10, $p<0$ 05 vs controls). Occasional sniffing of the air or container sides was also observed

At 10 mg/kg, CY 208-243 promoted rearing (11.2 ± 2 5 rears, n = 8) and grooming (103.0 ± 12 7 s, n = 8) that were no different from the effects of 1 mg/kg However, the normally ponderous locomotion was interspersed by occasional frantic bouts of explosive running, giving rise to a greatly elevated locomotor

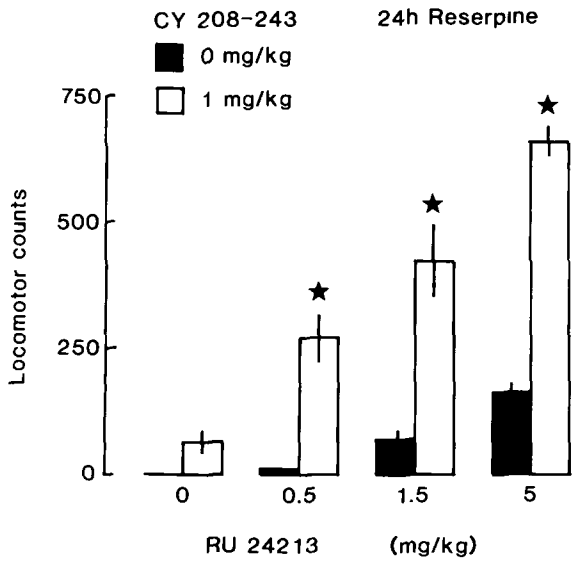

FIG 3 Dose-related effects of CY 208-243 and RU 24213, administered alone and in combination, on the locomotor activity of mice treated 24 h beforehand with reserpine (5 mg/kg) Each column is the mean ± S E of 6–10 experiments Stars denote $p<0$ 05 versus CY 208-243 or RU 24213 alone by ANOVA

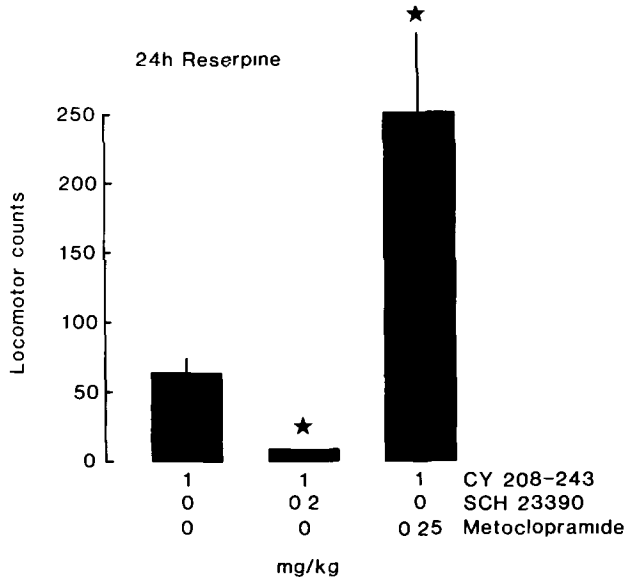

FIG 4 Differential effects of D-1 and D-2 receptor blockade on the locomotor activity induced by 1 mg/kg CY 208-243 in 24 h reserpine-treated mice The D-1 antagonist SCH 23390 and the D-2 antagonist metoclopramide were injected IP 30 min prior to CY 208-243 Each column is the mean ± S E of 8 experiments Stars denote $p<0$ 05 versus CY 208-243 alone by ANOVA

count (Fig. 2) This bizarre response may have been associated with the convulsant action noticed recently with D-1 agonists in reserpine-treated mice (1), since 5/8 mice subsequently exhibited a fatal, tonic extensor motor seizure, 90–170 min after receiving CY 208-243

RU 24213, 0.5–5 mg/kg, reinstated locomotion dose-dependently and was quantitatively, though not qualitatively, more effective than CY 208-243 (Fig. 3) Prominent head-down sniffing occurred at 5 mg/kg.

Effects of D-1 and D-2 Antagonists on CY 208-243-Induced Motor Behaviours in 24-h Reserpine-Treated Mice

The stimulation of locomotion by 1 mg/kg CY 208-243 was reduced by 87.3% ($p<0$ 01) by pretreatment with SCH 23390 (0.2 mg/kg, Fig 4). Rearing and grooming were abolished completely by the D-1 antagonist ($p<0.01$).

By contrast, prior injection of the D-2 blocker metoclopramide (0 25 mg/kg) markedly and unexpectedly potentiated CY 208-243-induced locomotion (+291%, $p<0.01$, Fig. 4) and rearing (+61%, $p<0$ 05), whilst decreasing grooming frequency (−37.6%, $p<0.05$), as compared to 1 mg/kg CY 208-243 alone

Behavioural Interactions Between CY 208-243 and RU 24213 in 3-h and 24-h Reserpine-Treated Mice

The combined effects of treatment with CY 208-243 (1 mg/kg) and RU 24213 (0.5–5 mg/kg) are shown in Figs. 1 and 3 All D-1/D-2 drug mixtures elicited a greater than additive, and better coordinated locomotion than was achieved by either agonist alone (Fig. 1). A wide range of other activities were also evident with a higher frequency, including rearing against the sides of the container; grooming of the face, body and genitals, gnawing at faeces, vacuous chewing

A similar synergistic interaction was noted when the two drugs were injected into 24-h reserpine-treated mice (Fig 3) Here, too, locomotion was significantly greater than that achieved by a simple summation of individual drug effects, and more closely resembled that of normal mice. There was clearly also a greater preponderance of other elements of motor behaviour, such as rearing (8.1 ± 1 0, 11.4 ± 1.8 and 16 9 ± 2.3 rears for 1 mg/kg CY 208-243 in combination with 0.5, 1 5 and 5 mg/kg RU 24213 respectively, n = 6–10, $p<0.05$), licking, sniffing and dyskinetic jaw movements.

DISCUSSION

The introduction of CY 208-243 has brought a new twist to the debate on the antiparkinson potential of D-1 agonist drugs, following the recent discovery that CY 208-243 was capable of relieving the motor disability of 5/8 patients with advanced idiopathic Parkinson's disease (32) This finding was in sharp contrast to the complete lack of antiparkinson effect of the traditional D-1 agonist, SKF 38393, in an earlier clinical trial (8).

The most notable difference between these two drugs lies in the manner of their binding to rat brain membranes. SKF 38393 exhibits a clear preference for D-1 sites (14,27), compared to CY 208-243 which has a demonstrable affinity for D-1, D-2, 5-HT_{1A} and opiate receptors, and to a lesser extent for α and 5-HT_2 sites as well (12, 18, 20). From these binding data, one might reasonably predict that the behavioural response to CY 208-243 would correspond to a melange of its interactions with these multiple receptor sites. In practice, however, this is not the case In the normal intact animal, CY 208-243 exhibits a behavioural profile that is remarkably similar to that of SKF 38393, promoting behavioural changes that bear the hallmark of a selective activation of D-1 receptors only (9, 10, 18, 20, 33). The present study extends this finding and shows that CY 208-243 retains its D-1 agonist-like behavioural properties under conditions of dopamine depletion, when the D-1 and D-2 receptors are undergoing functional changes (3, 10, 29).

We found that CY 208-243 gave rise to a spectrum of motor behaviours in the reserpine-treated mouse that was virtually indistinguishable from that previously described for its predecessor, SKF 38393 (3, 10, 29, 30). Thus both drugs (a) induced locomotion, rearing and grooming 24 h after reserpine, when postsynaptic dopamine receptors are held to be supersensitive, but not at 3 h when dopamine receptors are still normosensitive (3, 10, 29); (b) were antagonised by SCH 23390, but not by D-2 antagonists (3, 10, 29), and (c) interacted in a synergistic fashion with concomitant D-2 stimulation to promote a much higher level of locomotor activity, and a wider range of motor activities than could be achieved by activating D-1 or D-2 receptors on their own (3, 10, 29, 30). Where SKF 38393 is concerned, all of these attributes have been equated with a predominant (if not exclusive) interaction of the drug with D-1 receptors, as discussed in detail elsewhere (3, 10, 15, 29, 30) The remarkably close similarity of CY 208-243 to SKF 38393 in this test system suggests the actions of the phenanthridine in vivo are also mediated, to a large extent, by D-1 receptors. This conclusion is in close agreement with the results of Markstein et al. (18), who demonstrated that CY 208-243 evoked D-1-like contraversive circling in the unilaterally 6-hydroxydopamine-lesioned rat. At the same time, these authors failed to elicit any of the cardinal signs of in vivo D-2 stimulation with CY 208-243, such as emesis in dogs, inhibition of prolactin secretion or a decrease in dopamine turnover. Other functional tests indicated just as convincingly a lack of effect of CY 208-243 at α_1 or α_2 receptor sites (18)

The unexpected facilitation of locomotion induced by CY 208-243, which we noted in the presence of the D-2-blocking drug metoclopramide, may indicate CY 208-243 also stimulates a population of inhibitory (D-2?) receptors under these conditions, which are rendered inoperative by the benzamide Evidence for the existence of dual excitatory and inhibitory postsynaptic D-2 receptors, which can be revealed separately under appropriate circumstances, has recently been discussed in detail elsewhere [see (9)]. We think it unlikely that metoclopramide increased locomotion in our experiments by reducing behavioural competition from grooming (which was significantly decreased), as Markstein et al. (18) observed a similar increase in the rotational response to CY 208-243 in the presence of sulpiride, which tends to *increase* the grooming mediated via D-1 receptors (9,19). A more detailed analysis of this phenomenon with other classes of D-2 antagonists may shed further light on the nature of this apparent bimodal excitatory/inhibitory effect of CY 208-243 on locomotion in these animal models.

On the basis of the limited experiments performed to date with CY 208-243, it is difficult to say why CY 208-243 combats the motor deficits of marmosets (31,32) and squirrel monkeys (18) treated with MPTP, as well those of parkinson sufferers (32), when SKF 38393 is inactive (8, 21, 22). The rodent behavioural data portray CY 208-243 as a selective D-1 agonist, like SKF 38393, yet clearly there must be some fundamental difference between them, which reflects CY 208-243's more diverse receptor binding capabilities One possibility is that the receptor selectivities of CY 208-243 and SKF 38393 are different in the primate. In support of this argument is the finding that SKF 38393 *antagonises* the antiparkinson activity of the D-2 agonist, LY 171555, in the MPTP-treated marmoset (22), yet greatly facilitates the same motor stimulant actions of LY 171555 in rodent models of Parkinson's disease (3, 10, 13, 15, 24, 25, 29, 30, 33) Thus while there is evidence that SKF 38393 binds to D-1 receptor sites in the caudate-putamen of nonhuman primates (16) and man (23), it is by no means certain that these points of attachment are the same as those D-1 receptors engaged in motor control, or that they are functionally linked to D-2 receptors in the same cooperative fashion as in the rodent (5–7, 10, 28, 33, 35). In a review of the topic, Waddington and O'Boyle (34) have speculated that SKF 38393 may elicit predominantly oppositional D-1·D-2 behavioural interactions in the primate, as compared to mainly cooperative D-1 D-2 behavioural interactions in the nonprimate According to this argument, CY 208-243 must always tilt the D-1 D-2 balance in favour of cooperativity, regardless of the species.

A second point to consider is that CY 208-243 is less specific for D-1 receptors in higher animal species For example, both we and Markstein et al (18) noted that the locomotor stimulant actions of CY 208-243 in the mouse and rat were not attenuated by D-2 blockade (if anything the opposite was true) By contrast, Temlett et al (31) significantly inhibited this effect of CY 208-243 in the MPTP-treated marmoset with sulpiride, suggesting part of the motor response to CY 208-243 was mediated by D-2 receptors in this animal, even though other signs of D-2 stimulation were not observed (e.g , vomiting) Given the unusual mix of affinities that CY 208-243 has for the receptors of different neurotransmitters in vitro [e g , dopamine, noradrenaline, 5-hydroxytryptamine, opioid peptides, (12, 18, 20)], it is not surprising that this compound should have enigmatic behavioural properties that reflect a similar diversity of actions in vivo Consequently, CY 208-243's effects on motor activity may involve a subtle interaction with receptors other than D-1 Once again, these anomalies can only be resolved by further experimentation.

A third reason why CY 208-243 and SKF 38393 might differ in the primate is that they act upon separate subclasses of D-1 receptor. Until recently the D-1 receptor, by definition, has traditionally been equated with dopamine-sensitive adenylate cyclase. There is increasing biochemical evidence, however, to suggest that not all D-1 receptors are necessarily coupled to this enzyme and hence, by implication, that functionally discrete forms of the D-1 receptor probably also exist For example, the binding of SCH 23390 to presumed D-1 recognition sites in rat brain can occur in regions (e.g., amygdala) which have no detectable dopamine-sensitive cyclase activity (17), and can be affected independently of the enzyme by a number of chemical treatments (2). More recently, De Keyser et al (11) distinguished two types of D-1 receptor in human brain. Since the binding affinities of these two D-1 receptors were differentially affected by guanine nucleotides, the authors proposed that one receptor was linked to adenylate cyclase whilst the other was not. There was also a partial anatomic separation of the two D-1 receptors, which was offered as further evidence that the receptors were probably functionally discrete. The choice of two sites of action for D-1 agonists, which have different transduction mechanisms, would circumvent the problem of having to reconcile why the behavioural efficacies of D-1 agonist drugs do not always match their ability to stimulate the synthesis of cyclic AMP (4) It also provides us with a simple, and experimentally testable explanation for the observed differences between CY 208-243 and SKF 38393 discussed above.

Temlett et al. (32) proposed a fourth alternative, by suggesting that CY 208-243 either penetrates the primate brain more readily than does SKF 38393, or is perhaps less affected by metabolism. Future work will undoubtedly address these issues.

In summary, these and other experiments have shown that the motor properties of the two D-1 agonists, CY 208-243 and SKF 38393, are closely comparable in dopamine-depleted rodents, and therefore give no clues as to why only CY 208-243 has antiparkinson activity in primates. It is suggested, therefore, that CY 208-243 produces its beneficial effects in the primate either by engaging a different D-1 receptor subtype from SKF 38393, or by interacting with a different, hitherto undisclosed receptor (not necessarily for dopamine)

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REFERENCES

1 Al-Tajir, G , Chandler, C J , Starr, B S , Starr, M S Opposite effects of stimulation of D-1 and D-2 dopamine receptors on the expression of motor seizures in mouse and rat Neuropharmacology 29 657–661, 1990
2 Andersen, P H , Braestrup, C Evidence for different states of the dopamine D1 receptor clozapine and fluperlapine may preferentially label an adenylate cyclase-coupled state of the D1 receptor J Neurochem 47 1822–1831, 1986
3 Arnt, J Behavioural stimulation is induced by separate dopamine D-1 and D-2 receptors sites in reserpine-pretreated but not in normal rats Eur J Pharmacol 113 79–88, 1985
4 Arnt, J , Hyttel, J , Meier, E Inactivation of dopamine D-1 or D-2 receptors differentially inhibits stereotypies induced by dopamine agonists in rats Eur J Pharmacol 155 37–46, 1988
5 Barone, P , Davis, T A , Braun, A R , Chase, T N Dopaminergic mechanisms and motor function characterisation of D-1 and D-2 dopamine receptor interactions Eur J Pharmacol 123 109–114, 1986
6 Bordi, F , Meller, E Enhanced behavioural stereotypies elicited by intrastriatal injection of D1 and D2 dopamine agonists in intact rats Brain Res 504 276–283, 1989
7 Braun, A R , Chase, T N Obligatory D1/D2 receptor interactions in the generation of dopamine agonist related behaviours Eur J Pharmacol 131 301–306, 1986
8 Braun, A R , Fabbrini, G , Mouradian, M M , Serrati, C , Barone, P , Chase, T N Selective D-1 dopamine receptor agonist treatment of Parkinson's disease J Neural Transm. 68 41–50, 1987
9 Chandler, C J , Wohab, W , Starr, B S , Starr, M S. Motor depression a new role for D-1 receptors? Neuroscience 38 437–445, 1990
10 Clark, D , White, F J D1 dopamine receptor—the search for a function A critical evaluation of the D1/D2 receptor classification and its functional implications Synapse 1 347–388, 1987
11 De Keyser, J , Walraevens, H , Ebinger, G , Vauquelin, G In human brain two subtypes of D_1 dopamine receptors can be distinguished on the basis of differences in guanine nucleotide effect on agonist binding J Neurochem 53 1096–1102, 1989
12 Foote, R W , Buscher, H H , Romer, D , Maurer, R , Enz, A , Gahwiler, A B H , Shearman, G T , Seiler, M P , Wuthrich, H CY 208-243 a unique combination of atypical opioid antinociception and D-1 dopaminomimetic properties Life Sci 42 137–152, 1988
13 Gershanik, O , Heikkila, R E , Duvoisin, R C Behavioural correlations of dopamine receptor activation Neurology 33 1489–1492, 1983
14 Hyttel, J Functional evidence for selective D-1 receptor blockade by SCH 23390 Neuropharmacology 23 1395–1401, 1984
15 Jackson, D M , Hashizume, M Bromocriptine induces marked locomotor stimulation in dopamine-depleted mice when D-1 receptors are stimulated with SKF 38393 Psychopharmacology (Berlin) 90 147–149, 1986
16 Madras, B K , Fahey, M A , Canfield, D R., Spealman, R D D1 and D2 dopamine receptors in caudate-putamen of nonhuman primates (*Macaca fascicularis*) J Neurochem 51 934–943, 1988
17 Mailman, R B , Schulz, D W , Kilts, C D , Lewis, M H , Rollema, H , Wyrick, S Multiplicity of D-1 dopamine receptor In Breese, G R , Creese, I , eds Neurobiology of central D-1 dopamine receptors New York Plenum Press, 1986 53–72
18 Markstein, R , Seiler, M P , Vigouret, J M , Urwyler, S , Enz, A , Dixon, K Pharmacologic properties of CY 208-243, a novel D1 agonist In Sandler, M , Dahlstrom, A , Belmaker, R H , eds Progress in catecholamine research part B Central aspects New York Liss, 1988 59–64
19 Molloy, A G , Waddington, J L Pharmacological characterisation in the rat of grooming and other behavioural responses to the D1 dopamine receptors agonist R-SK&F 38393 J Psychopharmacol 1 177–183, 1987
20 Murray, A M , Waddington, J L 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 35 105–110, 1990
21 Nomoto, M , Jenner, P , Marsden, C D The dopamine D2 agonist LY 141865, but not the D1 agonist SKF 38393, reverses parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the common marmoset Neurosci Lett 57 37–41, 1985
22 Nomoto, M , Jenner, P , Marsden, C D The D1 agonist SKF 38393 inhibits the antiparkinsonian activity of the D2 agonist LY 171555 in the MPTP-treated marmoset Neurosci Lett 93 275–280, 1988
23 O'Boyle, K M , Waddington, J L [^{3}H]SCH 23390 binding to human putamen D-1 dopamine receptors Stereochemical and structure-activity relationships among 1-phenyl-1H-3-benzazepine derivatives as a guide to D-1 receptor topography J Neurochem 48 1039–1042, 1987
24 Robertson, G S , Robertson, H A Synergistic effects of D1 and D2 dopamine agonists on turning behaviour in rats Brain Res 384 387–390, 1986
25 Rouillard, C , Bedard, P J Specific D1 and D2 dopamine agonists have synergistic effects in the 6-hydroxydopamine circling model in the rat Neuropharmacology 27 1257–1264, 1988
26 Setler, P , Sarau, H M , Zirkle, C L , Saunders, H L The central effects of a novel dopamine agonist Eur J Pharmacol 50 419–430, 1978
27 Sibley, D R , Leff, S E , Creese, I Interactions of novel dopaminergic ligands with D-1 and D-2 dopamine receptors Life Sci 31 637–645, 1982
28 Starr, M S D_1/D_2 behavioural interactions in the rat involving striatal dopamine D_1 receptors Eur J Pharmacol 151 479–482, 1988
29 Starr, B S , Starr, M S , Kilpatrick, I C Behavioural role of dopamine D-1 receptors in the reserpine-treated mouse Neuroscience 22 179–188, 1987
30 Starr, M S , Starr, B S. Behavioural synergism between the dopamine agonists SKF 38393 and LY 171555 in dopamine-depleted mice Antagonism by sulpiride reveals only stimulant postsynaptic D-2 receptors Pharmacol Biochem Behav 33 41–44, 1989
31 Temlett, J A , Chong, P N , Oertel, W H , Jenner, P , Marsden, C D The D-1 dopamine receptor partial agonist, CY 208-243, exhibits antiparkinsonian activity in the MPTP-treated marmoset Eur J Pharmacol 156 197–206, 1988
32 Temlett, J A , Quinn, N P , Jenner, P , Marsden, C D , Pourcher, E , Bonnet, A -M , Agid, Y , Markstein, R , Lataste, X Antiparkinsonian activity of CY 208-243, a partial D-1 dopamine receptor agonist, in MPTP-treated marmosets and patients with Parkinson's disease Movement Disord 4 261–265, 1989
33 Waddington, J L Behavioural correlates of the action of selective D-1 dopamine receptor antagonists impact of SCH 23390 and SKF 83566, and functionally interactive D-1 D-2 receptor systems Biochem Pharmacol 35 3661–3667, 1986
34 Waddington, J L , O'Boyle, K M Drugs acting on brain dopamine receptors a conceptual reevaluation five years after the first selective D-1 antagonist Pharmacol Ther 43 1–52, 1989
35 White, F J , Bednarz, L M , Wachtel, S R , Hjorth, S , Brooderson, R J Is stimulation of both D1 and D2 receptors necessary for the expression of dopamine-mediated behaviours? Pharmacol Biochem Behav 30 189–193, 1988