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Locomotor Behaviors in Response to New Selective D-1 and D-2 Dopamine Receptor Agonists, and the Influence of Selective Antagonists

ANTHONY G. MOLLOY, KATHY M. O'BOYLE, MARK T. PUGH AND JOHN L. WADDINGTON[1]

Department of Clinical Pharmacology, Royal College of Surgeons in Ireland St. Stephen's Green, Dublin 2, Ireland

MOLLOY, A. G., K. M. O'BOYLE, M. T. PUGH AND J. L. WADDINGTON. *Locomotor behaviors in response to new selective D-1 and D-2 dopamine receptor agonists, and the influence of selective antagonists.* PHARMACOL BIOCHEM BEHAV **25**(1) 249–253, 1986.—With the introduction of the selective D-1 dopamine receptor agonist and antagonist benzazepines, especially as enantiomeric pairs, there is now a range of D-1 compounds to complement the previously available selective D-2 agents. These have been used to investigate whether sub-types of dopamine receptors might be differentially involved in locomotor behavior. Stereotyped locomotion induced by the non-selective D-2 agonist apomorphine and by the selective D-2 agonist RU 24213 were blocked by the selective D-2 antagonists metoclopramide and Ro 22-2586 ((−)-piquindone). Responses to either D-2 agonist were also blocked by the selective D-1 antagonists SCH 23390 and *R*- (but not S-) SK&F 83566. Non-stereotyped locomotion was induced by *R*- but not *S*-SK&F 38393, a stereoselective D-1 agonist, and was blocked by SCH 23390. Responses to the D-1 agonist were also antagonised by metoclopramide. Such results suggest concerted D-1:D-2 interplay in the regulation of at least some dopaminergic behaviors, such as locomotion.

D-1 and D-2 dopamine receptors Locomotion Behavior

RECENT reviews have documented the extensive literature on the important primary role of dopaminergic (DAergic) function in locomotor behavior. Issues such as the distinct or concerted involvement of mesolimbic, mesocortical and nigrostriatal DAergic pathways, the modulatory and/or serial role of non-DAergic neuronal function, the varying topographies of locomotion and how these behaviors should best be assessed, have been widely investigated and debated [1, 2, 9, 14, 32, 34]. One issue that has received considerably less attention is whether sub-types of dopamine receptor might be differentially involved in locomotor behavior.

The first scheme for the classification of DA receptors to attain widespread acceptance, that of D-1 and D-2 sub-types, was derived essentially from neurochemical rather than behavioral criteria [16]. Further sub-typing resulted in quadruplet heterogeneity with sites defined according to drug displacement affinities in radioligand binding assays [35]. Recent rationalisation of the four receptor hypothesis within a revised D-1:D-2 scheme [5, 18, 37] also had a substantial basis in radioligand binding. Behavioral considerations have not been prominent in these arguments. Within all of these schemes, indirect data have been interpreted as indicating the prepotent role of D-2 receptor function in typical dopaminergic behaviors such as locomotion and stereotypy; any role for the D-1 receptor in such behaviors has been either questioned or denied [5, 17, 35]. These views arose in the absence of selective D-1 antagonists with which they might be tested directly. They depended on correlational data, the 'subtraction' strategy (i.e., the ability of selective D-2 agonists and antagonists to mimic the actions of agents which do not discriminate between DA receptor sub-types) and the failure of the only available D-1 agonist, the benzazepine SK&F 38393 [36], to induce locomotion and stereotypy in the manner of typical non-selective DA agonists such as apomorphine.

With the recent introduction of the halogenated benzazepine derivative SCH 23390 as the first selective D-1 antagonist [6, 11, 13, 25] it has been possible to investigate directly any involvement of D-1 receptor function in such DAergic behaviors. Subsequently we have described further benzazepine analogues, including the resolved *R*- and *S*-enantiomers of SK&F 38393 [25] and the new selective D-1 antagonist SK&F 83566 [26]. Thus, there is now available for behavioral studies a modest range of selective D-1 agents, with some information on structure-affinity relationships [27].

A further requirement for investigating the role of DA

[1]Requests for reprints should be addressed to Dr. John L. Waddington.

TABLE 1

AFFINITIES OF SOME INVESTIGATIONAL AGENTS FOR D-1 AND D-2 DOPAMINE RECEPTORS

Drug	IC_{50}(nM) ^{3}H-piflutixol (D-1)	^{3}H-spiperone (D-2)	D-1 / D-2
D-1 agonists			
R-SK&F 38393	810	33,300	0.024
S-SK&F 38393	>100,000	>50,000	—
D-1 antagonists			
SCH 23390	1.0	1,565	0.0006
R-SK&F 83566	1.9	2,710	0.0007
S-SK&F 83566	561	11,400	0.049
D-2 agonists			
RU 24213	>50,000	377	>133
D-2 antagonists			
Metoclopramide	>100,000	330	>303
Ro 22-2586	18,300	84	217
Non-selective antagonists			
cis (Z)-Flupenthixol	1.1	2.4	0.48

TABLE 2

EFFECTS OF SELECTIVE D-2 ANTAGONISTS ON RESPONSES TO NON-SELECTIVE AND SELECTIVE D-2 AGONISTS

	mg/kg	Stereotypy score	Locomotion (%)
Apomorphine	0.5	3.2 ± 0.4	4/7(57%)
+ metoclopramide	1.0	1.2 ± 0.3*	3/8(37%)
	5.0	0 ± 0†	0/7(0%)*
RU 24213	15.0	3.0 ± 0.2	6/8(75%)
+ Ro22-2586	0.04	2.6 ± 0.2	6/8(75%)
	0.20	0.8 ± 0.2†	0/8(0%)*

Means ± S.E.M. †$p<0.01$; *$p<0.05$ vs. agonist + vehicle.

TABLE 3

EFFECTS OF A SELECTIVE D-1 ANTAGONIST ON RESPONSES TO D-2 AGONISTS

	mg/kg	Stereotypy score	Locomotion (%)
Apomorphine	0.5	3.2 ± 0.4	4/7(57%)
+ SCH 23390	0.04	0 ± 0†	0/6(0%)*
	0.20	0 ± 0†	0/6(0%)*
RU 24213	15.0	3.0 ± 0.2	6/8(75%)
+ SCH 23390	0.04	1.4 ± 0.3†	4/8(50%)
	0.20	1.1 ± 0.3†	1/8(12%)*

Means ± S.E.M. †$p<0.01$; *$p<0.05$ vs. agonist + vehicle.

receptor subtypes in behaviors such as locomotion is a clear concept of how these behaviors are to be assessed. Locomotion often has to be extracted from a syndrome composed of several behaviors, as in exploration or stereotypy, and the inherent problems are widely recognised [31–33]. A common strategy has been recourse to more sophisticated devices for the automated assessment of behavior [20]. However, we share with some others a preference for an approach based on refinements of direct visual observation procedures [10, 19, 22, 23, 31, 38]. This allows some specification of the qualitative manner in which locomotion is expressed, including situations in which other behaviors are present.

STATUS OF NEW SELECTIVE AGENTS

We have compared [25–27] a number of putative selective D-1 and D-2 agonist and antagonist drugs for their ability to displace the binding of ^{3}H-piflutixol (^{3}H-PIF) to D-1 receptors and of ^{3}H-spiperone (^{3}H-SPIP) to D-2 receptors in striatal membrane preparations from male Sprague-Dawley rats. For ^{3}H-PIF binding (0.3 nM), 1 μM of the selective D-2 antagonist domperidone was added to all assay tubes to occlude residual binding to D-2 receptors, with specific binding defined by 1 μM butaclamol. For ^{3}H-SPIP (0.1 nM), specific binding was defined as that displaced by 1 μM domperidone.

The IC_{50} values for displacement of ^{3}H-PIF and ^{3}H-SPIP by, and associated D-1:D-2 selectivity ratios for, putative selective agents are given in Table 1. *R*- but not *S*-SK&F 38393 stereoselectively displaced ^{3}H-PIF, but showed little affinity for and negligible stereoselectivity at D-2 receptors. ^{3}H-PIF binding was selectively displaced by SCH 23390 and stereoselectively displaced by *R*- but not *S*-SK&F 83566, with these antagonists also having little affinity for and negligible stereoselectivity at D-2 receptors. Conversely, ^{3}H-SPIP was selectively displaced by the agonist diphenylethylamine derivative RU 24213 [8,30] and by two antagonists, the substituted benzamide metoclopramide and the pyrroloisoquinoline derivative Ro 22-2586 ((−)-piquindone), [7, 26, 29, 30]. The non-selective antagonist cis (Z)-flupenthixol displaced both ligands.

EFFECTS OF SELECTIVE ANTAGONISTS ON LOCOMOTOR RESPONSES TO NON-SELECTIVE AND SELECTIVE D-2 AGONISTS

Our procedure [22–24] has been to challenge male

TABLE 4

EFFECTS OF THE *R*- and *S*-ENANTIOMERS OF A D-1 ANTAGONIST ON RESPONSES TO D-2 AGONISTS

	mg/kg	Stereotypy score	Locomotion (%)
Apomorphine	0.5	2.5 ± 0.3	7/8(87%)
+ *S*-SK&F 83566	0.20	2.3 ± 0.3	3/3(100%)
+ *R*-SK&F 83566	0.04	0.4 ± 0.2†	0/10(0%)*
	0.20	0.2 ± 0.1†	0/9(0%)*
RU 24213	15.0	2.4 ± 0.2	10/10(100%)
+ *S*-SK&F 83566	0.20	2.1 ± 0.3	4/7(57%)
+ *R*-SK&F 83566	0.04	1.2 ± 0.2†	4/9(44%)
	0.20	0.8 ± 0.2†	2/9(22%)†

Means ± S.E.M. †$p<0.01$; *$p<0.05$ vs. agonist + vehicle.

TABLE 5

RESPONSE TO THE *R*- and *S*-ENANTIOMERS OF A D-1 AGONIST AND THE EFFECTS OF SELECTIVE D-1 AND D-2 ANTAGONISTS

	mg/kg	Locomotion (%)	Locomotion counts
Vehicle		1/22(5%)	0.7 ± 0.3
S-SK&F 38393	20.0	2/17(12%)	1.3 ± 0.6
R-SK&F 38393	20.0	22/38(58%)‡	5.2 ± 0.8‡
+ SCH 23390	0.1	2/8 (25%)	0.5 ± 0.3†
	0.5	0/8 (0%)†	0 ± 0†
+ metoclopramide	1.0	4/8 (50%)	1.8 ± 0.7
	5.0	2/8 (25%)	1.3 ± 0.8*

Means ± S.E.M. ‡$p<0.01$ vs. vehicle. †$p<0.01$; *$p<0.05$ vs. *R*-SK&F 38393 + vehicle.

Sprague-Dawley rats SC with 0.5 mg/kg of the non-selective agonist apomorphine hydrochloride or 15 mg/kg of the selective D-2 agonist RU 24213. Each animal is observed for a 1 min period at 10 min intervals during which the presence or absence of one or more individual behaviors were recorded using a behavioral checklist [10] and the overall stereotypy syndrome assessed by a rating scale [33]. The data presented are stereotypy scores and the prevalence of locomotion (% of total group showing co-ordinated movement of all four paws resulting in a change in the animal's location) at 30 min after agonist challenge. Antagonists were given SC, 30 min prior to challenge.

This dose of apomorphine induces a typical syndrome of stereotyped behavior consisting predominantly of continuous sniffing with locomotion. Both the overall syndrome and the prevalence of constituent locomotion were antagonised by 1.0–5.0 mg/kg metoclopramide. A similar, but less compulsive, syndrome was induced by the given (and higher) dose of RU 24213, and the overall stereotypy syndrome and the prevalence of locomotion were antagonised by 0.04–0.2 mg/kg Ro 22-2586 (Table 2). Stereotypy and locomotor responses to both apomorphine and RU 24213 were similarly antagonised by 0.04–0.2 mg/kg SCH 23390 (Table 3). This action of SCH 23390 was mimicked by 0.04–0.2 mg/kg of its close homologue SK&F 83566, with these effects residing stereoselectively in the *R*-enantiomer (Table 4).

EFFECTS OF SELECTIVE ANTAGONISTS ON LOCOMOTOR RESPONSES TO THE SELECTIVE D-1 AGONIST *R*-SK&F 38393

Rats were similarly challenged SC with the D-1 agonist SK&F 38393 after a period of prolonged habituation (2.5 hr) to the observation cage. Each animal was assessed [22,23] using a rapid time-sampling behavioral checklist procedure, whereby observations were made for 5 sec periods at 1 min intervals over 5 consecutive minutes; during each period the presence or absence of one or more individual behaviors were recorded using the same behavioral checklist. Also, an overall estimate of any stereotyped nature to observed behaviors was made using the rating scale. This cycle of observations was repeated at 10 min intervals. The prevalence of similarly defined locomotion over the 30 min cycle of observations is presented. Additionally, the number of recordings of locomotion were expressed as behavioral counts; the number of 5 sec periods in which the presence of locomotion was noted were summed for each animal over the 30–50 min cycles of observations.

SK&F 38393 induced a discontinuous and diffuse activation of behaviors in well-habituated animals when compared with vehicle-injected controls. These non-stereotyped behaviors were similar to those of a naive animal when first placed in the novel environment of the test cage. Locomotion was induced by 20 mg/kg *R*-SK&F 38393; this action was stereoselective, 20 mg/kg of its *S*-antipode being without significant activity (Table 5). Ratings with the stereotypy scale confirmed that episodes of locomotion were not occurring as part of a typical syndrome of stereotyped behavior. Stereotypy scores for the 30 min cycle of observations were: vehicle, 1.0±0.3; 20 mg/kg *R*-SK&F 38393, 1.9±0.1 (means± S.E.M., n=13–14); scores <2 indicate the absence of stereotyped behavior(s), scores >2 indicate a stereotyped nature to behavior(s). It should be emphasized that stereotypy ratings are neither interval nor ratio scales of measurement, and even the ordinal nature of such scales has been questioned [10].

These non-stereotyped episodes of locomotion in response to *R*-SK&F 38393, in terms of either prevalence or counts, were antagonised by 0.1–0.5 mg/kg SCH 23390. Pretreatment with 1.0–5.0 mg/kg metoclopramide attenuated locomotor counts and tended to reduce the overall prevalence of locomotion (Table 5).

DISCUSSION

We have used the term locomotion in the simple sense of co-ordinated movements of all four limbs resulting in a change in the animal's location. Our measures do not reflect hyperlocomotion or heightened running, though these can be assessed by similar techniques when induced under other drug treatments [39]. In no instance was locomotion the sole response to any of the present drugs. With the D-2 agonists it occurred as part of a typical syndrome of stereotyped behavior, with sniffing and some rearing [23,30], while with the D-1 agonist it occurred as episodes of non-stereotyped behavior interpolated among sniffing, rearing and a particularly prominent grooming response [22,23]. Our measures of locomotion in these differing circumstances were made together with assessments both of other individual behaviors and of any stereotyped nature to their manifestation.

In keeping with the previously prevailing view that typical

DA agonist-induced behaviors are mediated through D-2 receptors [5, 17, 35], the ability of the selective D-2 antagonist metoclopramide to antagonise locomotion induced by the mixed agonist apomorphine caused no surprise. Antagonism by the selective D-2 antagonist Ro 22-2586 of locomotion induced by the selective D-2 agonist RU 24213 would appear to confirm this view. Therefore, the ability of the selective D-1 antagonist SCH 23390 also to antagonise potently these effects requires careful analysis. This is a detailed example of a more general finding that SCH 23390 can antagonise behavioral syndromes such as stereotyped behavior that are induced by typical dopaminergic agonists [4, 13, 21–23, 30].

Clearly, one issue is whether SCH 23390 does indeed act *in vivo* as a selective D-1 antagonist. Recent studies have extended the original observations [6, 11, 13, 25] on SCH 23390. A variety of radioligand binding, neurochemical and pharmacological studies are consistent with selective *in vivo* D-1 antagonist activity, and fail to indicate a basis for the present effects in an action on any known non-DAergic system [3, 4, 12, 28, 30]. Therefore, a genuine basis for their effects in D-1 receptor blockade must be considered. The stereoselective action of the enantiomers of SK&F 83566 to antagonise locomotion induced by the D-2 agonists is powerful additional evidence for such a process; D-1 but not D-2 receptors are stereoselectively blocked by the *R*-enantiomer [26]. This would suggest that tonic D-1 dopaminergic activity is required for the expression of locomotion (and other behaviors) induced by D-2 receptor stimulation, i.e., that D-1 tone serves an 'enabling' function in relation to D-2 initiated processes. The less compulsive nature of stereotypy induced by the selective D-2 agonist in comparison with the non-selective agonist apomorphine indirectly suggests a role for D-1 stimulation in enabling the full expression of stereotypy. No mechanisms for such interactions yet suggest themselves, but they appear to occur beyond the level of D-1 and D-2 recognition sites [28,30].

Since the selective D-1 antagonists, SCH 23390 and *R*-SK&F 83566, indicate a role for D-1 receptors in the maintenance of many behaviors, one might expect some behavioral consequence of D-1 receptor stimulation. SK&F 38393 has been assumed to be behaviorally inert in the whole animal [36]. However, our impression of some activation of non-stereotyped behaviors [39] prompted us to re-evaluate this assumption. When the baseline of activity in control animals is reduced to a very low level by prolonged habituation to the test cage, then using sensitive visual observation techniques, non-stereotyped behavioral effects of SK&F 38393 can indeed be demonstrated. Among the fragmented episodes of grooming, sniffing and rearing described above, and in detail elsewhere [22,23], episodes of locomotion are seen. Their induction by SK&F 38393 resides stereoselectively in the *R*-enantiomer, as does D-1 agonist activity [15, 22, 25]. These locomotor responses were readily blocked by SCH 23390, further consistent with their induction through D-1 receptor stimulation.

However, unexpected effects were again noted, as locomotion induced by *R*-SK&F 38393 was attenuated by metoclopramide. These locomotor responses appeared somewhat more resistant to blockade by metoclopramide than those induced by apomorphine, but significant antagonism was demonstrable. We have previously shown [23] that episodes of rearing induced by *R*-SK&F 38393 are similarly sensitive to antagonism by both SCH 23390 and by metoclopramide. Episodes of grooming induced by *R*-SK&F 38393 did not show such a consistent profile of antagonism by metoclopramide when compared with their profound antagonism by SCH 23390; global grooming measures were insensitive to any action by metoclopramide, while counts but not overall prevalence of intense grooming showed some attenuation. Thus, interactions between D-1 and D-2 function seem to show some degree of reciprocity: just as blockade of tonic D-1 activity appeared to influence locomotion and other behaviors initiated through D-2 receptors, so blockade of tonic D-2 activity appeared to influence locomotion and at least some other behaviors initiated through D-1 receptors.

CONCLUSION

New specific and stereoselective D-1 agonist and antagonist drugs have caused us to reconsider our view of D-1 receptor function, and suggest new concepts of concerted D-1:D-2 interplay in the regulation of dopaminergic behaviors such as locomotion in the whole animal. Perhaps distinct D-1 and D-2 receptor systems can in some instances each exert an influence over what is ultimately the same efferent pathway, possibly in the manner of a neuronal logic gate. The associated 'truth table' might be more apparent when future studies investigate further the physiological mechanisms which may be involved. One important caveat must be that the above concepts derive from studies with only the benzazepines available as selective D-1 agents. Ideally, one would like confirmation of these effects from chemical classes other than the benzazepines, to clarify the generality of the complex results derived from their exclusive use.

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