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COMMENTARY

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

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Proposals for receptor subclassification historically stem from pharmacological inconsistencies, usually anomalous physiological responses to putative agonist and antagonist drugs. By analogy with the cholinergic and adrenergic systems, where receptor heterogeneity is well established and has important functional consequences, a question remains as to whether subtypes of central dopamine (DA) receptor can be reliably differentiated in terms of function; it is argued here that the indices most fundamental to the central nervous system are surely behavioural in nature, and that functional discriminants should ideally be sought in such terms. It may seem strange that such a basic question needs to be posed about any system of receptor multiplicity. However, unlike cholinergic or adrenergic subtyping, prevailing schemes for DA receptor subtyping evolved substantially from neurochemical and radioligand binding techniques. The extent of confusion over the nature of dopamine receptor heterogeneity stems to a considerable degree from excessive reliance on the significance of the binding of drugs to synaptic membrane preparations, and other *in vitro* indices, in isolation from functional measures. By proceeding in this inverse manner, a system for the subclassification of DA receptors has evolved and achieved widespread acceptance, yet its behavioural correlates are not clear.

Situation pre-SCH 23390

A number of formal schemes for DA receptor subclassification have emerged over the past decade [1], but the majority have failed to achieve widespread acceptance. While those that were to lapse drew attention to important distinctions and anomalies in particular areas of dopaminergic function, the small number of drugs and behaviours specified as showing selectivity within each scheme has limited the possibility of investigating the generality of these proposals [2, 3]. The scheme that has become the basis for most of the subsequent work on dopamine receptor multiplicity [4] originally defined D-1 receptors as those coupled to the stimulation of adenylate cyclase activity, and D-2 receptors as those not having an adenylate cyclase linkage; it is worth emphasising that this scheme had its origins essentially in neurochemical considerations and, crucially, evolved in the absence of any agent known to block selectively the D-1 receptor.

Subsequent studies, focusing extensively on radioligand binding techniques, were to extend this scheme to four binding sites (D-1 to D-4) with differing research groups sometimes using such nomenclature in contradictory ways [5–8]. This quadruplet heterogeneity has been resolved and subsumed within the basic D-1:D-2 concept [9]. In a recent review of this scheme, the original definitions of D-1 and D-2 receptors have been modified in only one fundamental way, to accommodate subsequent data indicating that D-2 receptors can mediate the inhibition of adenylate cyclase activity [10]. It is this scheme which will be adhered to throughout this commentary.

Prior to mid-1983, in the absence of selective D-1 antagonists, associations between D-1 or D-2 receptors and typical dopamine-mediated behaviours were studied by indirect and/or correlational analyses. On the basis of (i) impressive correlations between the *in vitro* affinities of drugs for D-2 receptors and their *in vivo* potencies as stimulants or antagonists of conventional dopaminergic behaviours and (ii) the general ability of selective D-2 agonists and antagonists to mimic the behavioural actions of typical non-selective agents, a prepotent role in behaviour was ascribed to the D-2 receptor [5, 8, 11]. Without a selective antagonist, any behavioural role for D-1 receptors could only be probed through similar correlational analyses and via the "subtraction" strategy, i.e. clarifying any behavioural distinctions between selective D-2 and mixed D-1/D-2 agents; on the best available evidence, D-1 receptors were described as not having any known behavioural role [5, 8] or, more confidently, as without any such role [12, 13].

Initial impact of SCH 23390

In 1983, Hyttel [14], drawing on an earlier abstract by Iorio and his colleagues [15], identified SCH 23390

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(7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, occasionally referred to as an 8-chloro-7-hydroxy compound if the phenyl substitution on the heterocyclic ring is redesignated the 5- rather than the 1- position) as the first compound to show the properties expected of a selective D-1 antagonist; SCH 23390 potently inhibited both the stimulation of striatal adenylate cyclase induced by DA and the binding of [^{3}H]piflutixol to striatal D-1 receptors, but showed negligible activity either to displace striatal [^{3}H]spiperone binding or to elevate pituitary prolactin secretion, two prototype indices of D-2 antagonist activity [14, 16–18]; in our hands, using displacement of [^{3}H]piflutixol and of [^{3}H]spiperone binding as indices of D-1 and D-2 receptor activities, respectively, SCH 23390 was >1500-fold selective for D-1 receptors [18]. If typical dopaminergic behaviours such as agonist-induced stereotyped behaviour were indeed D-2-mediated responses, then the double-dissociations typical of selective antagonists in non-dopaminergic receptor systems might predict their insensitivity to blockade by SCH 23390. However, such behavioural double-dissociations have not been found; SCH 23390 is consistently a highly potent antagonist of stereotyped behaviour and hyperlocomotion induced in the whole animal by apomorphine, amphetamine, methylphenidate and 2-amino-6,7-dihydroxytetraline (ADTN) [16, 19–21]. These actions of SCH 23390 are qualitatively indistinguishable from those of typical neuroleptics and of selective D-2 antagonists; for example, we have found SCH 23390 and metoclopramide to block similarly both the sniffing and locomotor components of apomorphine stereotypy [19]. Such data throw into some confusion the earlier apparently consistent series of arguments which indicated, in the absence of D-1 antagonist studies, the exclusivity of the role of D-2 receptors in the regulation of dopaminergic behaviour.

A possible way out of this dilemma is presented by the nature of the agents inducing SCH 23390-sensitive stereotyped behaviour, as apomorphine and ADTN are non-selective agonists, and amphetamine and methylphenidate both exert non-selective dopaminergic activity by way of actions on release and reuptake mechanisms; perhaps their resultant effects on D-1 as well as D-2 receptors render their behavioural actions sensitive to SCH 23390 in some as yet unappreciated way. However, our subsequent studies found SCH 23390 to be a potent antagonist of stereotyped sniffing and locomotion induced by the selective D-2 agonist RU 24213; in fact, SCH 23390 was both qualitatively and quantitatively indistinguishable from the selective D-2 antagonist piquindone in blocking RU 24213-induced stereotypy [22]. Similarly, SCH 23390 can antagonise stereotypy and locomotor stimulation induced by the selective D-2 agonists pergolide and quinpirole [23, 24] and, consistent with these paradoxes, RU 24213 and quinpirole can antagonise catalepsy induced by SCH 23390 [25]. Such unexpected properties of SCH 23390 are not exclusive to the motor responses of stereotypy/hyperlocomotion and catalepsy, and generalise to other forms of dopaminergic behaviour. Thus, SCH 23390 also mimics the actions of selective D-2 antagonists by inhibiting conditioned avoidance behaviour and blocking the amphetamine cue in drug discrimination responding [26]. The totality of such results clearly poses problems for current assumptions about the receptor pharmacology of these agents and/or current concepts of the functional roles of D-1 and D-2 receptors. One interpretation of these data is that there is only one brain DA receptor, such that behavioural responses do not show consistent selectivity for receptor antagonists; this would question the behavioural relevance of the D-1:D-2 subdivision that is usually made on *in vitro* considerations. However, further studies suggest that it may not be necessary to accept so radical a conclusion at this stage.

Reappraisal of SCH 23390

After such behavioural results began to unfold, further studies were devoted to re-evaluating the selectivity of SCH 23390. The original results were reconfirmed and extended in a variety of test systems of *in vitro* D-1 versus D-2 antagonist activity [27–29]. In our own studies, saturation isotherms for [^{3}H]piflutixol binding to D-1 receptors were performed in the presence of increasing concentrations of SCH 23390. As little as 0.2 nM SCH 23390 elevated apparent K_D without influencing B_{max}, consistent with potent competitive antagonism at D-1 receptors; conversely, 200–1000 nM SCH 23390 was required to elevate K_D for [^{3}H]spiperone binding, suggesting weak residual competitive D-2 antagonist activity only at concentrations >1000-fold above those required to influence the D-1 receptor [28]. [^{3}H]SCH 23390 has been shown to bind *in vitro* with high affinity to membrane preparations from rat striatum [30, 31] and human putamen [32, 33] with the pharmacological profile expected of a D-1 receptor ligand; it is displaced by agents known to influence DA-sensitive adenylate cyclase activity, in rank order proportionate with their potency to influence this enzyme system. In human putamen, we have found the selective D-2 antagonist domperidone to be >2000-fold less active than SCH 23390 itself to displace the binding of [^{3}H]SCH 23390, with sulpiride, ketanserin, prazosin and rauwolscine being essentially inactive [32]. Steric exclusion high performance liquid chromatography (HPLC) has been used to isolate solubilised [^{3}H]SCH 23390-labelled D-1 receptors from canine caudate, and this chromatographic peak is unaltered by a concentration of spiperone substantially in excess of that required to label D-2 receptors similarly [34].

At the pituitary D-2 receptor, recent studies have confirmed the failure of SCH 23390 to induce the potent elevations in prolactin secretion that characterise selective and non-selective D-2 antagonists. Only a weak, transient elevation of prolactin by SCH 23390 was noted, shortly after doses above those known to be behaviourally active [35]; conversely, a weak and dose-independent trend for decreased prolactin levels after SCH 23390 has also been reported [36]. In electrophysiological studies, microiontophoretically-applied SCH 23390 fails to affect the activity of nigrally-excited striatal cells whose firing rate is inhibited by the selective D-2 antagonist domperidone [37].

These results, obtained in so diverse a range of test

systems, consistently indicate that the unexpected behavioural actions of SCH 23390 cannot be explained in terms of mis-designation as a selective D-1 antagonist. The failure of peripherally-administered SCH 23390 to elevate prolactin levels and to inhibit D-2 agonist-induced emesis [16, 20] argues against any significant formation *in vivo* of an active metabolite with D-2 antagonist activity; this is consistent with the limited data available on the biotransformation of the 1-phenyl-1*H*-3-benzazepines in relation to what is known of structure–affinity relationships within such compounds (see below). Peripherally-administered SCH 23390 retains its ability to inhibit both DA-sensitive adenylate cyclase activity and amphetamine-induced hyperlocomotion for over 8 hr, with brain levels of SCH 23390 persisting long after plasma concentrations have declined [38]. Also, chronic treatment of animals with SCH 23390 increases the density of D-1 but not D-2 receptors [39].

It could be argued that non-dopaminergic actions of SCH 23390 might contribute to its unexpected behavioural effects, but it has little affinity for non-dopaminergic receptors [14, 17, 20]. SCH 23390 has some 5-HT_2 antagonist activity [20, 40], but we have found that doses which block stereotyped behaviour induced by the selective D-2 agonist RU 24213 fail to influence the classical serotonergic behavioural syndrome induced by the 5-HT agonist 5-methoxy-*N*,*N*-dimethyltryptamine [22]. This also indicates that SCH 23390 is not exerting a non-specific effect to suppress behaviour. Though actions of SCH 23390 on some unknown but behaviourally significant non-dopaminergic system(s) cannot be incontrovertably excluded, the available evidence strongly suggests that its behavioural effects have their basis in D-1 receptor blockade.

Interactive D-1:D-2 receptor systems?

Unexpected actions of SCH 23390 are not only evident in terms of behaviour. Thus, SCH 23390 can antagonise the decrease in K^+-evoked release of [^{3}H]acetylcholine induced in rat striatal slice preparations by the selective D-2 agonist LY 141865 [41]. It is notable that SCH 23390 appears to be a selective D-1 antagonist not only in isolated, non-functional synaptic membrane preparations, as used in *in vitro* ligand binding assays; it also appears selective when the criterion involves an *in vivo* physiological system that is rich in D-2 receptors, such as regulation of emesis by the chemoreceptive trigger zone and of prolactin secretion by the pituitary [16, 20]. However, when the test system is one that is rich in both D-1 and D-2 receptors in the forebrain, such as in the above behavioural studies, or in those striatal slice preparations where local functional integrity of D-1 and D-2 systems is preserved [41, 42], SCH 23390 appears to mimic effects previously equated with D-2 receptor blockade and exerts paradoxical antagonism of D-2 agonist responses. The explanation may be that SCH 23390 is genuinely exerting these effects through blockade of tonic activity in ascending forebrain D-1 dopaminergic systems. This implies that D-1 dopaminergic activity is regulating, in a facilitatory manner, processes initiated by D-2 dopaminergic activity, i.e. that D-1 and D-2 dopaminergic systems do not invariably function in an independent manner. This concept of interactive D-1:D-2 receptor systems [19, 43] requires mechanistic support, and there are a number of ways in which the various potential levels of interaction have been investigated.

Two laboratories have investigated in *in vitro* ligand binding assays whether SCH 23390 can influence the interaction between a D-2 agonist and the D-2 receptor. In our studies [28] SCH 23390, at a concentration 5-fold greater than that required to influence [^{3}H]piflutixol binding to D-1 receptors, failed to influence significantly the displacement of [^{3}H]spiperone from D-2 receptors by the selective D-2 agonist RU 24213. Seeman and colleagues [44] have reported that SCH 23390 caused slight but significant elevation in the apparent density (i.e. up-regulation) of D-2 sites labelled with [^{3}H]-(−)*N*-propylnorapomorphine; this *increase* in binding of a D-2 agonist in the presence of a D-1 antagonist, were it to be of functional significance, would be in the direction opposite to that required to account for the action of SCH 23390 to *antagonise* behavioural responses to a D-2 agonist. Thus, there are as yet no *in vitro* binding data available which indicate that SCH 23390, by occupying D-1 receptors, can attenuate the recognition of a D-2 agonist by the D-2 receptor.

Recent electrophysiological studies by Sasa and co-workers have examined the effects of SCH 23390 on D-2-mediated responses. The excitatory response of striatal cells to substantia nigra stimulation is inhibited by microiontophoretic application of the selective D-2 antagonist domperidone but is insensitive to similar applications of SCH 23390; also, excitatory responses of striatal cells to microiontophoretic application of the selective D-2 agonist bromocriptine are inhibited by concurrent application of domperidone, while these responses to bromocriptine are not influenced by concurrent application of SCH 23390 [Ref. 37 and M. Sasa, personal communication]. Such *in vivo* data complement the above *in vitro* binding studies by confirming that SCH 23390 fails to attenuate either the recognition of, or the immediate physiological response to, a D-2 agonist by the D-2 receptor. At these levels at least, SCH 23390 fails to influence D-2 function.

It is only at higher levels of integrative dopaminergic activity (*in vivo* neurochemical studies and *in vitro* studies in functional slice preparations) that SCH 23390 has been noted to influence D-2-mediated processes. SCH 23390 reduces the *in vivo* increase in striatal DA metabolites elicited by D-2 receptor blockade and attenuates the *in vitro* release of [^{3}H]ACh from striatal slices induced by D-2 antagonists [45]. These interactions are in the same general direction as the reciprocal relationship between D-1 and D-2 receptors in the regulation of striatal cAMP synthesis [46, 47] or of protein phosphorylation in the neurohypophysis [48]; however, it is difficult to see how such actions of SCH 23390 can explain its ability to *antagonise* rather than reciprocally enhance behavioural indices of D-2 receptor stimulation. Also, SCH 23390, at doses above those required to block D-2 agonist-induced stereotyped behaviour,

does not affect the ability of the selective D-2 agonist quinpirole to reduce striatal DA metabolite concentrations [45]. Thus, typical neurochemical indices of dopaminergic activity fail to reveal the functional interactions between D-1 and D-2 receptor systems that might account for the paradoxical ability of SCH 23390 to antagonise D-2-stimulated behaviours. It would, therefore, seem necessary to accumulate further, more direct, evidence that these behavioural actions of SCH 23390 are indeed mediated through D-1 receptor blockade and thus do imply such interactions.

R *and* S-*SKF* 83566

Since the introduction of SCH 23390, interest has developed in structural determinants of its selective affinity for D-1 receptors. Studies of structure–activity relationships have evolved substantially from differences between SCH 23390 and its 7-OH-3-H analogue SKF 38393, which has been known for some time to be a partial D-1 agonist of some selectivity [49, 50]. We have been able to investigate a total of ten 1-phenyl-1*H*-3-benzazepine compounds to explore such relationships [18, 51, 52]. These agents are chiral compounds, existing as true enantiomeric pairs. Stereochemically, affinity for D-1 receptors resides, with substantial enantioselectivity, in the *R*-configuration for SKF 38393 [18, 53] and SKF 83566, the 7-Br-homologue of SCH 23390 [51]; SCH 23390 is itself a resolved *R*-enantiomer [16, 30]. A 7-halogen substitution is a critical determinant of high-affinity selective antagonist action at D-1 receptors, with 3-substitutions having less profound and less specific influences on activity [52]. We have found these general relationships to apply in human putamen [54, 55] as well as rat striatum, and other studies support these interpretations [56–58].

SKF 83566 has proved to be an important tool for use in behavioural studies as D-1 receptors are potently blocked by the *R*-enantiomer but not by its *S*-antipode, while residual affinity for D-2 receptors shows negligible enantioselectivity [51]. We have found *R*-SKF 83566, like SCH 23390, to block potently stereotyped behaviour induced by apomorphine, while its *S*-antipode is essentially inactive [59]. In a more strict test of the mode of inhibition of stereotyped behaviour by D-1 antagonists, responses to the selective D-2 agonist RU 24213 were blocked by *R*-SKF 83566 with complete enantioselectivity [59, 60]. Such results strongly suggest that the blockade by D-1 antagonist benzazepines of behavioural effects initiated through D-2 receptor stimulation is mediated through blockade of D-1 receptors. This criterion of enantioselectivity of effect supports the notion [22] that reducing tonic D-1 dopaminergic activity can attenuate the expression of behaviours promoted through a D-2 system. A corollary of this would be [61] that tonic D-1 dopaminergic activity is required for the expression of behaviours induced by D-2 receptor stimulation in the intact animal.

D-1:D-2 receptor systems and dopaminergic behaviour

It is interesting to note that the unexplained ability of the DA synthesis inhibitor α-methyl-*p*-tyrosine to attenuate behavioural responses to the D-2 agonist bromocriptine [62] can be accounted for in the above terms; by reducing the amount of DA available for release, α-methyl-*p*-tyrosine would reduce tonic stimulation of D-1 receptors and, by this model, impede the expression of behaviours initiated through the D-2 agonist action of bromocriptine. If such considerations are to be the basis of a more general formulation of functionally-interactive D-1:D-2 receptor systems, they must make testable predictions. One would be that increasing D-1 dopaminergic activity should, in general, have behavioural consequences and, more specifically, enhance the expression of D-2 initiated behaviours.

The only available selective D-1 receptor stimulant, the partial agonist SKF 38393, has been assumed to be essentially inert in terms of behavioural response in the intact, adult rat, failing to induce the stereotyped behaviour and hyperlocomotion of typical DA agonists [49, 50]. However, under particular experimental conditions we have found SKF 38393 to be behaviourally active. Following a period of prolonged habituation to the observation cage, and with the use of a rapid time-sampling behavioural checklist procedure for assessment, SKF 38393 induces quantifiable episodes of fragmented, discontinuous and non-stereotyped sniffing, rearing and locomotor behaviour, interpolated between episodes of a particularly prominent grooming response [19, 43, 63, 64]. Grooming and sniffing are the most robust responses. They are induced by *R*- but not *S*-SKF 38393 and are potently blocked by SCH 23390 and by *R*- but not *S*-SKF 83566 [19, 43, 60, 61]. These pharmacological characteristics, particularly that of enantioselectivity of behavioural stimulation and blockade, which parallels enantioselectivity of agonist and antagonist action at D-1 but not at D-2 receptors [18, 51, 53], is strong evidence that these behaviours have their basis in D-1 receptor stimulation.

While we have noted both selective D-2 antagonists and non-dopaminergic antagonists to influence variably the expression of certain individual behaviours induced by SKF 38393, only SCH 23390 and *R*-SKF 83566 potently antagonise all of these behaviours [19, 43, 60, 61]. The attenuation of the expression of certain D-1 agonist-induced behaviours by selective D-2 antagonists would support the concept of interactive D-1:D-2 receptor systems, by complementing the blockade of D-2 agonist-induced behaviours by selective D-1 antagonists. It is interesting to note that the non-selective DA agonist apomorphine induces typical stereotyped behaviour rather than grooming; however, grooming to apomorphine is seen following pretreatment with modest (but not with high) doses of the selective D-2 antagonists metoclopramide and sulpiride [1, 43], presumably by unmasking of the D-1 component of apomorphine's action when D-2 receptors are occluded. The induction of such non-stereotyped behaviours by SKF 38393, particularly the grooming response, has been confirmed in several laboratories [23, 65, 66], though its effects on locomotion and rearing appear to be situationally determined [66]. Also, the induction by SKF 38393, of repetitive mouth opening and clonic jaw movements has been

noted [67, 68], but has not yet received extensive pharmacological characterisation. We have found this response to be most evident in senescent animals [68], where the relative density of D-1 receptors is increased because of a selective loss of D-2 receptors with ageing [69]. In drug discrimination studies, SKF 38393 can be distinguished from saline; this cue is blocked by SCH 23390 and does not generalise to the selective D-2 agonist quinpirole [70].

The above D-1 agonist studies support the general notion of a role for D-1 receptors in the promotion as well as the suppression of dopaminergic behaviours. However, the ability of selective D-1 antagonists to attenuate D-2 agonist-induced stereotyped behaviour prompted the more specific prediction that a D-1 agonist should enhance such responses, and we have been able to show recently that this is indeed the case. We have found it difficult to induce compulsive, fixated stereotyped behaviour even with high doses of the selective D-2 agonist RU 24213 [22], although these are typical responses to the mixed DA agonist apomorphine. Perhaps these distinctions reflect the absence and presence of D-1 agonist activity. In our studies a threshold dose of RU 24213, inducing weak stereotypy, produced both a greater and a more compulsive stereotypy response when given immediately after administration of SKF 38393; the D-1 agonist given alone did not induce stereotyped behaviour, though grooming was evident, and its combination with RU 24213 was synergistic rather than additive [55, 61]. Thus, the picture is a consistent one, with decreases and increases in D-1 receptor stimulation respectively attenuating and enhancing the intensity of D-2 agonist-induced stereotyped behaviour. More generally, alterations in D-1 dopaminergic tone in either direction appear to modulate importantly the behavioural expression of activity in D-2 systems in the corresponding direction.

As noted above, mechanisms for how D-1 agonists and antagonists might influence such agonist responses are not obvious; even less is known about how D-2 antagonists might influence certain D-1 agonist responses in the indicated directions. We have argued previously [61] that there are precedents for such forms of functional interaction in other receptor systems, and that the situation may be somewhat analogous conceptually (though not mechanistically) to the effects of selective adrenergic antagonists on cardiovascular parameters; for example both α- and β-adrenoceptor blockers can induce a reduction in blood pressure, though these effects are mediated via discrete receptor subtypes through which initially distinct mechanisms ultimately influence the same physiological process.

Conclusions and unresolved issues

Perhaps in the intact animal distinct D-1 and D-2 receptor systems can, in some instances, each exert an influence over what is ultimately a common efferent system for the expression of a certain behaviour or syndrome. More speculatively, at the neuropsychological level, the available evidence suggests that D-2 systems appear more to select a particular mode of expression of behaviour, such as stereotypy; conversely, D-1 systems appear more to influence the intensity of expression of the mode selected. Thus, during background levels of tonic D-2 activity, D-1 agonists and antagonists influence D-1 tone respectively to enhance and block normal behaviours such as non-stereotyped grooming and sniffing. However, when a D-2 agonist is given, it is a stereotyped mode of behaviour which is selected, and this is similarly enhanced and blocked by the effects of D-1 agonists and antagonists on D-1 tone. Additionally, it is evident that D-1 antagonists exert prominent effects on behaviour while those of the only available D-1 agonist, SKF 38393, are more subtle; this might suggest that the normal level of tonic D-1 dopaminergic activity is high, or it may alternatively reflect that SKF 38393 is only a partial agonist at D-1 receptors. There is a recent report that SKF 38393 has negligible action to antagonise catalepsy induced by SCH 23390 [71].

There are several other issues that remain to be resolved before we can assess the full significance of the introduction of SCH 23390 and *R*- and *S*-SKF 83566. At the receptor level [^{3}H]SCH 23390 appears to label *in vitro* a two-state D-1 receptor having high and low affinities for agonists, with shifts from the former to the latter state being favoured by the presence of guanine nucleotides and sodium ions [72, 73]. However, as relationships between dissociation constants for high and low affinity states were not predictive of the intrinsic activity of agonists in stimulating adenylate cyclase activity under the given assay conditions [73], the functional and ultimate behavioural significance of such interconverting sites remains to be determined. While the rank order of K_i values of drugs for inhibiting DA-stimulated adenylate cyclase activity are in good agreement with their K_i values for displacement of *in vitro* [^{3}H]SCH 23390 binding, their absolute values appear 80- to 240-fold higher [74]. There are preliminary data that some component of [^{3}H]SCH 23390 binding may be dissociable from DA-sensitive adenylate cyclase activity, in terms of both subcellular fractionation and regional localisation, and this has prompted the suggestion that D-1 receptors may require some appropriate re-definition [75, 76]. Originally, only D-1 receptors were defined by an association with adenylate cyclase [4]. This scheme has undergone revision to accommodate evidence that D-2 receptors can inhibit the activity of this enzyme [10]. If some D-2 receptors can be redefined as having an association with adenylate cyclase, it need not seem paradoxical to re-define some D-1 receptors as selectively recognising SCH 23390 yet not having any such cyclase linkage. Certainly, many of the behavioural actions of SCH 23390 and SKF 83566 reviewed above cannot be easily reconciled with the known physiology and pharmacology of adenylate cyclase.

One major problem in attaching a mechanism to the ability of SCH 23390 and *R*-SKF 83566 to mimic the behavioural actions of D-2 antagonists in the intact animal is that these paradoxical effects are not seen in animals either lesioned with 6-hydroxydopamine or depleted of DA by treatment with reserpine/α-methyl-*p*-tyrosine; in such animals, responses to D-2 agonists are not blocked by SCH 23390 and responses to D-1 agonists are insensitive

to D-2 antagonists [23, 24, 77–79]. Thus, the paradoxical effects of SCH 23390 depend upon the presence of normal dopaminergic transmission; a variety of adaptive mechanisms are recruited when dopaminergic function is perturbed, and may well contribute to these results. These dissociations between the intact animal and such artificial pharmacological preparations indicate the complexity of neuronal mechanisms subserving interactions between D-1 and D-2 receptor systems under normal conditions. They might be best approached by first trying to model the various contingencies involved, perhaps in terms of truth tables for putative neuronal logic gates, before proceeding to the mechanistic level. It should not be forgotten that there is only one group of drugs available as selective D-1 agents. Selective D-1 drugs from chemical classes other than the benzazepines are clearly required, to clarify the generality of the complex results deriving from their exclusive use.

If D-1 receptors do after all have a role in the regulation of dopaminergic behaviour, what might be the clinical potential of novel agents with D-1 selective actions? One might expect D-1 agonists to enhance the efficacy of selective D-2 agonists in Parkinson's disease, but this is complicated by the underlying degeneration of DA neurons. In animal studies 6-hydroxydopamine lesions and chronic dopaminergic perturbations alter the relationship between D-1 and D-2 receptor function; thus, the clinical effect of such combinations may be very much dependent on the extent both of disease progression and of previous treatment with conventional agents. In relation to schizophrenia, SCH 23390 and *R*-SKF 83566 are active in many of the behavioural models currently used to predict antipsychotic activity. As such activity has been equated previously with D-2 receptor blockade, any therapeutic effect of selective D-1 antagonists in psychosis would have implications for current theories on both neuroleptic drug action and the pathophysiology of schizophrenia. Additionally, clinical studies would constitute an important test of the relevance of current behavioural models for antipsychotic drug action. Several atypical neuroleptics have been shown recently to be surprisingly potent inhibitors of *in vivo* [^{3}H]SCH 23390 binding, in contrast to their lack of affinity *in vitro* for D-1 and in some instances also for D-2 receptors [80]. SCH 23390 induces only a low incidence of acute dyskinetic reactions, in non-drug naive primates, at doses that do impair conditioned avoidance responding; however, these animals had been rendered susceptible to this motor syndrome by prior exposure to typical neuroleptics, and SCH 23390 did potentiate the ability of haloperidol to induce such acute dyskinetic reactions [81]. Little is known on whether selective D-1 antagonists might promote late-onset involuntary movements (tardive dyskinesia). Though neuroleptic-induced D-2 receptor supersensitivity has been widely considered to constitute the pathophysiology of such involuntary movements, we and others [82–85] have drawn attention to the profound weaknesses of this hypothesis, which are being increasingly recognised. Therefore, it need not have any direct relevance for the issue of the extent to which SCH 23390 or other selective D-1 antagonists might or might not promote tardive dyskinesia.

There is an urgent need to identify novel potent and selective D-1 agonist and antagonist drugs, so that clinical studies can proceed in an area whose therapeutic potential is so intriguing yet has remained unexplored.

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