Compounds selective for dopamine receptor subtypes

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Novel dopamine (DA) receptor proteins of relatively low natural abundance and uncertain physiology can be expressed selectively in genetically transfected cultured cells to facilitate screening of novel DA receptor ligands. Selective agonists or antagonists for most of the five major DA receptor types are emerging, but better D_4 and D_5 agonists, D_3 and D_5 antagonists, and more selective D_2 antagonists are needed. Clinical development of such compounds as diagnostic neuroradiopharmaceuticals or neuropsychiatric drugs remains empirical and somewhat unpredictable. The search for novel receptor-selective agents can be enhanced by better understanding of the physiology and pharmacology of DA neuroreceptors.

Dopamine (3,4-dihydroxyphenethylamine; DA) is among the most widely studied neurotransmitters of the mammalian CNS. The anatomy, physiology and pharmacology of dopaminergic systems in the brain have been extensively characterized since the 1950s (Refs 1–3). In addition, the pharmaceutical industry and academic neuropharmacologists have been developing a growing series of novel compounds that mimic or block the actions of DA in the brain and in model systems, including cells genetically transfected to express specific DA receptor membrane proteins.

Interest in dopaminergic agents is encouraged by the importance of DA in the molecular neuropathology and therapeutics of several common neuropsychiatric disorders. Notably, selective degenerative loss of DA neurons of the midbrain and their projections to the basal ganglia is a specific feature of idiopathic Parkinson's disease. This has led to the development of a rational treatment based on replacement with the DA precursor L-dopa (L-3,4-dihydroxyphenylalanine), or use of direct DA agonists including bromocriptine and other ergolines[1–3]. In addition, virtually all clinically employed antipsychotic agents (phenothiazines, thioxanthenes, benzepines, butyrophenones and related compounds) have antagonistic actions at central D_2-like receptors and some are also D_1-like antagonists[4]. These agents are clinically useful in a broad range of psychotic disorders, including schizophrenia, mania, psychotic depression and organic psychoses[4,5]. Most of these drugs induce adverse extrapyramidal neurological effects resembling signs of Parkinson's disease (bradykinesia, tremor, restlessness), some of which can probably be ascribed to antidopaminergic actions; they can also both cause and suppress dyskinesias and perhaps dystonias. In addition, DA agonists may have useful mood-elevating effects, and may contribute to the treatment of addiction to cocaine and other stimulants, but such applications await development[4]. Finally, DA itself has an important role in the control of cardiovascular shock, and agents with

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antidopaminergic actions (e.g. substituted benzamides including metoclopramide and cisapride) have a role in gastroenterological disorders[5].

These clinical indications offer major economic and clinical incentives for currently intense industrial interest in the discovery of additional drugs that mimic or block the actions of DA in the brain. Novel agents are being targeted at the well-known D_1 and D_2 receptors, as well as recently described, less abundant DA receptor (DAR) types (D_3, D_4, D_5) or their subtypes[5]. In addition, many well-known agents and a growing list of novel compounds are widely used in the experimental investigation of molecular properties of DARs and their less well established molecular, physiological and behavioral functions.

Discovery of dopamine receptors

In the 1950s and 1960s, investigation of behavioral and neurochemical effects of the potent emetic DA agonist (–)-*R*-apomorphine (known since the 1870s as an acid-rearrangement product of morphine) led to the hypothesis that there are unique DARs in the extrapyramidal forebrain as well as in the emetic center of the brainstem[3,6,7]. This concept was further supported by the discovery that chlorpromazine is antiemetic, can block other behavioral and biochemical effects of apomorphine, and can produce neurobehavioral and neurochemical actions that are essentially opposite to those of apomorphine[3,7–9]. Apomorphine and chlorpromazine, respectively, increased or diminished arousal and reduced motility, and reduced or increased metabolic turnover of DA. Arvid Carlsson brilliantly proposed that increases of DA turnover produced by chlorpromazine and other neuroleptics represented a secondary, compensatory response to reduced stimulation of DA receptors in an effort of the brain to restore functional homeostasis[3,9]. Structural analogs of chlorpromazine (including other phenothiazines and thioxanthenes, as well as the butyrophenone haloperidol) also blocked apomorphine and produced extrapyramidal effects in animals as well as antipsychotic or antimanic effects in humans[4,7,8]. Thus, by the early 1970s, apomorphine and several types of neuroleptic–antipsychotic agents were the main pharmacological tools for investigating a putative DAR whose existence was proposed on the basis of behavioral and *in vivo* neurochemical evidence.

As early as 1972, John Kebabian, Paul Greengard and their associates proposed a molecular model of the behaviorally and neurochemically defined DAR (Ref.10). DA was found to stimulate adenylate cyclase activity in cell-free homogenates of caudate putamen tissue from the basal ganglia of rat forebrain. Apomorphine mimicked this molecular action of DA, and chlorpromazine potently blocked the stimulatory effect of DA and apomorphine. Haloperidol had some antagonistic effect, but at much lower potency than predicted by its behavioral antagonism of apomorphine or its clinical actions. These measurements in cell-free experimental systems permitted application of mathematical principles derived from the competitive antagonism of enzymes to computing the apparent affinity (K_i) of drugs for adenylate cyclase[11–13]. This biochemical model provided a convenient test system in which compounds could be screened rapidly for activity resembling that of DA or some of its antagonists, free of the complications of drug disposition and metabolism associated with *in vivo* models.

The DA-sensitive adenylate cyclase model presented some problems, including the aberrantly low potency of haloperidol and chemically related compounds, as well as sulpiride, metoclopramide and other substituted benzamides – all now known to be selective inhibitors of D_2-like receptors[5,14]. Likewise, ergot derivatives, including lergotrile or lisuride, like DA, stimulated a suspected DAR in the pituitary to inhibit release of prolactin but were inactive on brain adenylate cyclase or even blocked the stimulatory effect of DA on cyclase activity[15,16]. The DAR in pituitary evidently was also sensitive to virtually all neuroleptic agents, including butyrophenones and benzamides, that elevated prolactin levels in close correlation with their behavioral antiapomorphine and clinical antipsychotic potencies[17]. This state of information led to a growing suspicion that there were at least two types of DAR.

In the late 1970s, two groups independently proposed the existence of two types of DAR. Based on the actions of various ergot compounds, Pier Franco Spano and his colleagues proposed the presence of two DAR types in rat forebrain[18]. Based in part on this and other pharmacological findings, John Kebabian and his colleagues formulated a two-receptor hypothesis[19,20]. They proposed that the DA-sensitive adenylate cyclase in rodent forebrain was associated with one category of DAR (type 1) that is insensitive to bromocriptine and butyrophenones, whereas the DAR associated with the mammotrophs of the anterior pituitary (type 2) did not stimulate formation of cAMP but was stimulated by ergots and inhibited by most neuroleptics, including butyrophenones and benzamides. Although

identification of two types of DAR accounted for some of the pharmacological anomalies described above, the 'two-receptor' hypothesis was not widely accepted until additional compounds that clearly differentiated the two types of DAR were developed. The theory was even more securely validated by recent cloning and sequencing of the genes and proteins involved, with a confirmatory neuropharmacology in transfected cells expressing a single type of DAR.

Molecular biology of dopamine receptors

Following cloning of the β-adrenoceptor in 1986 (Ref. 21), molecular genetic methods were applied to identify the mRNAs and, ultimately, the peptide sequences for DARs by several research groups in the late 1980s (Ref. 22). Initially, the mRNA for the D_2 DAR was cloned by members of Olivier Civelli's team in 1988, based on applications of adrenoceptor nucleic acid sequences that are similar to those for DARs (Ref. 23). D_2 receptors are expressed in rodent and human brain with alternative splicing of DNA sequences to yield a relatively abundant 'long' form (D_{2L}) and a less prevalent 'short' form (D_{2S}) of the peptide chain lacking a 29-amino acid sequence in the third intracellular loop[24,25]. Expression of this receptor in cultured cells replicated the drug recognition properties of the native receptor in brain tissue[26]. The mRNA for the D_1 DAR also was cloned and uniquely expressed in genetically transfected cells by several laboratories in 1990 (Refs 27–30). Both types of DAR from several mammalian species retained strikingly similar amino acid sequences, particularly in the seven relatively hydrophobic membrane-spanning regions characteristic of monoaminergic receptor proteins. Larger differences occur in the third intracellular segment believed to interact with GTP-binding proteins and effector enzymes, as well as in the extracellular amino-terminus and intracellular carboxy-end of the peptides[22].

Following identification of the two principal types of DAR, an additional D_2-like entity (D_3) was cloned by Pierre Sokoloff, Jean-Charles Schwartz and their colleagues in 1990, and localized to the mammalian basal forebrain[31]. In 1991, another D_2-like entity (D_4) was cloned by Hubert van Tol, Philip Seeman and their colleagues[32]. This receptor type is expressed in several forms, with varying repeats (usually 2–7) of a 48 bp (16 amino acid) sequence[33]. Finally, a fifth entity (D_5, sometimes designated D_{1B}) with D_1 receptor-like peptide sequences and pharmacological properties was cloned by several groups in 1991 (Refs 34–37). The D_5 receptor can also be expressed with several minor variations within a single species, and some D_5-like genes have been cloned but are not expressed as proteins[34]. Additional DAR-like genetic sequences and proteins have been identified in lower vertebrates, invertebrates and insects that share some pharmacological properties of mammalian DARs despite having greater dissimilarities in amino acid sequences[38,39].

Studies of the functions of various DARs have relied mainly on biochemical studies with transfected cells expressing a specific DAR (Refs 5,22). These have clarified that D_1 (D_{1A}) and D_5 (D_{1B}) receptors both interact with G-proteins and stimulate adenylate cyclase. D_2 (D_{2L} and D_{2S}) receptors also interact with G-proteins and can probably inhibit adenylate cyclase as well as inhibiting phospholipase C (which may be stimulated by some D_1-like receptors) to participate in the ubiquitous phosphatidylinositol second-messenger system, and stimulating phospholipase A_2 to regulate conversion of phosphatidylinositol to arachidonic acid, and they may also be linked directly to ion channels to facilitate the cellular extrusion of potassium[22]. The status of the low-abundance D_3, D_4 and D_5 entities remains unresolved. D_3 has shown inconsistent interactions with G-proteins and second-messenger enzymes, and D_4 protein has been hard to detect in mammalian brain with certainty. Knowledge of the neurophysiological and behavioral effects of most of the DARs, particularly D_1, D_3, D_4 and D_5, remains fragmentary or nonexistent. Moreover, possible clinical effects of DAR agents, except for the neuroleptic effects of D_2 antagonists and antiparkinson effects of D_1 and D_2 agonists, remain little studied or unknown[5]. Several extensive reviews and a recent monograph summarize work leading to the present state of knowledge of the genetics and molecular forms of these various DARs (Refs 5,22,40–43).

Selective pharmacological agents

Classification of DARs has been greatly facilitated by identification or discovery of pharmacological agents that distinguish the various types[5,22,43]. Development of agonists and antagonists for the D_1-like and D_2-like families of DARs and their individual subtypes has obvious potential commercial, pharmaceutical and clinical interest, and is making striking progress in several areas.

D_1-like agents

Several examples of selective agents for the D_1-like receptors are known (Figures 1 and 2). Many are (+)-*R*-phenylhydroxybenzazepines, including SKF38393, the first selective

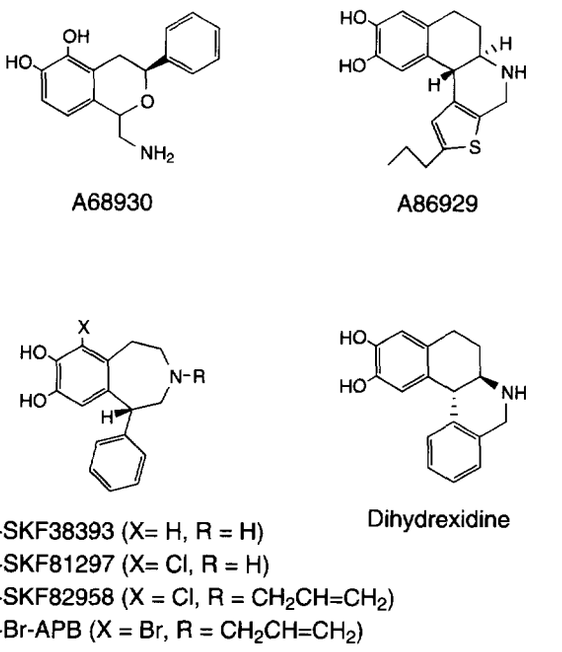

Figure 1. *Agonists with selectivity for D_1-like receptors.*

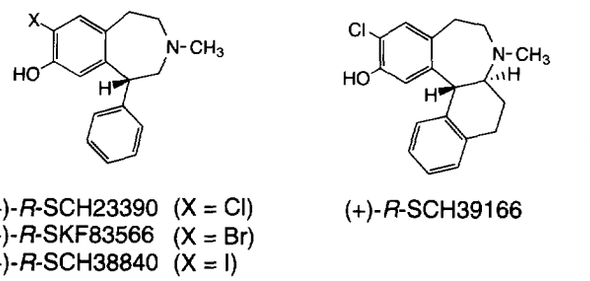

Figure 2. *Antagonists with selectivity for D_1-like receptors.*

D_1 agonist, or partial agonist, whose efficacy varies between species[44–46]. Other congeners [e.g. *N*-allyl-6-bromo-SKF38393 (Br-APB), SKF81297, SKF82526 (fenoldopam) and SKF82958] are more potent or even full D_1 agonists at native D_1-like receptors in rat brain, although their efficacy varies in other species[47,48]. Several isochromans (e.g. A68930, A77636) also show potent and selective D_1 agonist effects with high D_1 selectivity and intrinsic activity[49–53]. They show relatively prolonged antibradykinesia effects in laboratory animals with neurotoxin-induced parkinsonism, although tolerance is sometimes found with repeated administration[49–52]. In addition, the ergoline CY208243 and the heterocyclic A86929 (Refs 53–55) and structurally related dihydrexidine have potent D_1 agonist activity, although dihydrexidine and its analogs have some affinity for D_3 receptors[56,57]. None of these agonists clearly distinguishes D_5 from D_1 receptors[22,43], although A86929 shows some D_5 selectivity (Table 1)[53].

Halogenated (+)-*R*-phenylbenzazepines include several D_1/D_5 antagonists (e.g. SCH23390, SCH38840, SCH39166, SKF83566)[58–60]. Perhaps the most widely employed of these, including in tritiated form for labeling D_1 and D_5 receptors, is SCH23390, the first potent and selective D_1 antagonist reported[58]. In addition, a variety of radioactive (^{76}Br, ^{11}C, ^{18}F, and ^{123}I for neuroradiological applications, and ^{125}I), fluorescent and biotinylated derivatives and irreversible alkylating derivatives of such compounds have been studied[5,22,59,60]. As a potential pharmaceutical agent, SCH23390 was found to have an impractically short plasma half-life, although a modified structure (SCH39166) that incorporates the phenyl and azepine moieties into a fourth ring is longer acting; however, SCH39166 did not have clinically obvious psychotropic effects in clinical trials[61]. Again, none of these compounds is selective for the uncommon and rather diffusely distributed D_5 (D_{1B}) receptors in brain tissue or in transfected cells[22,35,36].

Although development of agonist, partial agonist and antagonist ligands selective for D_1-like receptors has been quite successful, and their application as test agents and receptor probes to screen for additional, even more selective agents remains promising, knowledge of the physiological and behavioral significance of D_1 receptors remains quite limited, and that of D_5 receptors unknown[22]. This is particularly ironic since the D_1-type receptors were the first identified, first associated with a specific molecular action (stimulation of cAMP synthesis), and also the most abundant of all DARs in mammalian forebrain[22]. Selected examples of reported structures of D_1-selective agents are provided in Figures 1 and 2.

D_2-like agents

Several agents effectively discriminate generally between the D_2-like and D_1-like families of DARs (Figures 3 and 4). These include quinpirole, a widely used D_2-like agonist which has some selectivity for D_3 sites[62–66]. N0434 and N0437 are additional agonists of unique structure with selectivity for D_2 receptors[67]. Among D_2-like antagonists, the butyrophenones and analogous compounds (e.g. haloperidol,

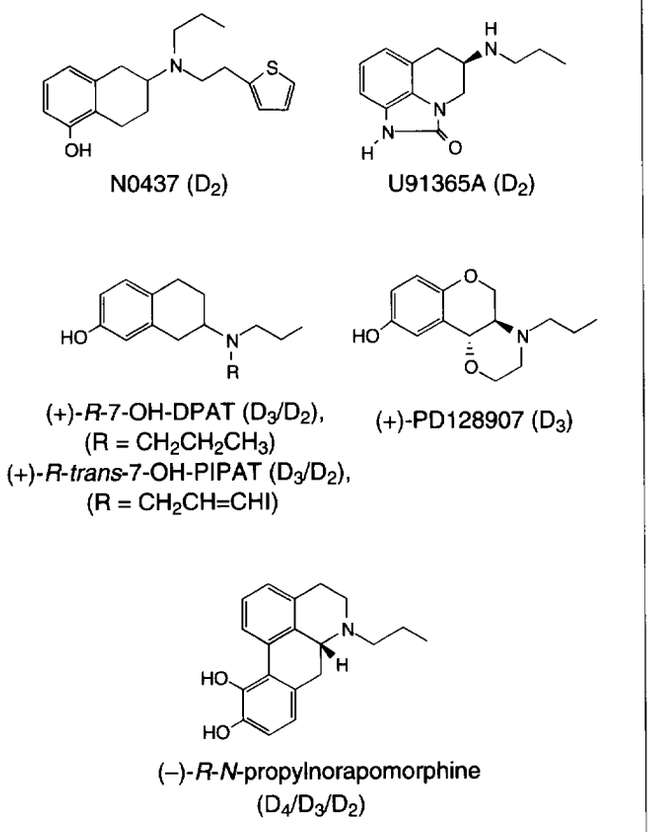

Figure 3. *Agonists with selectivity for D_2-like receptors.*

droperidol, spiperone) are relatively selective, and various substituted (–)-*S*-enzamides (e.g. eticlopride, nemonapride, raclopride, remoxipride) are highly selective for D_2-like receptors[68–71]. Several of these compounds are available in radiolabeled form to label D_2-like receptors in brain tissue or in membranes of transfected cells, or are being applied as radiopharmaceuticals for PET (positron emission tomography) or SPECT (single-photon emission computed tomography) brain imaging for diagnostic purposes and for clinical neuropharmacology. Others are under development as antipsychotic agents, sometimes with surprisingly limited extrapyramidal side effects[5,22,43].

Agents with selectivity for the abundant D_2 (particularly D_{2L}) receptors over D_3 and D_4 sites have been surprisingly difficult to find[22]. Recently discovered lead compounds include the D_2 agonists U91356A and U95666, which have up to several 100-fold selectivity for D_{2L} over D_3 or D_4 receptors in transfected cells, and a partially selective D_2 antagonist L741626 (Refs 64,72–74).

Both agonists and antagonists with at least partial selectivity for D_3 sites over D_2 and D_4 receptors have been reported and partially characterized. The D_2-like agonist quinpirole has some D_3 selectivity, as does the (+)-*R*-7-hydroxy-*N*,*N*-dipropylaminotetralin (7-OH-DPAT) and its *N*-propyl-*N*-iodopropenyl congener *trans*-7-OH-PIPAT, both of which are available in radiolabeled form[75–77]. Selectivity of these agonist or partial agonist compounds for relatively GTP-insensitive D_3 sites can be enhanced by forcing D_2

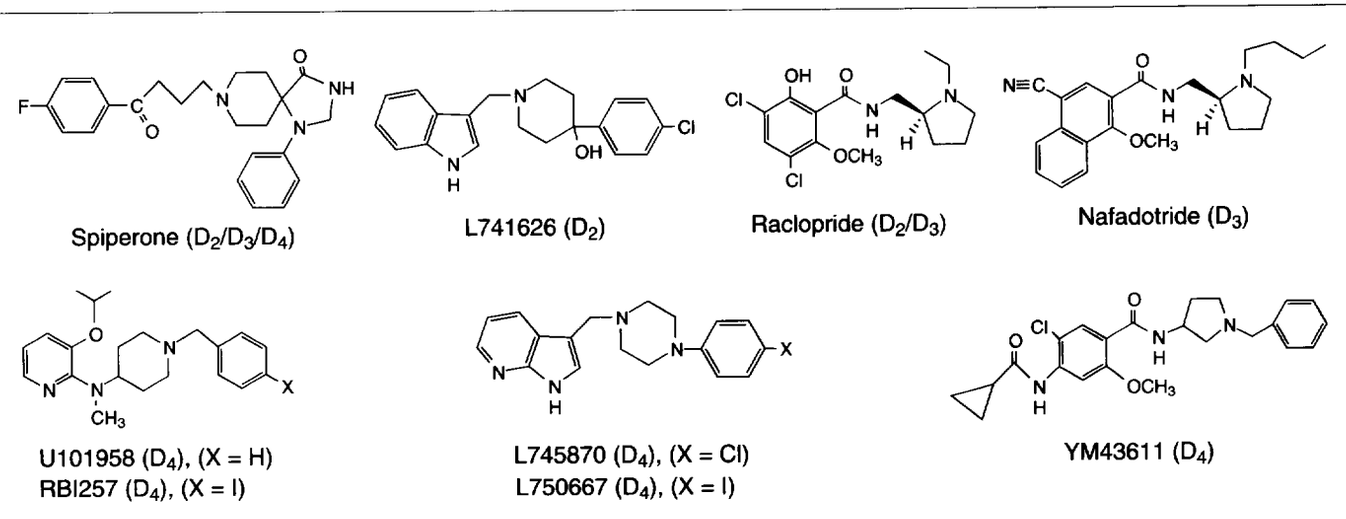

Figure 4. *Antagonists with selectivity for D_2-like receptors.*

Table 1. Affinity (K_i, nM) of selected compounds at dopamine receptors[a]

	D_1	D_2	D_3	D_4	D_5	Refs
Agonists						
Nonselective						
Dopamine	**0.80**	**7.5**	**3.9**	28	ND[b]	82
Low affinity state	2,000	4,300	**3.9**	28	228	82
(–)-*R*-Apomorphine	**0.70**	**0.66**	ND	4.1	ND	82
Low affinity state	450	127	73	ND	363	82
(–)-*R*-NPA[b]	340[c]	**0.80**	**0.30**	**0.12**	ND	d
D_1-like receptors						
(+)-*R*-SKF38393	**3.0**	157	ND	ND	ND	82
Low affinity state	200	9,500	5,000	1,800	100	82
Dihydrexidine	**≈10**	≈660	170	ND	ND	56,57
A68930	**3.0**[c]	776[c]	ND	ND	ND	50
A86929	51	750	1,000	350	**15**	53
D_2-like receptors						
N0437	2,170	**0.70**	ND	122	986	29,32
U91356A	≥5,000	**1.6**	36	195	ND	74
(–)-Quinpirole	1,900	**3.3**	**4.0**	18	ND	74,82
Low affinity state	>10,000	576	**5.1**	46	>10,000	31,82
(+)-*R*-7-OH-DPAT	5,300	61	**0.78**	610	ND	75
(+)-PD128907	>10,000	620	**1.0**	720	ND	80
Antagonists						
D_1-like receptors						
(+)-*R*-SCH23390	**0.30**	1,430	780	3,560	**0.35**	75,82
(+)-*R*-SCH39166	**5.0**	3,750	1,000	5,900	**4.4**	59
D_2-like receptors						
(–)-*S*-Eticlopride	>10,000	**0.02**	**0.03**	ND	>10,000	35
Spiperone	220	**0.08**	**0.60**	**0.08**	4,500	82
(–)-*S*-Nemonapride	1,900	**0.09**	**0.30**	**0.15**	ND	83
Haloperidol	60	**1.3**	**9.8**	**5.1**	48	82
(–)-*S*-Raclopride	>10,000	**2.9**	**3.5**	2,000	ND	82
L741626	ND	**7.0**	110	485	ND	65,72
(–)-*S*-Nafadotride	890	3.0	**0.31**	1,780	ND	81
RBI257	2,800	568	145	**0.30**	>10,000	93
L745870	ND	>1,700	>4,500	**0.43**	ND	72
L750667	≥4,500	>1,700	>4,500	**0.51**	≥4,500	72,89
YM43611	>10,000	220	21	**2.1**	>10,000	88
U101958	>10,000	2,000	552	**2.7**	>10,000	93
CP293019	>1,000	>3,300	>2,000	**3.4**	ND	95
U101387	8,300	5,100	2,700	**3.6**	270	87
Clozapine	141	262	180	**44**	250	31,35,84
(+)-*S*-NPA[b]	3,720[c]	774	150	**56**	ND	84,d

[a]Sites of highest affinity are indicated in boldface; K_i values are representative, not definitive.

[b]ND, not determined. NPA, *N*-n-propylnorapomorphine.

[c]D_1- and D_2-like affinity in rat striatal homogenate.

[d]Kula, N.S. *et al.* (1997) unpublished. Note that selective D_4 and D_5 agonists are needed, as are D_3 and D_5 antagonists, and more selective D_2 antagonists.

receptors into their low-affinity state for DA agonists by including Na^+ and GTP and excluding Mg^{2+} in assays, but substantial D_3 selectivity of these aminotetralins without such special assay conditions, or *in vivo*, is unlikely[78,79]. (+)-*S*-PD128907 is a chemically unique agonist with at least 20-fold selectivity for D_3 sites *in vitro* but somewhat uncertain selectivity *in vivo*[80]. Among D_2-like antagonists, the novel compound nafadotride shows moderate (10-fold over D_2) D_3 selectivity[81].

The search for agents selective for D_4 receptors is particularly intensive and increasingly successful for antagonists, although no D_4-selective agonist has been reported. Interest in novel, selective D_4 antagonists was greatly stimulated by the discovery that clozapine, the prototype atypical (low risk of adverse extrapyramidal effects) and clinically superior antipsychotic agent, shows some selectivity for D_4 (over D_2 and D_3) receptors[82–84]. The presence of D_4 receptors has usually been inferred indirectly by complex binding assays involving subtraction of number of binding sites defined with [^{3}H]raclopride (D_2/D_3 antagonist) from the total binding defined with tritiated nemonapride or spiperone[83], or by combining a nonselective D_2-like radioligand with masking concentrations of unlabeled raclopride to occlude D_2/D_3 receptors selectively[84]. Several recently developed antagonists show even greater D_4 selectivity over other DARs, and their affinity appears to be enhanced by halogenation. They include several chemically novel compounds, U101958, its *p*-iodinated (and radioiodinated) derivative RBI257, L745870 and its iodinated (and radioiodinated) congener L750667, the benzamide YM34611, as well as the novel compound NGD941 (including a tritiated derivative)[85–93]. Given intense current pharmaceutical interest in such compounds, some of these or others are likely to be tested clinically. Reported structures of selected agents with selectivity for D_2-like receptors (Figures 3 and 4) and a summary of the DAR affinities of representative compounds are provided (Table 1).

Conclusions and predictions

In the past four decades, understanding of the nature and properties of the DARs has advanced greatly, with particularly dramatic recent progress in identifying novel, but much less abundant, DAR subtypes as well-defined gene products. Knowledge of the structures and partial localization of common D_1 and D_2 receptors and their less prevalent homologs in mammalian brain has encouraged recent redoubling of efforts to discover novel and increasingly selective agonists and antagonists for them to modify dopaminergic neurotransmission. The selective expression of cloned DAR receptors in membranes of cultured cells is of great value in screening for novel lead structures. However, much more information is needed to clarify the cellular and behavioral neurophysiology of both the older and more recently discovered DAR subtypes to provide a rational basis for pharmaceutical development. Such knowledge is needed to predict potential clinical indications for such agents. Current development of dopaminergic agents as potential drugs remains largely empirical, with remarkably heavy reliance on early clinical trials to reveal what remains unknown, and so far largely unpredictable.

The relatively high prevalence and chronic nature of most of the disorders in whose pathophysiology DA has been implicated makes DARs very attractive targets for drug discovery. Moreover, the current state of therapeutics for such disorders as parkinsonism, schizophrenia and mania is imperfect, offering partial palliation, often with a heavy side-effect burden[4,5]. Although D_1, D_5, D_3 or D_4 antagonists are of interest as leads to novel antipsychotic agents, limited work with D_1-like compounds is not encouraging, and clinical studies with D_3 or D_4 compounds are currently in progress. In addition, the potential for applying DAR-targeted compounds to other very common clinical problems, including major and bipolar depression, anxiety disorders, and stimulant abuse, for example, is hardly being pursued currently. There are additional opportunities for drug discovery among radiopharmaceuticals targeted on DARs. Such agents have growing importance in clinical neuroradiology and are contributing to seminal ad-vances in neuropsychiatric diagnostics and clinical neuropharmacology[5]. Specific types of DAR compounds still needed include selective D_4 and D_5 agonists, D_3 and D_5 antagonists, and more potent D_2 antagonists. In addition to pure agonists and antagonists, there may be important therapeutic advantages to DAR-targeted compounds with partial agonist or mixed agonist–antagonist properties that minimize some side effects and long-term adaptations such as DAR supersensitivity[5,22,94]. Major efforts in drug discovery in the pharmaceutical industry certainly will continue to include the search for novel and improved compounds selective for specific DAR subtypes – hopefully, guided by a still slowly evolving understanding of the molecular, cellular and behavioral physiology and neuropharmacology of this important class of CNS receptors.

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