Dopamine Receptors

TOCRIS bioscience

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Professor Philip Strange has worked on the structure and function of G protein-coupled receptors for many years. A major focus of his work has been the receptors for the neurotransmitter dopamine, with particular emphasis on their role as targets for drugs and understanding the mechanisms of agonism and inverse agonism at these receptors.

Professor Kim Neve has studied dopamine receptors for most of his scientific career, with an emphasis on relating structural features of the receptors to specific functions and assessing how receptor responsiveness is altered by denervation or prolonged treatment with agonists.

Contents

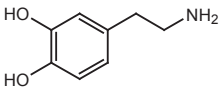
History

It was not until the late 1950s that dopamine was recognized as a neurotransmitter in its own right, but the demonstration of its non-uniform distribution in the brain, distinct from the distribution of noradrenaline, suggested a specific functional role for dopamine.[1] Interest in dopamine was intensified by the realization that dopamine had an important role in the pathogenesis or drug treatment of certain neurological disorders, e.g. Parkinson's disease and schizophrenia.[2,3] This led to much research on the sites of action of dopamine and the dopamine receptors (Box 1). One milestone was the suggestion by Cools and van Rossum, based on anatomical, electrophysiological and pharmacological studies, that there might be more than one kind of receptor for dopamine in the brain.[4] Biochemical studies on dopamine receptors in the 1970s based on second messenger assays (e.g. stimulation of cAMP production and ligand binding assays) supported the idea, and it was given a firm foundation by Kebabian and Calne in their 1979 review.[5] They extended an earlier suggestion by Spano *et al*,[6] and proposed that there were two classes of dopamine receptor, D_1 and D_2, with different biochemical and pharmacological properties, mediating different physiological functions. The properties of these two subtypes are summarized in Table 1. Selective agonists and antagonists exist to define the two subtypes in functional assays and some of these are shown in Table 1. Both the D_1 and D_2 subtypes are G protein-coupled receptors (GPCRs), yet different G proteins and effectors are involved in their signaling pathways (Figure 1, Table 1).

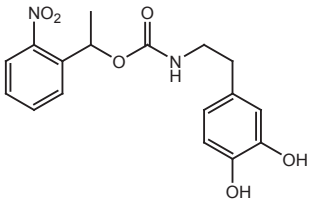
Although there were some indications of further heterogeneity of these dopamine receptor subtypes in biochemical studies, it was not until the late 1980s that the true extent of this was revealed with the application of gene cloning techniques. These studies have shown that there are at least five dopamine receptors (D_1-D_5) that may be divided into two subfamilies whose properties resemble the original D_1 and D_2 receptors.[7,8] The D_1-like receptor family, which comprises D_1 and D_5, corresponds to the original D_1 receptors whilst the D_2-like receptor family (D_2, D_3 and D_4 receptors) corresponds to the original D_2 receptors. A selection of the key properties of the receptor subtypes are summarized in Tables 2 and 3.

In subsequent discussion we refer to receptor subtypes defined from cloned genes as D_1, D_2, D_3, D_4, D_5, and where only the subfamily of receptor has been defined pharmacologically we use the D_1-like and D_2-like nomenclature.

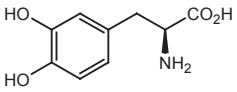
Box 1 | Dopamine synthesis and metabolism



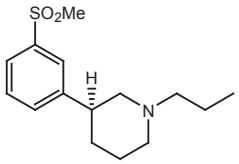
Dopamine (3548)
Endogenous dopamine receptor agonist



NPEC-caged-dopamine (3992)
Caged version of dopamine



L-DOPA (3788)
Dopamine precursor



OSU 6162 (2599)
Dopamine stabilizer

Properties of the Dopamine Receptor Subtypes

Common receptor properties

Analysis of the amino acid sequences of the dopamine receptor subtypes has shown that significant homologies exist among the subtypes, with the greatest being found between members of either subfamily.[7,8] Each receptor has been shown to contain seven stretches of amino acids that are hydrophobic and long enough to span the membrane. It seems therefore that each of the dopamine receptors conforms to the general structural model for a GPCR,[9-11] with an extracellular amino terminus and seven putative membrane spanning α-helices linked by intracellular and extracellular protein loops (Figure 2). One or more potential sites for glycosylation are found on the amino terminus and second extracellular loop. The helices are bundled together in the membrane to form the ligand binding site (Figure 2); some information is available on the residues that make contact with ligands.[11,12] There is an intracellular carboxyl terminus, probably bearing a palmitoyl group, which may form a further link to the membrane. The D_1-like receptors have short third intracellular loops and long carboxyl terminal tails, whereas the D_2-like receptors have long third intracellular loops and short carboxyl terminal tails. This provides a structural basis for the division of the receptors into two subfamilies but is also likely to have a functional significance, possibly related to the specificity of receptor/G protein interaction.

The third intracellular loop, termed 'I3', is important for the interaction of the receptor and G protein. For the D_2-like receptors, variants of the subtypes exist based on this loop. For example, there are short and long splice variants of the D_2 and D_3 receptors with the long forms having an insertion (29 amino acids for the long D_2, D_{2L}) in this loop.[13,14] Polymorphic variants of the D_2 receptor have been described with single amino acid changes in I3.[15] The D_4 receptor is highly polymorphic in the human population with variants containing different length insertions in I3.[16,17] In some cases, these D_2-like receptor variants may have differential abilities to couple to or activate G proteins,[18,19] and may also exhibit slightly different pharmacological properties.[16,20,21] Lines of mice have been developed in which the I3 insertion that produces the long D_2 receptor variant (D_{2L}) is deleted, resulting in the expression of only the short variant (D_{2S}). Characterization of these mice suggests that the splice variants are not fully interchangeable; some D_2 receptor responses are not observed in mice that express only D_{2S}.[22-24] The variants of the D_4 receptor have not been found to exhibit any substantive differences in agonist signaling or in coupling to G proteins.[25]

The individual properties of the different subtypes were initially probed by expressing the receptors in recombinant cells and examining the localization of the subtypes at the mRNA and protein level. More recently, the use of subtype-selective drugs and transgenic mice with one or more receptor subtypes genetically deleted has enabled further study of these receptors.

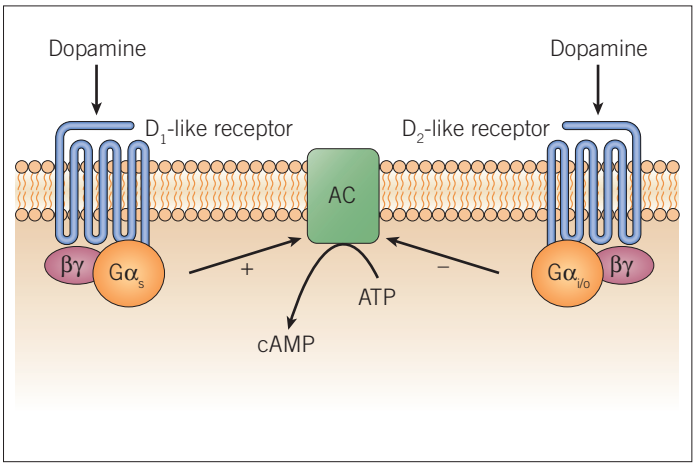
Individual receptor properties

The dopamine receptor subtypes exhibit different properties in terms of their pharmacological profile, localization, and mechanism of action; these differences will be briefly summarized below.

D_1-like receptors

Both the D_1 and D_5 receptors show pharmacological properties similar to those of the original pharmacologically defined D_1 receptor, that is, a high affinity for the benzazepine ligands SCH 23390, SCH 39166, and SKF 83566, which are selective antagonists for these subtypes. Although not as selective for D_1 over D_2 as the benzazepine antagonists, LE 300 is a potent D_1-like antagonist that is useful because it is structurally distinct from the benzazepines. Thioxanthines such as flupentixol and

Figure 1 | Regulation of adenylyl cyclase by D_1 and D_2 dopamine receptors



The diagram shows the effects of dopamine to stimulate or inhibit adenylyl cyclase (AC) via the D_1-like receptor and G protein $G\alpha_s$ or the D_2-like receptor and G protein $G\alpha_{i/o}$, respectively.

Table 1 | Dopamine receptor subtypes defined from physiological, pharmacological, and biochemical studies

	D_1-like Receptors	D_2-like Receptors
Physiological Functions	Aspects of motor and cognitive function (brain), cardiovascular function	Aspects of motor function and behavior (brain), control of prolactin and α-MSH secretion from pituitary, cardiovascular function
Biochemical Responses	Adenylyl cyclase↑ Phospholipase C↑	Adenylyl cyclase↓ K^+ channel activity↑ Ca^{2+} channel activity↓ GSK-3β↑
Localization	Caudate nucleus, putamen, nucleus accumbens, olfactory tubercle, cerebral cortex, cardiovascular system	Caudate nucleus, putamen, nucleus accumbens, olfactory tubercle, cerebral cortex, anterior and neurointermediate lobes of pituitary gland, cardiovascular system
Receptor Antagonists	**SCH 23390** **SCH 39166** **SKF 83566** **LE 300**	**Domperidone** **Nemonapride** **Raclopride** **(*S*)-(-)-Sulpiride**
Receptor Agonists	**A 77636** SKF 38393 SKF 81297 **A 68930** **SKF 81297** Doxanthrine	PHNO **Quinpirole** N-0437 **Rotigotine** **Sumanirole**
Radioligands	[^{3}H]-SCH 23390* [^{125}I]-SCH 23982	[^{3}H]-Nemonapride (YM-09151-2) [^{3}H]-Raclopride [^{3}H]-Spiperone**

(Bold text denotes compounds available from Tocris at time of publication)

The localization data are from functional and ligand-binding studies on dispersed tissues and tissue slices. *[^{3}H]-SCH 23390 can also bind to 5-HT_2 receptors if present; **[^{3}H]-Spiperone can also bind to 5-HT_{1A}, 5-HT_2 receptors, and α_1-adrenoceptors if present.

phenothiazines such as fluphenazine also show high affinity but are not selective for D_1-like over D_2-like receptors. The development of the first D_1-like receptor agonist, SKF 38393, was important for differentiating between activation of D_1-like and D_2-like receptors, although it was later realized that the partial agonist nature of SKF 38393 produced an under-appreciation of the contribution of D_1-like receptors to behavior.[26] The D_1-like receptors show moderate affinities for typical dopamine agonists such as apomorphine; full and/or selective D_1-like receptor agonists such as such as A 77636, A 68930, SKF 81297, dihydrexidine, and doxanthrine are now available (Box 2). There are minor differences in the affinities of some compounds for the D_1 and D_5 receptors (higher agonist and lower antagonist affinities for D_5), but no compounds that effectively distinguish between those subtypes are as yet available.[27,28]

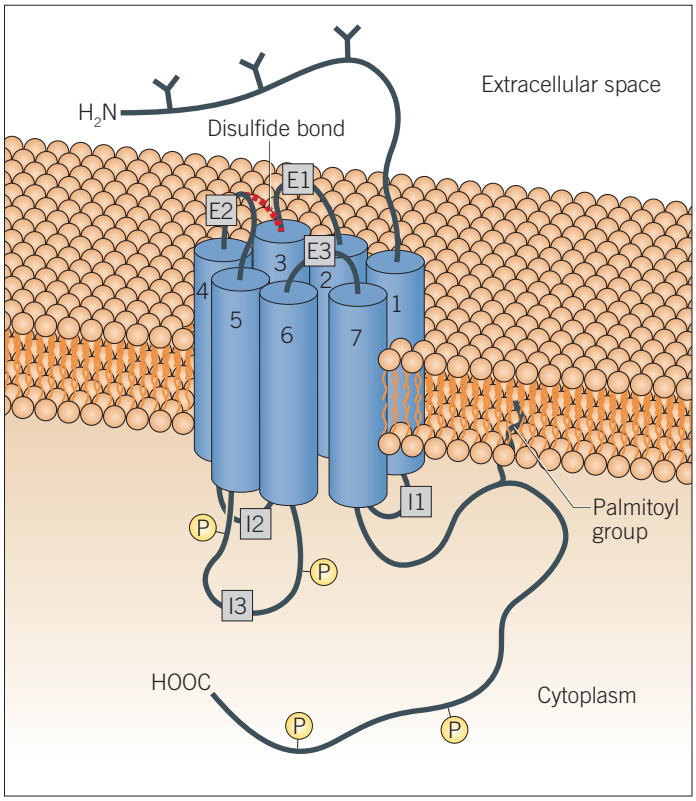
D_1 receptors are found at high levels in the typical dopamine-rich regions of brain such as the neostriatum, substantia nigra, nucleus accumbens, and olfactory tubercle, whereas the distribution of the D_5 receptors is much more restricted (Table 2); this subtype is found generally at much lower levels. Both receptors are able to stimulate adenylyl cyclase (Figure 1), with the D_5 receptor showing some constitutive activity for this response.[28] Inverse agonist activity at the D_1 and D_5 receptors is seen in recombinant systems for some compounds such as butaclamol,[28] which were previously considered to be antagonists. It has been known for some time that stimulation of a D_1-like receptor leads to activation of phospholipase C[29] and recently this response has been linked to the D_1/D_2 receptor heterodimer, providing a function for heterodimer formation.[30] Agonists that preferentially stimulate the cAMP response (SKF 83822) or the phospholipase C response (SKF 83959) associated with D_1-like receptors have been described.[31]

The D_1 receptor seems to mediate important actions of dopamine to control movement, cognitive function, and cardiovascular function. Direct interactions between D_1-like receptors and ion channel-linked receptors have been described (D_1/NMDA, D_5/$GABA_A$),[32] leading to modulation of receptor function. These interactions provide for cross talk between fast and slow neurotransmitter systems and may point towards a further functional role for the D_5 receptor, which is not well understood. Studies with null mutant 'knock-out' mice have suggested that in some respects, the functions of the D_1 and D_5 receptors are reciprocal – for example, with respect to spontaneous locomotion – and in other respects similar, for example with respect to grooming or psychostimulant-induced locomotion.[33,34]

D_2-like receptors

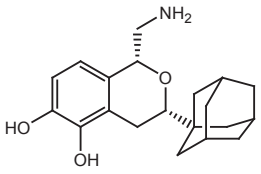
Overall, the D_2, D_3 and D_4 receptors exhibit pharmacological properties similar to those of the originally defined D_2 receptor; that is, they all show high affinities for drugs such as the butyrophenones (haloperidol, spiperone) and substituted benzamides (sulpiride, raclopride), and these classes of drugs provide selective antagonists for D_2-like receptors over D_1-like receptors (Table 3). As indicated above, the D_2-like receptors also show high affinities for phenothiazines and thioxanthines. Each D_2-like receptor has its own pharmacological signature, so there are some differences in affinities of drugs for the individual D_2-like receptors (Box 3). For example, sulpiride and raclopride show high affinity for the D_2 and D_3 receptors but

Figure 2 | Schematic representation of a G protein-coupled dopamine receptor

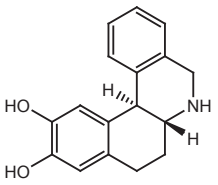


The diagram shows the seven helices bundled together in the membrane and the intra- (I1, I2, I3) and extracellular (E1, E2, E3) loops. The ligand binding site is contained in the cavity formed between the helices. There may be an eighth helix formed in the carboxyl terminus parallel to the membrane (not shown). There is also a disulfide bond between E2 and the top of helix 3. The helices have been drawn parallel to one another for clarity but in fact there are kinks in the helices and they are not fully parallel. I3 and the carboxyl terminus contain multiple sites for phosphorylation that are involved in regulation of receptor responsiveness and interactions with adapter proteins.

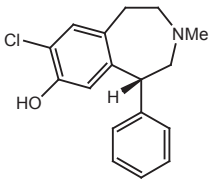
Box 2 | D_1/D_5 receptors



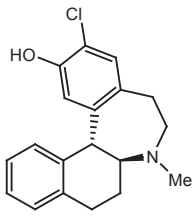
A 77636 (1701)
Potent, selective D_1-like agonist; orally active



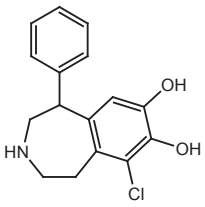
Dihydrexidine (0884)
Full D_1-like agonist



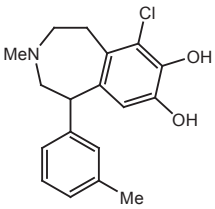
SCH 23390 (0925)
Standard selective D_1-like antagonist. Also 5-HT_{2C} agonist



SCH 39166 (2299)
High affinity D_1/D_5 receptor antagonist



SKF 81297 (1447)
D_1-like agonist



SKF 83959 (2074)
D_1-like partial agonist

a lower affinity for the D_4 receptor (Box 4). Clozapine displays moderate selectivity for the D_4 receptor. Most D_2 antagonists show a higher affinity for the D_2 receptor compared with the D_3 and D_4 receptors; this is because the D_2 receptor, being overall much more abundant in brain than the other D_2-like receptors, corresponds to the pharmacologically defined D_2-like receptor for which these drugs were developed. The molecular cloning of additional D_2-like receptors enabled the development of more selective antagonists that are invaluable in determining the functions of these subtypes. For example, L-741,626, NGB 2904, and L-745,870 are D_2 selective (~40-fold), D_3 selective (~200-fold) and D_4 selective (~2000-fold) antagonists respectively.[35,36]

Selective agonists for the D_2-like receptors relative to the D_1-like receptors, e.g. N-0437, PHNO, and quinpirole, have been developed. Sumanirole is a full-efficacy agonist that is highly selective for the D_2 receptor over other dopamine receptors.[37] There are a number of D_4 agonists of varying efficacy and selectivity, with A 412997 being an example of a highly selective full D_4 agonist (Box 5).[38] Many agonists appear to be highly selective for the D_3 receptor over other D_2-like receptors in radioligand binding assays, but this frequently reflects an invalid comparison between a mixed population of agonist high- and low-affinity D_2 receptors, and the D_3 receptor that is apparently constrained in an agonist-high affinity conformation,[39] rather than a difference in drug concentrations capable of activating the two subtypes.[40] When care is taken to compare functional responses or binding to the agonist high-affinity state of the receptors, dopamine and some agonists such as pramipexole are determined to be modestly D_3 selective.[41]

The D_2 receptor is the predominant D_2-like subtype in the brain, located at high levels in typical dopamine rich brain areas. D_3 and D_4 receptors are found at much lower levels and in a more restricted distribution pattern, located predominantly in limbic areas of the brain (Table 2). Some D_3 receptors are also found in regions associated with motor function such as the putamen. The D_2-like receptor subtypes have each been shown to inhibit adenylyl cyclase (Figure 1) when expressed in recombinant cells,[40,42,43] although the signal via the D_3 receptor has proven more difficult to demonstrate and is generally lower than for the other two subtypes. This may relate to preferential coupling of the D_3 receptor to specific adenylyl cyclase isoforms.[44]

Table 2 | Dopamine receptor subtypes identified by molecular biological studies

	D_1-like		D_2-like		
	D_1	D_5	$D_{2S/L}$	D_3	D_4
Amino Acids	446 (human, rat)	477 (human) 475 (rat)	414/443 (human) 415/444 (rat)	400 (human) 446 (rat)	387 (human*, rat)
Homology					
with D_1	100%	82%	44%	44%	42%
with D_2 (short)	44%	49%	100%	76%	54%
Localization	Caudate/putamen, nucleus accumbens, olfactory tubercle, hypothalamus, thalamus, frontal cortex	Hippocampus, thalamus, lateral mamillary nucleus, striatum, cerebral cortex (all low)	Caudate/putamen, nucleus accumbens, olfactory tubercle, cerebral cortex (low)	Nucleus accumbens, olfactory tubercle, islands of Calleja, putamen (low), cerebral cortex (low)	Frontal cortex, midbrain, amygdala, hippocampus, hypothalamus, medulla (all low), retina
Response	Adenylyl cyclase↑	Adenylyl cyclase↑	Adenylyl cyclase↓	Adenylyl cyclase↓	Adenylyl cyclase↓
Introns in Gene	None	None	Yes	Yes	Yes
Organization of Amino Acid Sequence					
Third intracellular loop	Short	Short	Long	Long	Long
Carboxyl terminal tail	Long	Long	Short	Short	Short
Reference	65	27	66	67	68

The properties of the principal dopamine receptor subtypes identified by gene cloning are shown. They are divided into 'D_1-like' and 'D_2-like' groups to reflect amino acid homology, functional similarity, structural similarity, and pharmacological properties. This grouping conforms with a previous classification based on pharmacological and biochemical properties (Table 1). D_{2S} and D_{2L} refer to different alternatively spliced forms of the D_2 receptor gene. The homology values are for the transmembrane-spanning regions.[69] The localizations and relative expression levels shown are the principal ones known at present from *in-situ* hybridization and use of the polymerase chain reaction. Some pharmacological data for the different receptor subtypes is given in Table 3. *The human D_4 receptor has many longer allelic variants. For further information on the properties of the dopamine receptor subtypes, please consult reference 8.

The D_2-like receptors will, upon activation, stimulate a range of processes including acute signaling events (inhibition of adenylyl cyclase, stimulation of K^+ channels, inhibition of Ca^{2+} channels, stimulation of arachidonic acid release) and longer term events (MAP kinase and β-arrestin-2/Akt/GSK-3 signaling, and mitogenesis).[45,46] D_3 receptor-mediated signaling events are often of lower magnitude than for the other D_2-like receptors. The relation of these signaling events to *in vivo* responses is only beginning to be clarified. Many compounds that were thought to be antagonists at D_2-like receptors – such as the antipsychotic drugs haloperidol, chlorpromazine, and clozapine – have been shown to possess inverse agonist activity at D_2 and D_3 receptors.[47-49] This inverse agonism may contribute to the increases in D_2 receptor number seen in the brain when experimental animals are treated chronically with these drugs.

The D_2 receptor is important for mediating the effects of dopamine to control movement, certain aspects of behavior in the brain and prolactin secretion from the anterior pituitary

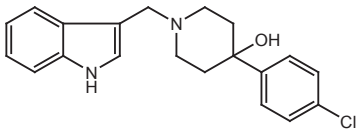
Table 3 | Pharmacological properties of the dopamine receptor subtypes

Drug	Receptor Affinity, K_i (nM)				
	D_1	D_5	D_2	D_3	D_4
Chlorpromazine	73	133	0.55	1.2	9.7
Clozapine	141	250	35	83	22
Dopamine†	2340	228	1705	27	450
Haloperidol	27	48	0.53	2.7	2.3
Raclopride	>72000	–	1	1.8	2400
SCH 23390	0.35	0.3	267	314	3560
SCH 39166	1.2	2	980	–	5520
SKF 83566	0.3	0.4	2000	–	–
(*S*)-(-)-Sulpiride	36000	77000	2.5	8	1000

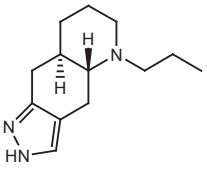
Values for the dissociation constants are given for ligands, determined using ligand binding assays for the five dopamine receptor subtypes. As far as possible, values are given that avoid artefacts present in ligand binding assays with high affinity radioligands.[3] †Data for dopamine were obtained in the presence of Gpp(NH)p and therefore represent the agonist low-affinity state. Data taken from references 3, 8, 21, 27 and 70.

Box 3 | D_2 receptors

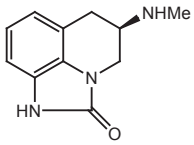
L-741,626 (1003)
High affinity D_2 antagonist



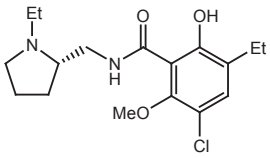
(-)-Quinpirole (1061)
Selective D_{2-4} agonist



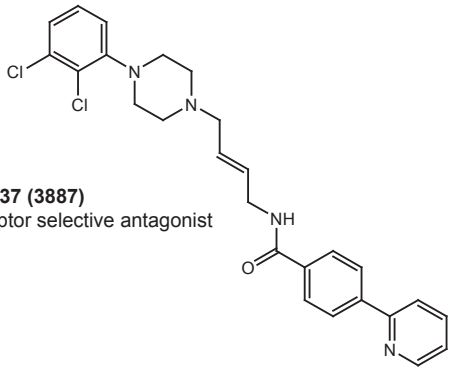
Sumanirole (2773)
D_2-selective agonist



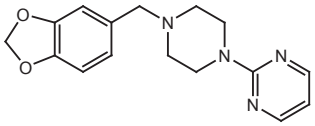
Box 4 | D_3 receptors



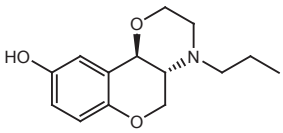
Eticlopride (1847)
Selective D_2/D_3 antagonist ($D_3 > D_2$)



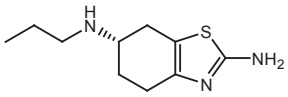
PG 01037 (3887)
D_3 receptor selective antagonist



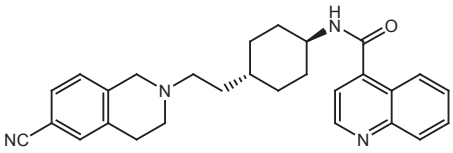
Piribedil (1031)
D_2/D_3 receptor agonist ($D_3 > D_2$)



(+)-PD 128907 (1243)
D_3 agonist ($D_3 \geq D_2 > D_4$)

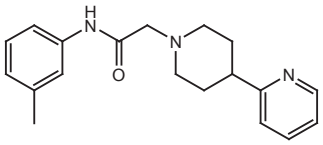


Pramipexole (4174)
Selective D_3 agonist

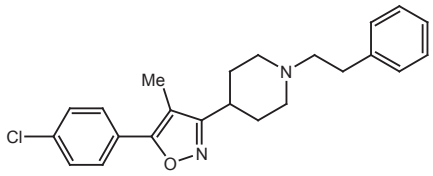


SB 277011A (4207)
Selective D_3 antagonist

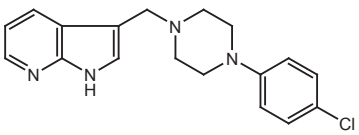
Box 5 | D_4 receptors



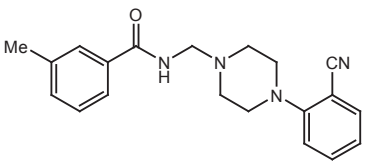
A 412997 (4552)
Selective D_4 agonist



L-741,742 (1004)
Highly selective D_4 antagonist



L-745,870 (1002)
Highly selective D_4 antagonist



PD 168077 (1065)
High affinity, selective D_4 agonist

gland. The functions of the D_3 and D_4 receptors are currently unknown, although their localizations in limbic areas of brain suggest roles in cognitive, emotional, and behavioral function. These properties have made them attractive targets for the design of potential selective antipsychotic drugs. The D_2-like receptors show high affinities for most of the drugs used to treat schizophrenia (antipsychotics) and Parkinson's disease (e.g. bromocriptine).[3] L-745,870 was the first highly selective D_4 antagonist synthesized, but it proved to be inactive against the psychosis of schizophrenia.[50]

Future Directions

Understanding the role of the dopamine receptor subtypes

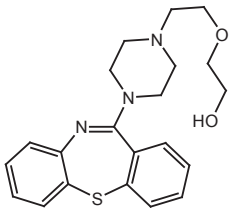
We are still a long way away from understanding the role of the different receptor subtypes. Although partially selective antagonists and transgenic 'receptor knock out' animals are available for some of the subtypes, much is still to be done here (see for example Waddington *et al* (2005)[31]).

Dopamine receptor subtypes in drug discovery

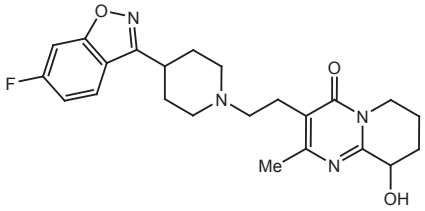
Due to the importance of dopamine for the pathogenesis or drug treatment of several important disorders e.g. Parkinson's disease, schizophrenia and pituitary prolactin dysfunction, dopamine receptors have been very popular as targets for drug discovery campaigns (Box 6). This continues to be the case and indications have expanded into areas such as drug dependence and penile erectile dysfunction. A new development in the search for effective antipsychotics has been the development of dopamine D_2-like partial agonists such as aripiprazole.[51] It had been thought that antipsychotics had to be antagonists/inverse agonists at the D_2 receptor,[3] yet the effective use of D_2 partial agonists as antipsychotics raises questions about the mechanism of D_2 receptor-mediated antipsychotic activity that need

Box 6 | Atypical antipsychotics

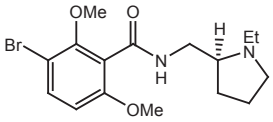
Quetiapine (4735)
5-HT$_2$/D$_2$ antagonist;
atypical antipsychotic



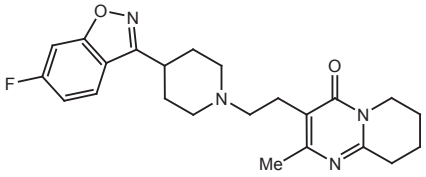
Paliperidone (4493)
5-HT$_{2A}$ and D$_2$ antagonist;
atypical antipsychotic



Remoxipride (0916)
Selective D$_2$ antagonist;
atypical antipsychotic



Risperidone (2865)
5-HT$_{2A}$/D$_2$ antagonist;
atypical antipsychotic



to be addressed.[52] It will be important, for example, to understand the relationship between the efficacy of the ligands in signaling assays and their therapeutic effects.

An important new tool for the rational design of subtype-selective drugs is the availability of crystal structures for the D$_3$ receptor and the β_2-adrenoceptor.[10,11] These structures and the precise models that can be constructed on the basis of their close homology with other D$_2$-like receptors and the D$_1$-like receptor, respectively, make it possible to predict the affinity of a receptor for molecules that may be novel scaffolds.[53,54]

Biochemical mechanisms underlying the effects of dopamine receptor activation

It will be very important to define clearly how activation of dopamine receptors leads to changes in the function of cells such as neurons. In time, this will lead to a better understanding of how drugs act on the brain. Important progress has been made in this area. For example, in striatal neurons it has been shown that a protein strongly regulated by dopamine receptors is DARPP-32 (dopamine and cAMP-regulated phosphoprotein 32 kD). DARPP-32 seems to be a key protein in striatal neuronal function.[55] Important progress has also been made in understanding temporal aspects of signaling processes in the brain. It has been suggested that there may be two waves of dopamine-mediated responses: one set of faster responses associated with changes in cAMP and DARPP-32 phosphorylation, and another slower set of non-cAMP mediated processes associated with β-arrestin-2/Akt/GSK-3 signaling.[46]

Interactions of dopamine receptors with other proteins

It is becoming clear that interactions of the dopamine receptors with other proteins are very important in determining their function; this will be an active field of research in the future. As a group, the cytoskeletal, adapter, and signaling proteins that interact with dopamine receptors have been termed DRIPs (dopamine receptor-interacting proteins).[56] An example includes the neuronal Ca^{2+} sensor-I (NCS-1) which interacts with D$_2$.[57] In this case, the interacting proteins may mediate the effects of Ca^{2+} on the D$_2$ receptor. Interactions also occur with other receptors including ligand-gated ion channels, and GPCRs leading to homo- and heterodimer formation. A role for D$_1$/D$_2$ heterodimer formation has been suggested,[58] and roles for homodimer formation, e.g. D$_2$ homodimers,[59,60] are being actively pursued.

Development and characterization of biased ligands

A promising new avenue for drug development is based on the observation that many ligands do not engage, to the same extent, all of the mechanisms that are consequences of activation of a receptor; activation of a receptor by its endogenous agonist may activate G protein- and β-arrestin-mediated signaling, phosphorylation of the receptor by one or more protein kinases, desensitization, and receptor internalization followed by either recycling or degradation of the receptor. A given ligand may be fully efficacious (i.e., a full agonist) for some of these responses, and a partial agonist or an antagonist at other responses mediated by the same receptor.[61,62] This phenomenon is referred to as functional selectivity, and a ligand that engages only some of the repertoire of responses available to a receptor is a functionally selective (or 'biased') ligand.

The D$_1$ receptor is a promising target for treatment of Parkinson's disease, with two impediments to the use of D$_1$ agonists being rapid development of tolerance and the side effects of hypotension and seizures.[63] Both of these impediments could potentially be addressed through the development of biased agonists. For example, SKF 83822 is a functionally selective ligand biased towards D$_1$-mediated signaling via adenylyl cyclase that also induces seizures at high doses,[64] while SKF 83959 preferentially activates the D$_1$/D$_2$ receptor heteromer and the associated phospholipase C response.[30] Ligands biased towards either G protein- or β-arrestin-mediated signaling pathways modulated by the D$_2$ receptor are also of considerable interest as pharmacological tools and as potential antipsychotic drugs that may be more efficacious or have fewer side effects.

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Dopamine Compounds Available from Tocris

Cat. No.	Product Name	Primary Action
D_1 and D_5 Receptors		
1534	A 68930	Potent, selective D_1-like agonist
1701	A 77636	Potent, selective D_1-like agonist; orally active
1249	CY 208-243	Selective D_1-like agonist
0884	Dihydrexidine	Selective D_1-like agonist
1659	Fenoldopam	Selective D_1-like partial agonist
1674	LE 300	Potent and selective dopamine D_1 antagonist
0925	SCH 23390	Standard selective D_1-like antagonist. Also 5-HT_{2C} agonist
2299	SCH 39166	High affinity D_1/D_5 receptor antagonist
0922	SKF 38393	Selective D_1-like agonist
1662	SKF 77434	Selective D_1-like partial agonist
1447	SKF 81297	D_1 agonist
1586	SKF 83566	Potent, selective D_1-like antagonist
2075	SKF 83822	Selective D_1-like agonist
2074	SKF 83959	D_1-like partial agonist
D_2 Receptors		
0524	AMI-193	5-HT_2/D_2 antagonist
2132	Amisulpride	Selective D_2/D_3 receptor antagonist; atypical antipsychotic agent
2759	B-HT 920	D_2 receptor agonist. Also α_2 agonist and 5-HT_3 antagonist
2664	Cabergoline	D_2/D_3 agonist
2193	Carmoxirole	Selective, peripherally acting D_2 agonist
0475	Dihydroergotamine	Partial D_2 agonist. Also partial α agonist and 5-HT antagonist
2536	Domperidone	Peripheral D_2/D_3 antagonist
0701	3'-Fluorobenzylspiperone	Potent D_2 receptor ligand
3940	GSK 789472	D_2 partial agonist; D_3 antagonist
0931	Haloperidol	High affinity dopamine receptor antagonist; displays some D_2 selectivity
1003	L-741,626	High affinity D_2 antagonist
2495	Melperone	D_2/5-HT_{2A} receptor antagonist; neuroleptic
1746	Nemonapride	Highly potent, selective D_2-like antagonist. Also 5-HT_{1A} agonist
4349	Olanzapine	5-HT_{2A}/D_2 antagonist; atypical antipsychotic
4493	Paliperidone	5-HT_{2A} and D_2 antagonist; atypical antipsychotic
3287	Prochlorperazine	D_2 receptor antagonist. Also 5-HT_3 and nAChR antagonist
4735	Quetiapine	5-HT_2/D_2 antagonist; atypical antipsychotic
1519	Quinelorane	D_2 and D_3 agonist
1061	(-)-Quinpirole	Selective $D_{2\text{-}4}$ agonist
1810	Raclopride	Potent, selective D_2/D_3 antagonist
0916	Remoxipride	Selective D_2 antagonist; atypical antipsychotic
2865	Risperidone	D_2/5-HT_{2A} antagonist; atypical antipsychotic
3896	Rotigotine	Dopamine D_2/D_3 agonist
0995	Spiperone	D_2-like antagonist (D_2 > D_4 > D_3). Also 5-HT_{2A} antagonist
0894	(*RS*)-(±)-Sulpiride	Selective D_2/D_3 receptor antagonist
2773	Sumanirole	D_2-selective agonist
0775	(+)-UH 232	D_2 autoreceptor antagonist. Also D_3 partial agonist
3085	Ziprasidone	5-HT_{2A}/D_2 antagonist; atypical antipsychotic
3996	Zotepine	5-HT_{2A}/D_2 antagonist; atypical antipsychotic

Cat. No.	Product Name	Primary Action
D_3 Receptors		
2132	Amisulpride	Selective D_2/D_3 receptor antagonist; atypical antipsychotic agent
0427	Bromocriptine	Selective D_2/D_3 agonist ($D_3 > D_2$)
0706	7-Hydroxy-DPAT	Dopamine agonist ($D_3 \geq D_2 = D_4$)
1847	Eticlopride	Selective D_2/D_3 antagonist ($D_3 > D_2$)
1109	GR 103691	Highly selective D_3 antagonist
3940	GSK 789472	D_3 antagonist. Also D_2 partial agonist
1347	Nafadotride	Highly potent, preferential D_3 antagonist
2635	NGB 2904	Potent and selective D_3 antagonist
1243	(+)-PD 128907	D_3 agonist ($D_3 \geq D_2 > D_4$)
3887	PG 01037	D_3 receptor selective antagonist
0719	7-Hydroxy-PIPAT	D_3 agonist ($D_3 > D_2$)
1031	Piribedil	D_2/D_3 receptor agonist ($D_3 > D_2$)
3355	PNU 177864	Highly selective D_3 antagonist
4174	Pramipexole	Selective D_3 agonist
1519	Quinelorane	D_2 and D_3 agonist
1061	(-)-Quinpirole	Selective $D_{2\text{-}4}$ agonist
1810	Raclopride	Potent, selective D_2/D_3 antagonist
3680	Ropinirole	Selective D_2-like agonist ($D_3 > D_2 > D_4$)
3896	Rotigotine	Dopamine D_2/D_3 agonist
4207	SB 277011A	Selective D_3 antagonist
0895	(*S*)-(-)-Sulpiride	Selective D_2-like receptor antagonist ($D_3 > D_2 > D_4$)
1357	U 99194	Potent, selective D_3 antagonist
D_4 Receptors		
4552	A 412997	Selective D_4 agonist
2214	ABT 724	Potent, selective D_4 partial agonist; proerectile
0444	Clozapine	Dopamine antagonist with some D_4 selectivity. Also 5-$HT_{2A/2C}$ antagonist
0782	2-CMDO	D_4/D_2 antagonist
2645	Fananserin	D_4 antagonist. Also 5-HT_{2A} antagonist
1004	L-741,742	Highly selective D_4 antagonist
1002	L-745,870	Highly selective D_4 antagonist
3298	NGD 94-1	Selective D_4 receptor ligand
1065	PD 168077	High affinity, selective D_4 agonist
3529	PD 168568	Potent and selective D_4 antagonist
2735	PNU 96415E	D_4 and 5-HT_{2A} antagonist; antipsychotic
1061	(-)-Quinpirole	Selective $D_{2\text{-}4}$ agonist
2329	Ro 10-5824	Selective D_4 receptor partial agonist
4185	Sonepiprazole	Selective D_4 receptor antagonist
Dopamine Receptors (Non-selective)		
0678	(+)-AJ 76	Dopamine receptor antagonist; displays preferential action at D_2-like autoreceptors
2073	(*R*)-(-)-Apomorphine	Dopamine receptor agonist; non-subtype-selective
3737	Asenapine	Novel antipsychotic agent; dopamine receptor antagonist
0474	Dihydroergocristine	Partial dopamine receptor agonist. Also partial adrenergic agonist and 5-HT antagonist
3548	Dopamine	Endogenous agonist at dopamine $D_{1\text{-}5}$ receptors
4057	Flupenthixol	Dopamine receptor antagonist
4052	Lisuride	Dopamine receptor agonist; antiparkinson's agent

Cat. No.	Product Name	Primary Action
1644	Mesulergine	Dopamine receptor partial agonist. Also 5-HT_{2A} and 5-HT_{2C} antagonist
0937	Pimozide	D_2-like antagonist. Also binds with high affinity to 5-HT_7 receptor. Ca^{2+} channel blocker
1559	Roxindole	Dopamine D_2 autoreceptor agonist. Also displays affinity for D_3, D_4, 5-HT_{1A} receptors and 5-HT transporters
3070	Thioridazine	Dopamine receptor antagonist; antipsychotic
Dopamine Transporters		
4357	Bicifadine	Noradrenaline, 5-HT and dopamine re-uptake inhibitor
4798	(*S*)-Duloxetine	Potent 5-HT and noradrenaline reuptake inhibitor; also blocks dopamine reuptake
0513	GBR 12783	Potent, selective dopamine uptake inhibitor
0421	GBR 12909	Selective dopamine uptake inhibitor. Also σ ligand
4351	JHW 007	High affinity dopamine uptake inhibitor
2742	Reserpine	Inhibitor of vesicular monoamine transport
2175	Tetrabenazine	Potent inhibitor of vesicular monoamine transport; depletes dopamine stores
Related Products		
2813	D-Amphetamine	Induces dopamine, 5-HT and noradrenaline release
3788	L-DOPA	Dopamine precursor
2547	6-Hydroxydopamine	Selective catecholaminergic neurotoxin
3992	NPEC-caged-dopamine	Caged version of dopamine (Cat. No. 3548)
2599	OSU 6162	Dopamine stabilizer
0730	4-Phenyl-1,2,3,4-tetrahydroisoquinolone	Dopamine release inhibitor

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