Dopamine Receptors

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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.

History

It was not until the late 1950's that dopamine was recognised as a neurotransmitter in its own right but the demonstration of its non uniform distribution in the brain suggested a specific functional role for dopamine.[1] Interest in dopamine was intensified by the realisation that dopamine had an important role in the pathogenesis or drug treatment of certain brain diseases e.g. Parkinson's disease, schizophrenia.[2] This lead to much research on the sites of action of dopamine and the dopamine receptors. A 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.[3] Biochemical studies on dopamine receptors in the 1970's, based on second messenger assays e.g. stimulation of cAMP production and ligand binding assays, supported the idea of more than one kind of dopamine receptor. This idea was given a firm foundation by Kebabian and Calne in their 1979 review.[4] They extended an earlier suggestion by Spano,[5] and proposed that there were two classes of dopamine receptor, D_1 and D_2, with different

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

	D_1 Receptors	D_2 Receptors
Physiological functions	Aspects of motor function (brain), cardiovascular function	Aspects of motor function and behaviour (brain), control of prolactin and α MSH secretion from pituitary, cardiovascular function
Biochemical responses	Adenylyl cyclase↑ Phospholipase C↑	Adenylyl cyclase↓ K^+ channel↑ Ca^{2+} channel↓
Localisation	Caudate nucleus, putamen, nucleus accumbens, olfactory tubercle, cerebral cortex (brain), cardiovascular system	Caudate nucleus, putamen, nucleus accumbens, olfactory tubercle, cerebral cortex (brain) anterior and neurointermediate lobes of pituitary gland, cardiovascular system
Selective antagonists	**SCH 23390** **SCH 39166** **SKF 83566**	**Domperidone** **Nemonapride** **Raclopride** **(-)-Sulpiride**
Selective agonists	**A 77636** **R-(+)-SKF 38393**† **R-(+)-SKF 81297**† **Dihydrexidine**	PHNO **Quinpirole** N-0437
Specific radioligands	[^{3}H]-SCH 23390* [^{125}I]-SCH 23982	[^{3}H]-Nemonapride [^{3}H]-Raclopride [^{3}H]-Spiperone**

(Bold Text Denotes Compounds Available From Tocris)

With the advent of molecular biological studies (Table 2), these subtypes should be termed D_1-like and D_2-like receptors. The localisation data are from functional and ligand-binding studies on dispersed tissues and tissue slices. *[^{3}H]SCH23390 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. †Racemate available from Tocris

biochemical and pharmacological properties, mediating different physiological functions. The properties of these two subtypes are summarised 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), however different G proteins and effectors are involved in their signalling 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 1980's that the true extent of this was revealed with the application of gene cloning techniques. This has 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.[6,7] The two subfamilies are often termed D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4) and some of their key properties are summarised in Tables 2 and 3.

In subsequent discussion I shall 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 I shall use the D_1-like and D_2-like nomenclature.

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.[6,7] 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 G-protein-coupled receptor,[8-10] 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

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 receptor and G protein $G\alpha_s$ or the D_2 receptor and G protein $G\alpha_{i/o}$ respectively.

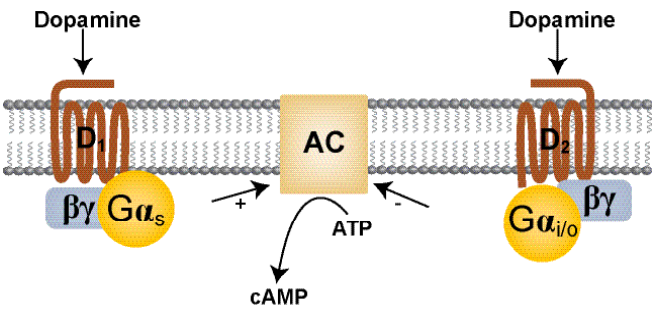


Figure 2 | Schematic representation of a G protein coupled dopamine receptor

The diagram shows the arrangement of the seven transmembrane spanning α-helices and their associated loops.

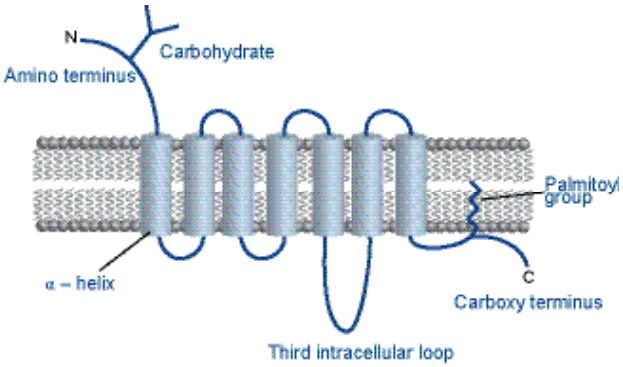
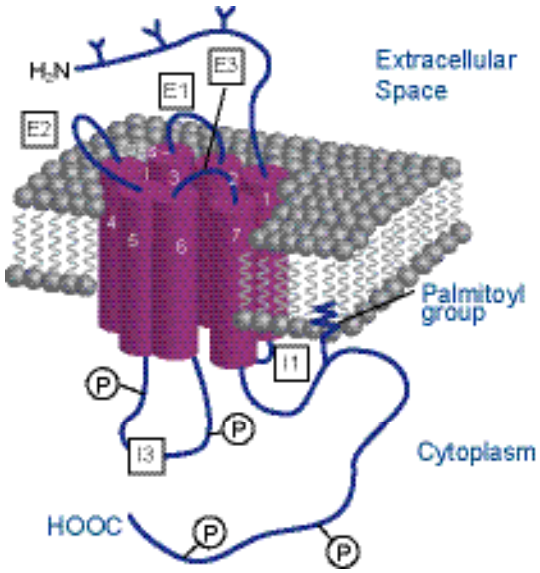


Figure 3 | Bundling of the helices to form the ligand binding site

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 disulphide 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.



to form the ligand binding site (Figure 3) and some information is available on the residues that make contact with ligands.[10,11] 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 (I3) is thought to be 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 variants of the D_2 and D_3 receptors with the long forms having an insertion (29 amino acids for D_2 long) in this loop.[12,13] Polymorphic variants of the D_2 receptor have been described with single amino acid changes in I3.[14] The D_4 receptor is highly polymorphic in the human population with variants containing different length insertions in I3.[15,16] In some cases these D_2-like receptor variants may have differential abilities to couple to or activate G proteins[17,18] and may also exhibit slightly different pharmacological properties.[15,19,20] The variants of the D_4 receptor have not been found to exhibit any differences in agonist signalling or in coupling to G proteins.[21]

The individual properties of the different subtypes have been probed by expressing the receptors in recombinant cells and by examining the localisation of the subtypes at the mRNA and protein level.

Individual Receptor Properties

The dopamine receptor subtypes exhibit different properties in terms of their pharmacological profiles, localisations and mechanisms of action, these differences will be briefly summarised 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 i.e. a high affinity for the benzazepine ligands SCH 23390,

Table 2 | Dopamine receptor subtypes from molecular biological studies

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 I). D_{2short} and D_{2long} refer to different alternatively spliced forms of the D_2 receptor gene. The homology values are for the transmembrane-spanning regions.[50] The localisations shown are the principal ones known at present from in-situ hybridisation and use of the polymerase chain reaction. Some pharmacological data for the different receptor subtypes is given in Table 3. For further information consult reference.[7]

	'D_1-like'		'D_2-like'		
	D_1	D_5	$D_{2short/long}$	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 with D_2 (short)	 100 44	 82 49	 44 100	 44 76	 42 54
Localisation	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
Organisation of amino acid sequence Putative third intracellular loop Carboxyl terminal tail	 Short Long	 Short Long	 Long Short	 Long Short	 Long Short
Reference examples	51	22,52	53	33	54

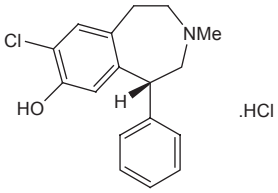
SCH 39166 and SKF 83566 which are selective antagonists for these subtypes. Thioxanthines e.g. flupentixol and phenothiazines e.g. fluphenazine also show high affinity but are not selective for D_1-like over D_2-like receptors. The D_1-like receptors show moderate affinities for typical dopamine agonists such as apomorphine and selective agonists such as A 77636, SKF 38393, SKF 82526, SKF 81297 and dihydrexidine are now available. There are differences in the affinities of some compounds for the D_1 and D_5 receptors (higher agonist and lower antagonist affinities[22,23]) but no truly selective compounds are as yet available.

D_1 receptors are found at high levels in the typical dopamine regions of brain such as the neostriatum, substantia nigra, nucleus accumbens, olfactory tubercle whereas the distribution of the D_5 receptors is much more restricted (Table 2) and this subtype is found generally at much lower levels. Both receptors are able to stimulate adenylyl cyclase (Figure 1) and the D_5 receptor shows some constitutive activity for this response.[23] Inverse agonist activity at the D_1 and D_5 receptors is seen in recombinant systems for some compounds such as butaclamol[23] which were previously considered to be antagonists. It has been established for some time that stimulation of the D_1 dopamine receptor leads to activation of phospholipase C[24] and recently this response has been linked to the D_1/D_2 receptor heterodimer[25] providing a function for heterodimer formation (see below). Agonists selective for the cAMP response (SKF 83822) or the phospholipase C response (SKF 83959) associated with D_1 receptors have been described.[26]

The function of the D_5 receptor is not understood although roles in brain function have been proposed.[27] 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/$GABA_A$)[28] 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.

SCH 23390, Standard Selective D_1-like Antagonist

SCH 23390
Cat. No. 0925

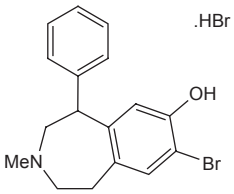


SCH 23390 is a potent D_1 antagonist (K_i values are ~ 0.2, 0.3, ~ 1100, ~ 800 and ~ 3000 nM at D_1, D_5, D_2, D_3 and D_4 receptors respectively). The compound is also an agonist at 5-HT_{2C} receptors (K_i = 6.3 nM) *in vitro*.

Barnett *et al* (1986) Relative activities of SCH 23390 and its analogs in three tests for D_1/D_{1A} dopamine receptor antagonism. Eur.J.Pharmacol. ***128*** 249. **Briggs** *et al* (1991) Activation of the 5-HT1C receptor expressed in Xenopus oocytes by the benzazepines SCH 23390 and SKF 38393. Br.J.Pharmacol. ***104*** 1038. **Seeman and Van Tol** (1994) Dopamine receptor pharmacology. TiPS. ***15*** 264.

SKF 83566, Potent, Selective D_1-like Antagonist

SKF 83566
Cat. No. 1586



SKF 83566 is a potent and selective D_1-like dopamine receptor antagonist (K_i values are 0.3 and 0.4 nM for D_1 and D_5 receptors respectively). Also antagonist at the vascular 5-HT_2 receptor (K_i = 11 nM). The antagonist is centrally active following systemic administration *in vivo*.

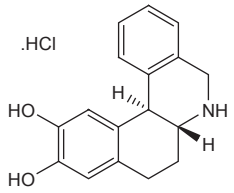
Ohlstein and Berkowitz (1985) SCH 23390 and SK&F 83566 are antagonists at vascular dopamine and serotonin receptors. Eur.J.Pharmacol. ***108*** 205. **Sunahara** *et al* (1991) Cloning of the gene for a human dopamine D_5 receptor with higher affinity for dopamine than D_1. Nature ***350*** 614. **Meyer** *et al* (1993) Effects of dopamine D_1 antagonists SCH23390 and SK&F83566 on locomotor activities in rats. Pharmacol.Biochem.Behav. ***44*** 429.

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 i.e. they all show high affinities for drugs such as the butyrophenones e.g. haloperidol and substituted benzamides e.g. sulpiride and these classes of drugs provide selective antagonists for the D_2-like receptors over D_1-like receptors (Table 3). As indicated above,

Dihydrexidine, Selective D_1-like Agonist

Dihydrexidine
Cat. No. 0884

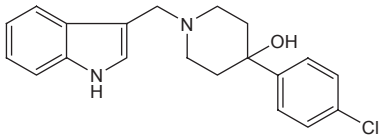


Dihydrexidine is a potent, full efficacy dopamine D_1 agonist which shows no agonist activity at peripheral D_2 receptors or adrenoceptors at doses which cause maximal stimulation of D_1 sites. The compound appears to be fully bioavailable in the brain and exhibits profound anti-Parkinsonism effects *in vivo*.

Lovenberg *et al* (1989) Dihydrexidine, a novel selective high potency, full dopamine D-1 receptor agonist. Eur.J.Pharmacol. ***166*** 111. **Brewster** *et al* (1990) *Trans*-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine: a highly potent selective dopamine full agonist. J.Med.Chem. ***33*** 1756. **Taylor** *et al* (1991) Dihydrexidine, a full dopamine D_1 agonist, reduces MPTP-induced parkinsonism in monkeys. Eur.J.Pharmacol. ***199*** 389. **Kholi** *et al* (1993) Dihydrexidine: a new potent peripheral dopamine D_1 receptor agonist. Eur. J.Pharmacol. ***235*** 31.

L-741,626, High Affinity D_2 Antagonist

L-741,626
Cat. No. 1003



L-741,626 is a potent D_2 dopamine receptor selective antagonist, with affinities of 2.4, 100 and 220 nM for D_2, D_3 and D_4 receptors respectively. The antagonist is centrally active following systemic administration *in vivo*.

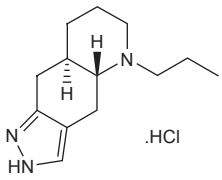
Kulagowski *et al* (1996) 3-[[4-(4-Chlorophenyl)piperazin-1-yl]methyl]-1H-pyrrolo[2,3-b]pyridine: an antagonist with high affinity and selectivity for the human dopamine D_4 receptor. J.Med.Chem. ***39*** 1941. **Bowery** *et al* (1996) Antagonism of the effects of (+)-PD 128907 on midbrain dopamine neurones in rat brain slices by a selective D_2 receptor antagonist L-741,626. Br.J.Pharmacol. ***119*** 1491. **Pillai** *et al* (1998) Human D_2 and D_4 dopamine receptors couple through βγ G-protein subunits to inwardly rectifying K^+ channels (GIRK1) in a Xenopus oocyte expression system: selective antagonism by L-741,626 and L-745,870 respectively. Neuropharmacology ***37*** 983. **Millan** *et al* (2000) S33084, a novel, potent, selective, and competitive antagonist at dopamine D_3-receptors: II. Functional and behavioral profile compared with GR218,231 and L741,626. J.Pharmacol.Exp.Ther. ***293*** 1063.

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 (Table 3). For example, the substituted benzamides sulpiride and raclopride show high affinity for the D_2 and D_3 receptors but a lower affinity for the D_4 receptor. Clozapine shows a slight selectivity for the D_4 receptor. More selective antagonists have been synthesised and these will be invaluable in determining the functions of these subtypes. For example L-741,626, GR 103691 and L-745,870 are D_2 selective (~40 fold), D_3 selective (~100 fold) and D_4 selective (~2000 fold) antagonists respectively.[29-31] The aminotetralins UH 232 and AJ 76 have been reported to be selective D_2-like autoreceptor antagonists[32] but they also possess some selectivity for the D_3 receptor[33] where UH 232 is a partial agonist.[34] Most antagonists show a higher affinity for the D_2 receptor compared with the D_3 and D_4 receptors. The D_2-like subtypes show moderate affinities for typical dopamine agonists with the D_3 receptor generally showing higher affinities for agonists than the other subtypes. There are compounds available that are selective agonists for the D_2-like receptors relative to the D_1-like receptors e.g. N-0437, PHNO, quinpirole. There are no highly selective agonists for the individual D_2-like subtypes as yet.

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

(-)-Quinpirole, Selective D_2-like Agonist

(-)-Quinpirole
Cat. No. 1061



(-)-Quinpirole is a selective dopamine D_2 receptor agonist. K_i values are 4.8, ~ 24, ~ 30 and 1900 nM for D_2, D_3, D_4 and D_1 receptors respectively.

Clark and White (1987) Review: D_1 dopamine receptor - the search for a function: a critical evaluation of the D_1/D_2 dopamine receptor classification and its functional significance. Synapse ***1*** 347. **Levant** *et al* (1996) Modulation of [^{3}H]quinpirole binding in brain by monoamine oxidase inhibitors: evidence for a potential novel binding site. J.Pharmacol.Exp.Ther. ***278*** 145. **Sullivan** *et al* (1998) Effects of quinpirole on central dopamine systems in sensitized and non-sensitized rats. Neuroscience ***83*** 781.

Table 3 | Pharmacological properties of the dopamine receptor subtypes

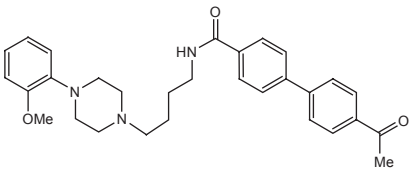
Values for the dissociation constants are given for ligands, determined using ligand binding assays for the five dopamine receptor subtypes. As far as possible values are given that avoid artefacts present in ligand binding assays with high affinity radioligands.[43] Data taken from [7,20,22,43,55]. Data for dopamine are obtained in the presence of Gpp(NH)p and so are for the free receptor uncoupled from G proteins.

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

(Bold Text Denotes Compounds Available From Tocris)

GR 103691, Highly Selective D_3 Antagonist

GR 103691
Cat. No. 1109



GR 103691 is a potent and selective dopamine D_3 receptor antagonist, with a K_i value of 0.3 nM and > 100-fold selectivity over D_2 and D_4 sites.

Murray *et al* (1995) A novel series of arylpiperazines with high affinity and selectivity for the dopamine D_3 receptor. Bioorg.Med.Chem.Lett. ***5*** 219. **Hurley** *et al* (1996) Dopamine D_3 receptors are not involved in the induction of c-fos mRNA by neuroleptic drugs: comparison of the dopamine D_3 receptor antagonist GR 103691 with the typical and atypical neuroleptics. Eur.J.Pharmacol. ***318*** 283. **Audinot** *et al* (1998) A comparative *in vitro* and *in vivo* pharmacological characterization of the novel dopamine D_3 receptor antagonists (+)-S 14297, nafadotride, GR 103,691 and U 99194. J.Pharmacol.Exp.Ther. ***287*** 187

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,[35-38] 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.[39]

The D_2-like receptors will, upon activation, stimulate a range of processes including acute signalling 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, mitogenesis, β-arrestin-2/AKt/GSK-3).[7,40] D_3 receptor-mediated signalling events are often of lower magnitude than for the other D_2-like receptors. The relation of these signalling 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 e.g. haloperidol, chlorpromazine, clozapine have been shown to possess inverse agonist activity at D_2 and D_3 receptors.[36,41,42] This inverse agonism may be associated with 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 behaviour in the brain and prolactin secretion from the anterior pituitary gland. The functions of the D_3 and D_4 receptors are currently unknown although their localisations in limbic areas of brain suggest roles in cognitive, emotional and behavioural function. 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).[43] The D_3 and D_4 receptors are located predominantly in limbic brain regions and this has made them particularly attractive targets for the design of potential selective antipsychotic drugs. L-745,870 was the first highly selective D_4 antagonist synthesised but it proved to be inactive against the psychosis of schizophrenia.[30]

Future Directions

Understanding the Role of the Dopamine Receptor Subtypes

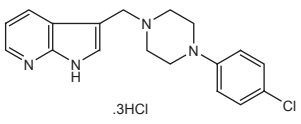
We are still a long way away from understanding the role of the different subtypes. Although partially selective antagonists are available for some of the subtypes and transgenic "receptor knock out" animals are available, much is still to be done here (see for example[26]).

Dopamine Receptor Subtypes in Drug Discovery

Because of 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. This continues to be the case and indications have expanded in to 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.[44] It had been thought that antipsychotics had to be antagonists/inverse agonists at the D_2 receptor[43] and the effective use of partial agonists as antipsychotics raises questions about mechanism that need to be addressed.[45] It will be important, for example, to understand the relationship between the efficacy of the ligands in signalling assays and their therapeutic effects.

L-745,870, Highly Selective D_4 Antagonist

L-745,870
Cat. No. 1002



L-745,870 is a highly potent and selective D_4 dopamine receptor antagonist. The antagonist has K_i values of 0.51, 2300 and 960 nM for D_4, D_3 and D_2 subtypes respectively and > 1000-fold selectivity over 5-HT_2, D_1 and D_5 receptors.

Kulagowski *et al* (1996) 3-[[4-(4-Chlorophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine: an antagonist with high affinity and selectivity for the human D_4 receptor. J.Med.Chem. ***39*** 1941. **Bristow** *et al* (1997) Schizophrenia and L-745, 870 a novel dopamine D_4 receptor antagonist. TiPS ***18*** 186. **Patel** *et al* (1997) Biological profile of L-745,870, a selective antagonist with high affinity for the dopamine D_4 receptor. J.Pharmacol.Exp.Ther. ***283*** 636. **Pillai** *et al* (1998) Human D_2 and D_4 dopamine receptors couple through βγ G-protein subunits to inwardly rectifying K^+ channels (GIRK1) in a *Xenopus* oocyte expression system: selective antagonism by L-741,626 and L-745,870 respectively. Neuropharmacology ***37*** 983.

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 phospho protein 32 kD). DARPP-32 seems to be a key protein in striatal neuronal function.[46] Important progress has also been made in understanding temporal aspects of signalling 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 signalling.[40]

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 and this will be an active field of research in the future. One class of cytoskeletal, adapter and signalling proteins that interact with dopamine receptors has been termed DRIPs (dopamine receptor interacting proteins).[47,48] An example includes the neuronal Ca^{2+} sensor-I (NCS-1) which interacts with D_2. In this case the interacting proteins may mediate the effects of Ca^{2+} on the D_2 dopamine receptor. Interactions also occur with other receptors including ligand-gated ion channels (see above) and GPCRs leading to homo- and heterodimer formation. A role for D_1/D_2 heterodimer formation has been suggested above,[25] roles for homodimer formation e.g. D_2 homodimers[49] are being actively pursued.

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Dopamine Receptor Compounds Available from Tocris

D_1-like Receptors

1534 A 68930
Potent, selective D_1-like agonist

1701 A 77636
Potent, selective D_1-like agonist. Orally active

2073 (*R*)-(-)-Apomorphine
Dopamine agonist; non-subtype-selective

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

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-like Receptors

Agonists

2073 (*R*)-(-)-Apomorphine
Dopamine agonist; non-subtype-selective

0427 Bromocriptine
Selective D_2-like agonist

2664 Cabergoline
Selective D_2-like agonist

2193 Carmoxirole
Selective, peripherally acting D_2-like agonist

0474 Dihydroergocristine
Partial dopamine receptor agonist

0475 Dihydroergotamine
Partial D_2-like agonist

1031 Piribedil
Dopamine agonist

1519 Quinelorane
D_2 and D_3 agonist

1061 (-)-Quinpirole
Selective D_2-like agonist

1559 Roxindole
Dopamine D_2 autoreceptor agonist. Also has affinity for D_3 and D_4 receptors

Antagonists

0678 (+)-AJ 76
Antagonist; preferential action at D_2-like autoreceptors

0524 AMI-193
D_2-like receptor antagonist

2132 Amisulpride
Selective D_2/D_3 receptor antagonist; atypical antipsychotic agent

0782 2-Chloro-11-(4-methylpiperazino)dibenz[b,f]oxepin
D_2-like antagonist. Displays some D_4 selectivity

0444 Clozapine
Dopamine antagonist with some D_4 selectivity

2536 Domperidone
Peripheral D_2-like antagonist

1847 Eticlopride
Selective D_2/D_3 antagonist

0701 3´-Fluorobenzylspiperone
D_2-like receptor ligand

0931 Haloperidol
Antagonist, partly D_2 selective

1746 Nemonapride
Highly potent D_2-like antagonist

0937 Pimozide
D_2-like antagonist

1810 Raclopride
Potent, selective D_2/D_3 antagonist

0916 Remoxipride
Selective D_2-like antagonist

0995 Spiperone
D_2-like antagonist

0894 (*RS*)-(±)-Sulpiride
Standard selective D_2-like antagonist

0895 (*S*)-(-)-Sulpiride
Standard selective D_2-like antagonist

0775 (+)-UH 232
D_2-like autoreceptor antagonist. D_3 partial agonist.

D_2-selective

2759 B-HT 920
D_2 receptor agonist

1003 L-741,626
High affinity D_2 antagonist

2495 Melperone
D_2/5-HT_{2A} receptor antagonist; neuroleptic

2865 Risperidone
D_2 antagonist

3085 Ziprasidone
5-HT_{2A}/D_2 antagonist; atypical antipsychotic

D_3-selective

1847 Eticlopride
D_3 antagonist ($D_3 > D_2$)

1109 GR 103691
Highly selective D_3 antagonist

0706 7-Hydroxy-DPAT
Dopamine agonist ($D_3 \geq D_2 > D_4$)

0719 7-Hydroxy-PIPAT
D_3 agonist ($D_3 > D_2$)

1347 Nafadotride
Highly potent, preferential D_3 antagonist

2635 NGB 2904
Potent and selective D_3 antagonist

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

1357 U 99194
Potent, selective D_3 antagonist

D_4-selective

2214 ABT 724
Potent, selective D_4 partial agonist; proerectile

2645 Fananserin
D_4 antagonist

1004 L-741,742
Highly selective D_4 antagonist

1002 L-745,870
Highly selective D_4 antagonist

1065 PD 168077
High affinity, selective D_4 agonist

2735 PNU 96415E
D_4 and 5-HT_{2A} antagonist; antipsychotic

2329 Ro 10-5824
Selective D_4 receptor partial agonist

Dopamine Transporters

0918 3α-Bis-(4-fluorophenyl) methoxytropane
Potent dopamine uptake inhibitor

0702 BTCP
Potent dopamine uptake inhibitor

2831 Bupropion
Non-selective inhibitor of dopamine and noradrenalin transporters

0917 3α-[(4-Chlorophenyl)phenylmethoxy] tropane
Dopamine uptake inhibitor

2833 Cocaine
Inhibitor of monoamine transporters

0513 GBR 12783
Potent, selective dopamine uptake inhibitor

0421 GBR 12909
Selective DA uptake inhibitor

0514 GBR 12935
Selective dopamine uptake inhibitor

0420 GBR 13069
Potent dopamine uptake inhibitor

1588 Indatraline
Potent dopamine uptake inhibitor

2148 (±)-McN 5652
Dopamine uptake inhibitor

2742 Reserpine
Inhibitor of vesicular monoamine transport

1497 Rimcazole
DAT inhibitor

2175 Tetrabenazine
Potent inhibitor of vesicular monoamine transport; depletes dopamine stores

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