

# Dopamine Receptors

## Key References

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## Overview

Dopamine receptors were initially divided into two general categories (designated as the dopamine D<sub>1</sub> receptor and dopamine D<sub>2</sub> receptor) based on differences in receptor pharmacology and biochemical mechanisms of signal transduction. Following the application of the techniques of molecular biology, the D<sub>1</sub> and D<sub>2</sub> dopamine receptors were cloned by several groups. Subsequently, additional dopamine receptors with homology to either the D<sub>1</sub> or the D<sub>2</sub> receptor were identified. At the present time, two families of vertebrate dopamine receptors (designated as D<sub>1</sub>-like and D<sub>2</sub>-like) are recognized. The D<sub>1</sub>-like family is composed of two distinct receptors (D<sub>1</sub> and D<sub>5</sub>). The D<sub>2</sub>-like family is comprised of three distinct receptors (D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub>). For any given receptor, some species-specific molecular variations occur. Furthermore, a homolog of the D<sub>1</sub>-like receptor occurs in at least one invertebrate species.

Certain of the dopamine receptors (D<sub>1</sub> and D<sub>2</sub>) occur in tissues at sufficiently high concentrations so that they can be studied *in situ*. Other receptors (D<sub>3</sub>, D<sub>4</sub> and D<sub>5</sub>) occur at such low concentrations that experimental investigation of the receptors *in situ* is more difficult. These latter receptors and their proposed effector mechanisms have been studied subsequent to their expression in cell lines, but care must be taken in extrapolating the results obtained with the cloned receptor to the *in vivo* situation.

Drugs can discriminate between different dopamine receptors at different levels of selectivity. Identification of compounds that discriminate between D<sub>1</sub>-like and D<sub>2</sub>-like receptors strongly supports division of the dopamine receptors into two families.

However, family-selective compounds are of limited use in discriminating between the different receptors within each family. No agents have been identified that are selective for D<sub>1</sub> versus D<sub>5</sub> receptors, for example. However, in the D<sub>2</sub>-like receptor family, subtype-selective agonists and antagonists have been identified.

The availability of agonists and antagonists selective for subtypes of dopamine receptors raises the possibility that physiological roles can be attributed to the specific molecular species. In the case of tissues enriched with specific dopamine receptors (e.g., the D<sub>2</sub> receptor in the intermediate lobe of the pituitary gland or the D<sub>1</sub> receptor in the parathyroid gland), a connection between the specific molecular species of receptor and a physiological response can be made. Once this connection has been established, the experimental questions asked have usually focused on the biochemical mechanisms that link receptor and physiology.

In complex tissues such as brain, where multiple classes of dopamine receptors coexist, establishing a connection between a dopamine receptor and a physiological response is more difficult. The search for improved (or novel) therapeutic agents based on targeting a particular class of dopamine receptors remains a speculative venture. Although selective agents may be promising in preclinical models of CNS disease, efforts to develop them into therapeutic agents have not yet been successful. The selective D<sub>1</sub> agonist, fenoldopam, is used clinically to produce renal vasodilatation.

# Dopamine Receptors

CURRENTLY ACCEPTED NAME	D <sub>1</sub> (D-178)	D <sub>2</sub> (D-180)	D <sub>3</sub> (D-181, D-152)	D <sub>4</sub> (D-177)	D <sub>5</sub>
STRUCTURAL INFORMATION	446 aa (human)	short: 414 aa (human) <sup>a</sup> long: 443 aa (human) <sup>a</sup>	400 aa (human)	386 aa (rat) <sup>b</sup>	477 aa (human)
SUBTYPE SELECTIVE AGONISTS	R(+)-SKF-38393 (S-101) A-68930 A-86929 A-77636 (A-255) Fenoldopam (F 6800) Dihydropyridine (D 5814)	U-91,356A	PD 128,907 (P-216) R(+)-7-OH-DPAT (H-168) BP 897 (B 9708)	PD 168,077 (P-233) CP-226,269	R(+)-SKF-38393 (S-101) A-68930
SUBTYPE SELECTIVE ANTAGONISTS	R(+)-SCH-23390 (D-054) SCH-39166	L-741,626 (L-135)	S(-)-Nafadotride S33084	CP-293,019 L-745,870 (L-131) L-750,667 (L-133) NGD-94-1 RBI-257 (R-123) U-101,387	R(+)-SCH-23390 (D-054) SCH-39166
SIGNAL TRANSDUCTION MECHANISMS	G <sub>s</sub> (increase cAMP)	G <sub>i</sub> (cAMP modulation) G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG)	G <sub>i</sub> (cAMP modulation) (?)	G <sub>i</sub> (cAMP modulation) ↑ arachadonic acid release Stimulate phospholipid methylation	G <sub>s</sub> (increase cAMP)
RADIOLIGANDS OF CHOICE	[ <sup>3</sup> H]-SCH-23390 [ <sup>125</sup> I]-SCH-23982	[ <sup>3</sup> H]-Nemonapride [ <sup>3</sup> H]-Spiperone [ <sup>3</sup> H]-Raclopride	[ <sup>3</sup> H]-7-OH-DPAT [ <sup>125</sup> I]-7-OH-PIPAT	[ <sup>3</sup> H]-Nemonapride [ <sup>3</sup> H]-Spiperone	[ <sup>3</sup> H]-SCH-23390 [ <sup>125</sup> I]-SCH-23982

## ABBREVIATIONS

**A-68930:** 1R,3S-1-Aminomethyl-5,6-dihydroxy-3-phenylisochroman hydrochloride  
**A-77636:** (-)-(1R,3S)-3-Adamantyl-1-(aminomethyl)-3,4-dihydro-5,6-dihydroxy-1H-2-benzopyran  
**A-86929:** (-)-trans-9,10-Hydroxy-2-propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene hydrochloride  
**BP 897:** N-[4-[4-(2-Methoxyphenyl)-1-piperazinyl]butyl]-2-naphthylcarboxamide  
**CP-226,269:** 5-Fluoro-2-[[4-(2-pyridinyl)-1-piperazinyl]methyl]-1H-indole  
**CP-293,019:** 7-[(4-Fluorophenoxy)methyl]-2-(5-fluoro-2-pyrimidinyl)octahydro-(7R,9aS)-2H-pyrido[1,2-a]pyrazine  
**7-OH-DPAT:** 2-Dipropylamino-7-hydroxy-1,2,3,4-tetrahydronaphthalene  
**R(+)-7-OH-DPAT:** R(+)-2-Dipropylamino-7-hydroxy-1,2,3,4-tetrahydronaphthalene  
**7-OH-PIPAT:** (+)-7-Hydroxy-2-(N-n-propyl-N-3'-iodo-2-propenyl)aminotetralin  
**L-741,626:** (±)-3-[4-(4-Chlorophenyl)-4-hydroxypiperidinyl]-methylindole  
**L-745,870:** 3-[[4-(4-Chlorophenyl)piperazin-1-yl]methyl]-1H-pyrrolo(2,3-b)pyridine  
**L-750,667:** (±)-3-[4-Iodophenyl]-1-piperazyl]methylpyrrol[2,3-b]pyrimidine  
**NGD-94-1:** 2-Phenyl-4(5)-[4-(2-pyrimidinyl)-piperzin-1-yl-methyl]-imidazole  
**PD 128,907:** 3,4,4a,10b-Tetrahydro-4-propyl-2H,5H-(1)benzopyrano(4,3-b)-1,4-oxazin-9-ol  
**PD 168,077:** N-[[4-(2-Cyanophenyl)-1-piperazinyl]methyl]-3-methyl-benzamide  
**RBI-257:** 1-[4-Iodobenzyl]-4-[[2-[3-isopropoxy]pyridyl]-methylamino]piperidine  
**S33084:** (3aR,9bS)-N[[4-(8-Cyano-1,3a,4,9b-tetrahydro-3H-benzopyrano[3,4-c]pyrrolo-2-yl)-butyl](4-phenyl)benzamide  
**SCH-23390:** 7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine  
**SCH-39166:** (-)-trans-6,7,7a,8,9,13b-Exahydro-3-chloro-2-hydroxy-N-methyl-5H-benzo-[d]-naphto-[2,1b]-azepine hydrochloride  
**R(+)-SKF-38393:** 1-Phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol  
**U-101,387:** 4-[4-[2-[(1S)-3,4-Dihydro-1H-2-benzopyran-1-yl]ethyl]-1-piperazinyl]-benzenesulfonamide  
**U-91,356A:** (R)-5,6-Dihydro-5-(propylamino)-4H-imidazo[4,5,1-ij]quinolin-2-(1H)-one monohydrochloride

## FOOTNOTES

**a** Deduced aa composition of putative third cytoplasmic loop differs between short and long isoforms.

**b** Deduced aa composition of putative third cytoplasmic loop varies due to the presence of 40 base pair repeats. The number of repeats is sometimes indicated (e.g., D<sub>4,2</sub> for two repeats).