1
Dopamine Receptors

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1. INTRODUCTION

Beginning with the initial suggestion that antipsychotic neuroleptic drugs block dopamine receptors *(1)*, and continuing with the demonstration that the affinity of antipsychotic drugs for dopamine receptors is highly correlated with clinical potency *(2,3)*, and that the density of [^{3}H]neuroleptic-labeled dopamine receptors is enhanced in postmortem brain tissue of schizophrenics *(4)*, the study of dopamine receptors has been inextricably linked with hypotheses for the mechanism of action of antipsychotic drugs and the etiology of schizophrenia. As described in other chapters in this volume, the role of dopamine in numerous other neuropsychiatric disorders, such as parkinsonism, attention deficit hyperactivity disorder, and addiction, has made consideration of the properties of dopamine receptor subtypes important for attempts to provide improved pharmacological treatments for these disorders. This chapter summarizes the molecular cloning of the five mammalian dopamine receptor subtypes, and reviews their structural, pharmacological, signaling, and regulatory properties.

2. DOPAMINE RECEPTOR SUBTYPES

2.1. Classification Into D1 and D2 Receptor Subfamilies

Although the existence of a receptor for dopamine was suggested indirectly by the effect of blockade of those receptors on dopamine turnover *(1)*, more direct evidence for such a receptor came in 1972 with the identification of dopamine-stimulated adenylate cyclase activity and cyclic adenosine monophosphate (AMP) accumulation first in retina *(5)*, and subsequently in rat neostriatum *(6)* and other basal forebrain nuclei including the nucleus accumbens and olfactory tubercle *(7)*. Importantly, the dopamine-stimulated adenylate cyclase was inhibited by antipsychotic drugs such as chlorpromazine, haloperidol, and fluphenazine much more potently than by drugs without antipsychotic or extrapyramidal actions such as imipramine and promethazine *(6–9)*. Dopamine receptors were first identified by radioligand binding in 1975 using both [^{3}H]dopamine and [^{3}H]haloperidol to label the receptors *(10–12)*, followed shortly by the synthesis and characterization of [^{3}H]spiperone *(13–15)*, still perhaps the most commonly used radioligand for D2-like dopamine receptors because of its high affinity and selectivity for the receptors.

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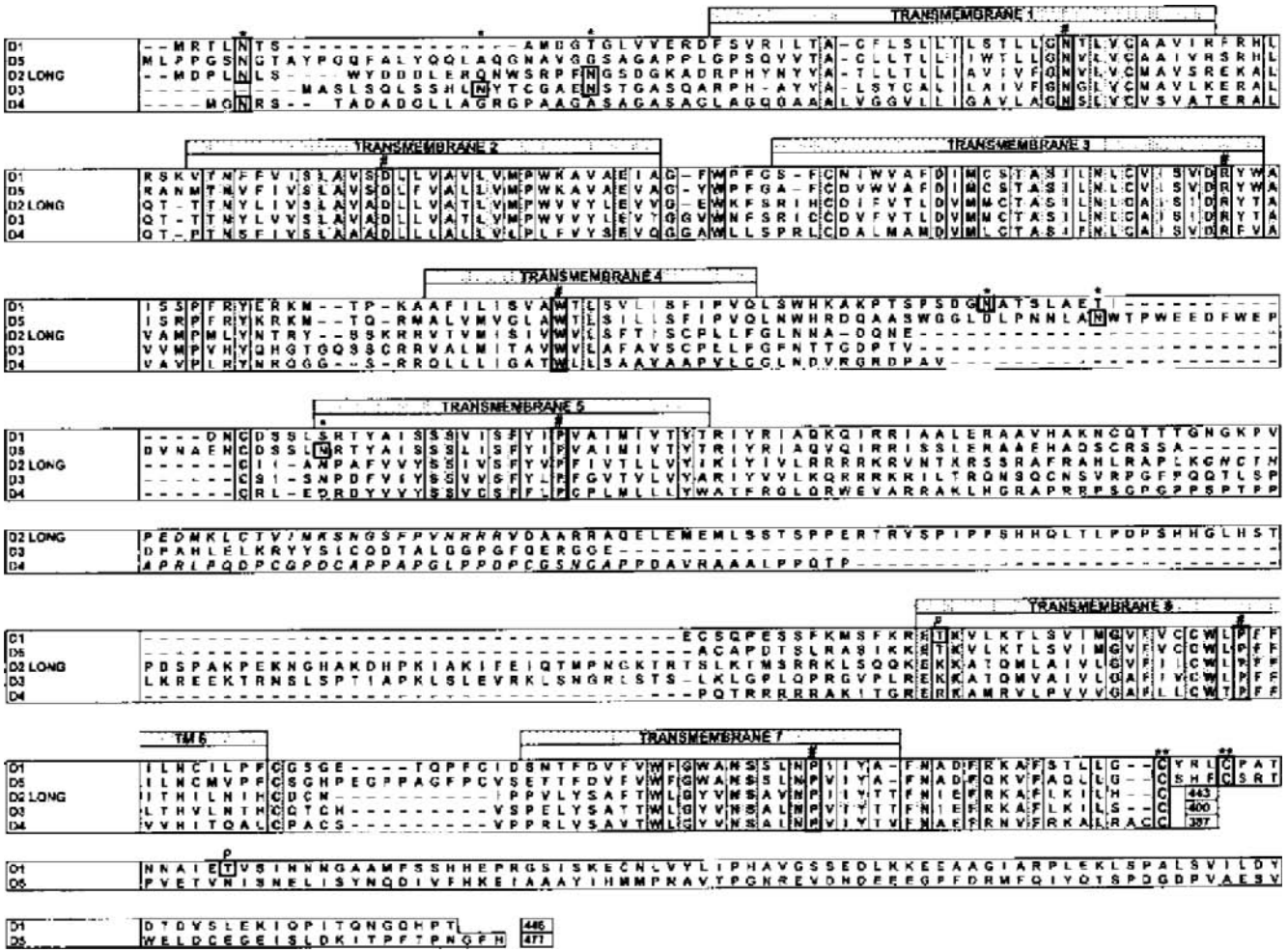
TRANSMEMBRANE 1
TRANSMEMBRANE 2
TRANSMEMBRANE 3
TRANSMEMBRANE 4
TRANSMEMBRANE 5
TRANSMEMBRANE 6
TM 6
TRANSMEMBRANE 7
D1
D5
D2 LONG
D3
D4

Fig. 1.

Two seminal papers in 1978 and 1979 summarized several lines of evidence that are inconsistent with the notion of a single type of dopamine receptor *(16,17)*. For example, the pharmacological profiles of dopamine-stimulated adenylate cyclase and the dopamine receptor identified by radioligand binding studies differ in key ways; in particular, domperidone and substituted benzamide derivatives, such as metoclopramide and sulpiride, that are potent inhibitors of radioligand binding are weak antagonists of dopamine-stimulated adenylate cyclase *(18–20)*, and butyrophenone antipsychotic drugs, such as spiperone and haloperidol, are also less potent inhibitors of enzyme activity than would be predicted based on their binding affinity *(21)*. Furthermore, dopamine-stimulated adenylate cyclase was shown to be physically distinct from the receptor predominantly labeled by most of the dopamine receptor radioligands in use at that time. Thus, dopamine does not stimulate adenylate cyclase activity in the anterior pituitary *(16)*, a tissue with abundant binding of several dopamine receptor ligands *(15,21)*, and axon terminal-sparing lesions of the cell bodies in the neostriatum (kainic acid) and substantia nigra (6-hydroxydopamine) selectively abolish or spare, respectively, dopamine-stimulated adenylate cyclase *(22–24)*. Data such as these led to the proposal that dopamine receptors belong to two subtypes, with the D1 subtype being coupled to adenylate cyclase and having low affinity for dopamine, ergots, such as bromocriptine, and substituted benzamine antagonists, and the D2 subtype being unassociated with adenylate cyclase, having high affinity for dopamine, substituted benzamide derivates, and butyrophenone antipsychotic drugs, and serving as the autoreceptor that regulates dopamine release *(17)*. This classification is still valid, with the major modifications to it being the recognition that, rather than being uncoupled from adenylate cyclase, D2 receptors are coupled to inhibition of adenylate cyclase *(25)*, and the fulfillment of the prediction that subcategories of D1 and D2 receptors would be discerned *(17)*; that is, D1 (henceforth referred to as D1-like) and D2 (D2-like) receptors are subfamilies, rather than subtypes.

2.2. Molecular Cloning of Dopamine Receptor Subtypes

The molecular cloning of a rat D2 receptor cDNA, reported in December of 1988 *(26)*, was the first step in the cloning of five dopamine receptor subtypes, all of which were discovered by 1991. As this work has been reviewed in detail elsewhere *(27)*, in this chapter I will summarize the cloning of the human receptors (Fig. 1). The cloning of the rat cDNA was rapidly followed by isolation of cDNA encoding the human D2 receptor, with four reports appearing in 1989 *(28–31)*. The first unanticipated result of the cloning of the dopamine receptors was the observation by all four of these reports that the D2 receptor gene product is alternatively spliced to produce long ($D2_L$; gene accession no. NM_000795) and short ($D2_S$; NM_016574) variants, 443 and 414 amino acids long, respectively. The variants differ by the presence or absence of an alternatively spliced

Fig. 1. Amino acid sequence-alignment of the human dopamine receptors. Positions that are conserved among all five subtypes are shaded. Residues that are marked with a dark border and a symbol above the alignment include the most highly conserved residue in each transmembrane domain (#), predicted sites of *N*-linked glycosylation (*), predicted sites of palmitoylation (**), and experimentally determined sites of phosphorylation (*p*). The alternatively spliced insert in $D2_L$ and the tandem repeat in the D4.2 variant are in italicized font.

exon encoding 29 amino acids in the third cytoplasmic loop of the receptor. $D2_L$ and $D2_S$ have essentially the same pharmacological profile, which corresponds to that of the pharmacologically defined D2-like receptor.

The following year saw the molecular cloning of DNA encoding the human D1 dopamine receptor (NM_000794), a 446 amino acid protein with a pharmacological profile corresponding to that of the pharmacologically defined D1-like receptor *(32–34)*. The same year brought a second major unanticipated result, the cloning of cDNA encoding a rat D3 receptor *(35)*, followed closely by the cloning of the human D3 receptor (NM_000796), a 400 amino acid protein with a pharmacological profile that, although similar to that of the D2 receptor, is distinct in ways that were not predicted by previous pharmacological studies of native dopamine receptors *(36,37)*. The distribution of D3 receptor mRNA also differs from that of the D2 receptor and D2-like receptor binding, being absent from the anterior pituitary and overall much less abundant than D2 receptor mRNA in brain, low in the dorsal neostriatum where the D2 receptor is most abundant, and highest in ventral forebrain nuclei such as the nucleus accumbens and the olfactory tubercle *(38)*.

The human D4 (gene accession no. NM_000797; ref. *39*) and D5 dopamine receptors (gene accession no. NM_000798; refs. *40,41*) were cloned in 1991. The D4 receptor is structurally and pharmacologically related to the D2 receptor, but has a unique distribution in brain, being relatively most abundant outside of the basal ganglia in retina, amygdala, cerebral cortex, hypothalamus, and hippocampus *(42)*. Although there are numerous allelic variants of the D4 receptor that differ in length (*see* Subheading 7.2.), the two-repeat version D4.2 is 387 amino acids long (Fig. 1). The 477 amino acid D5 receptor is very closely related to the D1 receptor, but its cognate mRNA is both much less abundant and more widely distributed, including in brain regions that do not have a substantial dopaminergic innervation *(38)*.

The criteria that are used to group the dopamine receptors into D1-like (D1, D5) and D2-like (D2, D3, D4) subfamilies include primary and secondary structure, organization of the genes, pharmacological profiles, and signaling properties. The D1 and D5 receptors have over 60% amino acid similarity, and each has only approx 30% similarity to the D2 receptor, whereas D2 and D3 are greater than 50% homologous, and the D4 receptor has approx 40% amino acid identity with the D2 or D3 receptors. The D1-like receptors have in common a relatively short third cytoplasmic loop and a long C-terminus, whereas the D2-like receptors have a long third cytoplasmic loop and a short C-terminus (Fig. 1). The D1-like receptor genes are intronless within their coding regions; in contrast, the D2-like receptor coding regions are interrupted by numerous introns of variable length, with a conserved intron/exon organization *(27)*. The D2-like receptors share high affinity for a number of D2 antagonists such as the prototypical D2 radioligand [^{3}H]spiperone, whereas the D1-like receptors are pharmacologically indistinguishable, particularly regarding antagonist affinity, and have high affinity for the prototypical D1 antagonist [^{3}H]SCH 23390 (Table 1).

3. STRUCTURAL FEATURES OF DOPAMINE RECEPTORS

3.1. Shared Structural Features

The dopamine receptors are all family A G protein-coupled receptors (GPCRs). Many dopamine receptor models are based primarily on the homology of the receptors

Table 1
Dopamine Receptor Affinity for Antagonists

	Affinity (K_i, n*M*)					
	Receptor subtype					
Drug	D2	D3	D4	D1	D5	References
A-69024	1320	—	—	19	—	*88,332*
Aripiprazole[a]	0.5	9.1	260	410	1200	*111*
(+)-Butaclamol	0.8	4.8	51	3	6	*333*
BW 737C89	54	—	—	0.3	—	*89,332*
Chlorpromazine	4	3	13	44	83	*333,334*
Clozapine	145	238	29	124	343	*333*
Domperidone	0.7	12	90	~10,000	—	*333,335,336*
Eticlopride	0.1	0.25	27	>10,000	>10,000	*333*
Flupentixol, *cis*	1.2	2.0	—	2.9	5.2	*40,333,334*
Fluperlapine	316	255	76	57	328	*333,334*
Fluphenazine	0.9	0.5	28	10	8	*333,334*
Haloperidol	2	10	4.2	124	87	*333*
L741,626	4	63	320	790	630	*337*
Metoclopramide	64	16	—	>10,000	—	*338*
NNC 756	782	—	—	0.34	0.6	*332,334*
Olanzapine	24	36	23	68	74	*333*
Perphenazine	0.6	0.6	40	30	—	*333*
Pimozide	3	4	30	>10,000	—	*333*
Quetiapine	470	506	1705	1900	1513	*333*
Raclopride	2.1	3.4	1990	>50,000	—	*333*
Remoxipride	344	1700	2600	>10,000	—	*333*
Risperidone	5	7	11	540	560	*333*
SCH23390	480	1450	2910	0.3	0.3	*333*
SCH39166	>1000	—	—	0.2	0.4	*87,339*
SDZ PSD 958	63		810	0.16	0.18	*90*
Spiperone	0.08	0.4	0.1	420	3550	*333*
Sulpiride	35	60	52	>10,000	>10,000	*35,39,333*
Thioridazine	7	4	14	100	300	*333*
YM-09151-2 (nemonapride)	0.05	0.13	0.32	2600	—	*333*

Affinity values are shown for dopamine receptor antagonists. Data were obtained from the cited papers except for ref. *333* which indicates that the data were obtained from the NIMH Psychoactive Drug Screening Program K_i database, and were obtained by averaging all the affinity values for each drug that were obtained using clone (i.e., heterologously expressed) receptors.

(http://kidb.bioc.cwru.edu/pdsp.php).

[a]Aripiprazole is a low-efficacy partial agonist.

to rhodopsin, the only member of this family for which the crystal structure has been determined *(43)*. Other data that contribute to receptor models are obtained from affinity-labeling studies, in which a chemically reactive moiety is attached to a receptor ligand, and by site-directed mutagenesis, in which the effect of mutations on ligand binding to and activation of receptors is determined, or in which the mutations are designed to create

a "binding" site for multivalent ions, cross-linking reagents, or specific side chain-reactive affinity reagents. The data that contributed to our dopamine receptor models have been reviewed in detail elsewhere *(44–46)*; in this chapter I will provide an overview of receptor domains thought to be important for ligand binding and signaling. Although there is no case in which the role of a particular residue has been confirmed in all dopamine receptor subtypes, the extensive conservation of GPCR structure and function makes it possible to generalize certain findings from one dopamine receptor subtype, or from other biogenic amine receptors, to all dopamine receptors. In referring to specific residues I will use the index of Ballesteros and Weinstein *(47)*, in which a residue is referred to by the transmembrane segment (TM) in which it resides and according to its position relative to the most highly conserved residue in that TM. Thus, the most highly conserved residue in TM1 of GPCRs is Asn1.50. In the D2 receptor this residue is Asn52$^{1.50}$, and Gly51$^{1.49}$ and Leu54$^{1.52}$ are immediately to the N terminal side and two residues to the C terminal side of Asn52$^{1.50}$, respectively. In Fig. 1, the most highly conserved residue in each TM is designated by this symbol: #.

The family A GPCRs have in common a relatively short N-terminal extracellular domain and seven α-helical membrane-spanning segments. In rhodopsin, the cytoplasmic extension of TM7 is an α helix (helix 8) extending parallel to the plane of the membrane, a structural feature thought to be shared by most family A GPCRs *(44)*. Broadly speaking, the intracellular loops and C-terminal tail form the contact surfaces for G proteins and other receptor-interacting proteins, whereas the binding of small molecule neurotransmitters such as the biogenic amines involves residues in the outer third of the TMs (i.e., toward the extracellular face of the membrane). With the possible exception of the second extracellular loop between TM4 and TM5 *(45)*, the extracellular regions are not thought to participate directly in ligand binding or receptor signaling. The primary binding pocket for dopamine consists chiefly of residues in TM3, TM5, and TM6 that are conserved among catecholamine receptors. These residues include Asp$^{3.32}$ (Asp103 in D1 and Asp114 in D2), which participates in an electrostatic interaction with the protonated amine of the ligand, Ser$^{5.42}$, Ser$^{5.43}$, and Ser$^{5.46}$, which interact with the catecholamine hydroxyl groups, and a cluster of aromatic residues in TM6 (Trp$^{6.48}$, Phe$^{6.51}$, Phe$^{6.52}$) that have been demonstrated to contribute to ligand binding to and activation of many biogenic amine receptors *(45,46)*. Other residues that contribute to the primary binding pocket formed by TM3, TM5, and TM6 are often adjacent to or one helix turn away from primary contact residues such as Asp$^{3.32}$ (residues 3.29, 3.33, and 3.36), Ser$^{5.46}$ (residue Phe$^{5.47}$), and Phe$^{6.51}$/Phe$^{6.52}$ (residue 6.56).

To use receptor models as tools to aid in the development of subtype-selective drugs, it is important to know not only binding pocket residues that are shared among the subtypes, but also residues that differ and could account for pharmacological differences between subtypes. Some of the primary pocket residues listed above differ between D1-like and D2-like receptors, or among the D2-like receptors *(46)*. Also important for subtype-selective binding is the ancillary binding pocket *(46,48)*, formed by residues in TM2, TM3, and TM7 on the extracellular side of the primary binding pocket. Elegant work by Javitch and colleagues determined that selectivity between D2 and D4 receptors is owing in large part to a cluster of nonpolar residues in this region that they refer to as a divergent aromatic microdomain, because the nonconserved D2 and D4 residues

often differ with respect to the presence or absence of an aromatic side chain *(49)*. The value of this work is demonstrated by the development of the highly selective D4 receptor antagonist FAUC 213, designed to exploit differences between the D2 and D4 receptor in this microdomain *(50)*. In addition to residues that line the binding pocket in the TMs, it has been proposed that the second extracellular loop, which reaches into the binding crevice and contacts retinal in rhodopsin *(43)*, also forms part of the binding pocket in dopamine receptors and other GPCRs and could contribute to pharmacological specificity *(44,45)*.

The structural basis for receptor activation may not be fully understood until a GPCR is crystalized in an active conformation, but studies of rhodopsin and other GPCRs have yielded a basic model of receptor activation that is probably valid for the dopamine receptors. In this model, a number of interhelical bonds constrain the receptor in an inactive conformation. Of particular importance is $Arg^{3.50}$, which forms an ion pair with $Glu^{6.30}$ and hydrogen bonds with residue 6.34. Activation of the receptor can result from disruption of interhelical bonds by agonist binding, by mutation of a residue participating in an interhelical bond, or by nonspecific disruption of helix packing *(51–54)*. Releasing the interhelical constraints allows the movement of TM6 so as to increase the distance between TM3 and TM6 at the cytoplasmic face of the membrane, also exposing residue 6.34 to the solvent *(46,55,56)*. Alterations in the relative positions of TM3, TM5, and TM6 presumably expose domains of the receptor cytoplasmic loops that bind to and activate heterotrimeric G proteins. These domains have not been mapped in detail for all of the dopamine receptors subtypes, although work with dopamine and other biogenic amine receptors has implicated the second cytoplasmic loop, the membrane-proximal portions of the third cytoplasmic loop, and the membrane-proximal region of the cytoplasmic tail in G protein selection and activation *(57–61)*.

3.2. *Posttranslational Modifications*

3.2.1. Glycosylation

All dopamine receptor subtypes have one or more potential sites of *N*-linked glycosylation in the amino-terminal region (Fig. 1). The D1-like receptors have additional consensus sequences in the second extracellular loop (one for D1 and two for D5), whereas the D3 receptor has potential sites in both the first and second extracellular loops. Endogenous D1-like receptors (probably mostly D1) are heavily glycosylated, and partial deglycosylation has little or no effect on [^{3}H]SCH 23390 binding to the receptors *(62)*. Studies of recombinant D1 receptor show that it is probably glycosylated at both potential sites, although preventing glycosylation does not alter receptor trafficking to the membrane *(63)*. The D5 receptor is glycosylated on the amino-terminal site and the first site (N-W-T) in the second extracellular loop, but perhaps not on the second site (N-R-T) in that loop. Prevention of glycosylation, by either mutation or treatment with tunicamycin, prevents trafficking of the D5 receptor to the plasma membrane. Interestingly, although glycosylation *per se* is not required for ligand binding because enzymatic deglycosylation does not affect binding levels, inhibition of glycosylation during receptor biosynthesis prevents the acquisition of ligand binding *(63)*. Endogenous and recombinant D2 receptors are also heavily glycosylated *(64,65)*, but enzymatic deglycosylation does not greatly affect ligand binding *(66)* or coupling of the receptors to G proteins *(67)*.

3.2.2. Palmitoylation

The D1-like receptors have two potential sites of palmitoylation in the cytoplasmic tail, whereas the D2-like receptors terminate in a cysteine that is thought to be palmitoylated; attachment of the palmitoylated cysteine to the membrane could create a fourth cytoplasmic loop out of helix 8. Many GPCRs are palmitoylated either constitutively or dynamically (e.g., agonist-stimulated palmitate turnover), and palmitoylation may be involved in receptor processing and targeting to the membrane, in coupling to G proteins and signaling, and in desensitization, sequestration, and internalization *(68)*. Although incorporation of [^{3}H]palmitic acid into the D1 receptor expressed in Sf9 cells has been reported to be enhanced by dopamine *(69)*, in other work by this group the D1 receptor was found to be constitutively palmitoylated, on both Cys347 and Cys351 *(70)*. Preventing palmitoylation by mutation of these residues does not hinder receptor expression, activation of G proteins, or dopamine-induced uncoupling from G proteins (desensitization) *(71)*. In contrast, another report described loss of desensitization (as measured by diminished stimulation of adenylate cyclase) after mutation of Cys351, and speculated that the mutant receptor was constitutively desensitized *(72)*. The $D2_L$ receptor is also constitutively palmitoylated in Sf9 cells *(73)*.

3.2.3. Phosphorylation

Phosphorylation by GPCR kinases (GRKs), second messenger-dependent kinases, such as protein kinase A (PKA) and protein kinase C (PKC), and other kinases, is a general mechanism for regulating the signaling and trafficking of GPCRs. All of the dopamine receptor subtypes have multiple potential sites of phosphorylation by these kinases in the cytoplasmic loops and tail. Agonist-dependent phosphorylation of the D1 receptor *(69,74)* is catalyzed by GRKs *(75)* and by PKA *(76)*. Mutagenesis studies in which potential phosphorylation sites are mutated to alanine suggest that Thr360 in the cytoplasmic tail is a site of phosphorylation by GRK2 *(77)*, whereas Thr268, at the junction of the third cytoplasmic loop and TM 6 (Fig. 1), is a site of phosphorylation by PKA *(76)*. The D2 receptor is phosphorylated both constitutively *(73)* and in an agonist-stimulated manner *(78)*, whereas agonist treatment causes little phosphorylation of the D3 receptor *(78)*. Agonist-dependent phosphorylation of the D2 receptor is enhanced by overexpression of GRK2 *(78,79)*.

4. PHARMACOLOGICAL PROFILES OF DOPAMINE RECEPTOR SUBTYPES

4.1. Differentiation Between D1-Like and D2-Like Receptors

At the time of the division of dopamine receptors into what were then considered D1 and D2 subtypes, characterization of D2-like receptors and their contribution to dopamine-dependent behaviors was aided by the development of butyrophenone radioligands that labeled D2-like receptors with high affinity and selectivity, of highly selective substituted benzamide antagonists, and D2-like receptor-selective agonists, such as bromocriptine. The addition of equally selective but more efficacious agonists, such as quinpirole *(80),* and substituted benzamide radioligands such as [^{3}H]YM-09151-2 ([^{3}H]nemonapride) *(81)*, facilitated what was already an explosion of research on the behavioral and biochemical properties of D2-like receptors. Progress on D1-like receptors was hindered by the lack of D1-selective agonists and antagonists until the identification

of selective benzazepine ligands, such as the antagonist SCH23390 *(82,83)*, also extremely useful as a [^{3}H]-labeled radioligand *(84)*, and the partial agonist SKF38393 *(85)*. Numerous D1-like receptor-selective agonists that vary in efficacy and D1/D2 selectivity have subsequently been developed *(86)*, as well as several D1-like receptor-selective antagonists (Table 1) including SCH39166 *(87)* and the non-benzazepines A-69024 *(88)*, BW 737C89 *(89)*, and SDZ PSD 958 *(90)*. Because different D1-like receptor antagonists may have different behavioral properties *(91)*, this research area is weakened by the shortage of structurally diverse and commercially available antagonists to supplement SCH23390, by far the most commonly used D1-like receptor antagonist.

The D1-like D1 and D5 receptors have similar affinities for most antagonists (Table 1) as would be predicted from their extensive homology in the TMs (Fig. 1). Although the D5 receptor has higher affinity for most agonists than does the D1 receptor *(40)*, this is because of the higher constitutive activity of the D5 receptor *(92)*, and probably does not reflect differences in the binding pockets of the two receptor subtypes that can be exploited to develop selective antagonists. Both because homology among the D2-like receptors is lower and because D2-like subtype-selective drugs held the promise of significant improvements in the treatment of schizophrenia and other disorders, many agonists and antagonists that differentiate among the D2-like receptors have been developed.

4.2. Differentiation Among D2-Like Receptors

The development of D3 receptor-selective ligands is challenging because of the close homology of D2 and D3 receptors. Thus, there are very few amino acid positions exposed to the binding pocket where there are nonconservative substitutions between the subtypes *(46)*. The affinity of the human D3 receptor for most D2-like receptor antagonists does not differ greatly from that of the D2 receptor; most of the antagonists have similar or modestly lower affinity for the D3 receptor *(37,93,94)*. In membrane-binding assays, the D3 receptor has higher affinity than the D2 receptor for D2-like receptor agonists, such as dopamine, quinpirole, and 7-OH-DPAT *(35,37,95)*, but much of the apparent selectivity of D2-like agonists for the D3 receptor is related to the unusual guanosine triphosphate(GTP)-resistant nature of the agonist binding to the D3 receptor, so that careful control of assay conditions is required to ensure that only the D3 receptor is being labeled, and not the D2 receptor in an agonist high-affinity conformation *(96–98)*. Nevertheless, because of the possible therapeutic benefits of selective blockade or stimulation of the D3 receptor *(99,100)*, considerable effort has been invested in the development of D3 receptor selective agonists and antagonists. A number of antagonists have been developed that have 100-fold or greater selectivity for the D3 receptor over the D2 receptor, including PD 5849, the benzopyranopyrrole S33084, the arylpiperazines NGD 2849 and NGD 2904, *N*-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butyl]-7-methoxy-2-benzofurancarboxamide (compound 41), and the tetrahydroisoquinoline SB-277011 (Table 2). As mentioned above, determination of the D3 receptor selectivity of agonists is complicated by differences in the coupling of D2 and D3 receptors to G proteins, but among the agonists thought to be at least modestly selective for the D3 receptor are 7-OH-DPAT, pramipexole (SND 919), quinerolane, PD128,907, and FAUC 725 *(35,101–104)*.

The initial pharmacological characterization of the D4 receptor demonstrated that the subtype has a pharmacological profile that, although clearly "D2-like," differs significantly

Table 2
D2-Like Receptor Affinity for Antagonists Differentiating Among Subtypes

	Affinity (K_i, n*M*)			
	Receptor subtype			
Drug	D2	D3	D4	Reference
D3-selective				
GR 103,691	24	0.4	81	*340*
GR 218,231	63	1.0	10000	*337*
Nafadotride	3	0.3	1780	*341*
NGB 2849	262	0.9	>5000	*342*
NGB 2904	217	1.4	>5000	*342*
PD 58491	2400	20	>3000	*343*
S 14297	300	13	1380	*344*
S33084[a]	32	0.3	2000	*337*
SB-277011	1000	10	—	*345*
U99194A	2280	223	>10000	*346*
Compound 41	373	720	0.13	*112*
D4-selective				
CI-1030	413	679	4.3	*347*
CP-293,019	>3000	—	3.4	*348*
FAUC 213	3400	5300	2.2	*50*
L-745,870 (CPPMA)	960	2300	0.43	*110*
L-750,667[a]	>1700	>4500	0.5	*110*
NGD 94-1[a]	2230	>10000	4	*349*
PB12[a]	1900	—	0.04	*350*
PD 89211	>5000	>3000	3.6	*351*
PD 172938	5882	2700	8	*352*
RBI-257	568	145	0.33	*353*
U-101387	5000	>2500	10	*354*

[a]Has been used as a radioligand.

from that of the D2 receptor *(39)*. Although D2 and D4 receptors have similar affinities for some D2 receptor antagonists, such as spiperone and YM-09151-2, and the D4 receptor has slightly higher affinity than the D2 receptor for clozapine, the D2 receptor has higher affinity than the D4 receptor for most D2 receptor antagonists, with marked D2 selectivity observed for raclopride, fluphenazine, and (+)-butaclamol (Table 1). These data tend to support a conclusion also suggested by the lower homology between the D2 and D4 receptors (compared to that between D2 and D3)—the binding pockets of the D2 and D4 receptors are sufficiently different that the development of highly selective drugs is straightforward. Among the D4 receptor-selective antagonists that have more than 1000-fold lower affinity for the D2 receptor are L-745,870 and its 4-iodo analog L-750,667, PB12, RBI-257, CP-293,019, PD 89211, and FAUC 213 (Table 2; *see* also ref. *42*). With the exception of PD 168077, an agonist with reasonable efficacy and greater than 300-fold selectivity for D4 over D2 and D3 receptors *(105)*, and FAUC 312 *(106)*, reports of high-efficacy D4 receptor-selective agonists have appeared only in

meeting proceedings. Interestingly, several of the antagonists listed above are partial agonists under some conditions *(107)*, and a number of other D4 receptor-selective partial agonists have also been developed *(108,109)*.

D2 receptor-selective drugs, i.e., drugs that bind with higher affinity to the D2 receptor than to the D3 or D4 receptors, would also be useful tools. As shown in Table 1, three compounds with moderate selectivity for the D2 receptor are L741,626 *(110)*, domperidone *(20)*, and aripiprazole *(111)*; these could be lead compounds for the development of more D2-selective drugs. Compounds have also been described that are quite selective for both D3 and D4 over the D2 receptor *(112)* and for both D2 and D4 over the D3 receptor *(113)*.

5. DOPAMINE RECEPTOR SIGNALING

5.1. G Protein Coupling

5.1.1. D1-Like Receptors and G Proteins

All dopamine receptor subtypes are GPCRs whose signaling is at least partially mediated by interaction with and activation of heterotrimeric G proteins. As receptors that stimulate adenylate cyclase, the D1-like receptors were assumed to couple to the adenylate cyclase stimulatory G protein $G\alpha_s$. $G\alpha_{olf}$, the heterotrimeric G protein involved in olfaction, is very closely related to $G\alpha_s$ (88% amino acid homology) and also stimulates adenylate cyclase *(114)*. In the neostriatum, the brain region with the densest dopamine innervation and the highest expression of the D1 receptor, expression of $G\alpha_{olf}$ is very high whereas expression of $G\alpha_s$ is very low *(115)*. The nucleus accumbens and olfactory tubercle also express abundant $G\alpha_{olf}$ and little $G\alpha_s$ *(116)*. Unlike wildtype mice, $G\alpha_{olf}$ null mutant mice do not increase their locomotor activity in response to cocaine or a D1-selective agonist and exhibit little dopamine-stimulated adenylate cyclase or cocaine-induced c-fos expression in the neostriatum or nucleus accumbens, strongly suggesting that $G\alpha_{olf}$ mediates D1 receptor signaling to adenylate cyclase in these basal ganglia nuclei *(115,117)*. When expressed in HEK293 cells, D1 receptor stimulation of adenylate cyclase, but not D5 receptor stimulation, requires the expression of endogenous γ_7 subunit, presumably as part of the heterotrimer $G\alpha_s\beta_1\gamma_7$ *(118)*. Because γ_7 is abundantly expressed in neostriatal medium spiny neurons *(119)*, particularly in neurons that also express D1 receptor mRNA *(118)*, neostriatal D1 receptors may signal via a G protein heterotrimer that includes both $G\alpha_{olf}$ and γ_7. In other brain regions, including dopamine target areas that express D1 and/or D5 receptors such as the cerebral cortex and hippocampus, where the expression of $G\alpha_{olf}$ is much lower than that of $G\alpha_s$ *(116)*, it seems likely that $G\alpha_s$ mediates D1 and D5 receptor signaling to adenylate cyclase. Coupling of D1 receptors to $G\alpha_s$, and to other heterotrimeric G proteins such as $G\alpha_o$ and $G\alpha_q$, has also been described *(120,121)*.

5.1.2. D2-Like Receptors and G Proteins

D2-like receptor signaling is mediated primarily by activation of the pertussis toxin-sensitive G proteins $G\alpha_{i/o}$. For the D2 receptor, the possibility that the alternatively spliced insert in the third cytoplasmic loop of $D2_L$ might influence G protein interactions and result in differential G protein selection by $D2_S$ and $D2_L$ has meant that analyses of G protein selection are often carried out in the context of comparisons between the two isoforms. As reviewed in detail elsewhere *(46,122)*, there is quite a bit of disagreement in the literature concerning which G proteins interact with $D2_S$ and $D2_L$. It seems likely that

both receptor isoforms are inherently able to activate multiple $G\alpha_{i/o}$ subtypes, including $G\alpha_{i2}$, $G\alpha_{i3}$, and $G\alpha_{o}$ *(123,124)*. $D2_S$ and $D2_L$ can also activate the pertussis toxin-insensitive G protein $G\alpha_z$ *(125,126)*. Recently, however, several different approaches have identified $G\alpha_o$ as the $G\alpha_{i/o}$ subtype that is most robustly activated by $D2_L$ *(127–129)* and by $D2_S$ *(130–132)* and, furthermore, the G protein subtype that is predominantly coupled to D2 receptors in the mouse brain *(133)*.

The D3 receptor is anomalous in that agonists bind to the receptor with a high affinity that is relatively insensitive to GTP. The GTP insensitivity could reflect GTP-resistant coupling to G proteins or a receptor structure that has inherently high affinity for agonists; interesting work by Leysen and colleagues expressing the D3 receptor in *Escherichia coli*, and thus in the absence of endogenous G proteins with which the receptor can interact, indicates that the latter explanation is more likely, and also suggests that G proteins bind to the D3 receptor with an affinity similar to that for the D2 receptor *(134)*. Work by several groups has identified $G\alpha_o$ as being activated by the D3 receptor and mediating D3 signaling, with some evidence for signaling via $G\alpha_z$ and $G\alpha_{q/11}$ *(126,135–137)*. The complexity of the mechanisms regulating G protein selection is indicated by the work of Zaworski et al. *(137)*, who found that the D3 receptor couples more efficiently to $G\alpha_o$ in SH-SY5Y cells than in HEK293 cells, despite the abundance of that G protein subtype in both cell lines. Zaworski et al. suggest that the additional presence in SH-SY5Y cells of effectors regulated by the D3 receptor contributes to the efficient activation of $G\alpha_o$ by the D3 receptor in those cells. This hypothesis is consistent with other work showing that receptors form complexes with effectors, and that G proteins participate in complex formation *(138)*.

The human D4 receptor is similar to D2 in that it activates multiple pertussis toxin-sensitive G proteins, including $G\alpha_{i2}$, $G\alpha_{i3}$, and $G\alpha_{o}$ *(135,139)*. The rat D4 receptor has been reported to couple preferentially to $G\alpha_z$ *(126)* and to the pertussis toxin-sensitive transducin subtype, $G\alpha_{t2}$ *(140)*.

5.2. Signaling Pathways

5.2.1. D1-Like Receptor Signaling

The most thoroughly characterized signaling pathway for the D1-like receptors is $G\alpha_s$- or $G\alpha_{olf}$-mediated stimulation of adenylate cyclase, primarily adenylate cyclase type 5 *(141,142)*, which increases cyclic AMP (cAMP) accumulation, activates PKA, and increases the phosphorylation of a number of proteins involved in signal transduction and regulation of gene expression *(143,144)*. D1 receptor-stimulated gene expression is mediated by PKA-dependent phosphorylation of the cAMP response element-binding protein (CREB) *(145,146)*. D1-like receptor stimulation of PKA increases the phosphorylation of the glutamate *N*-methyl-D-aspartate NMDA receptor NR1 subunit *(147)*, thus enhancing (NMDA)-evoked currents *(148)* and activating L-type calcium curents *(149,150)*. D1 receptor stimulation also causes PKA-dependent inhibition of voltage-gated sodium channels *(151)*, and γ-aminobutyric acid $(GABA)_A$ receptor currents *(152)*. DARPP-32 (dopamine and cAMP-regulated phosphoprotein, 32 kDa) plays a central role in signaling by dopamine receptors. DARPP-32 is a neostriatum-enriched bifunctional signaling protein that inhibits protein phosphatase 1 (PP1) when phosphorylated on Thr34 by PKA and several other kinases *(153,154)*, and inhibits PKA when phosphorylated on Thr75 by cyclin-dependent kinase 5 *(155)*. Thus, in addition to

direct phosphorylation of numerous PKA substrates including those mentioned above, D1 receptor stimulation of PKA prevents PP1-catalyzed dephosphorylation of the same phosphoproteins by phosphorylating DARPP-32 on Thr34. D1 receptor stimulation simultaneously disinhibits PKA by activating protein phosphatase-2A and promoting Thr75 dephosphorylation of DARPP-32. Studies with DARPP-32 null mutant mice have demonstrated that DARPP-32 is required for acute D1 receptor-mediated responses, at both the cellular and behavioral levels *(154)*, and mice deficient in degradation of cAMP as a result of a phosphodiesterase 1B null mutation have enhanced D1 agonist-induced phosphorylation of DARPP-32 and enhanced methamphetamine-stimulated locomotor activity *(156)*.

One finding that is difficult to reconcile with a model of D1 receptor signaling that includes a central role for a cAMP/PKA/(protein phosphatase)/DARPP-32 cascade is that a null mutation of adenylate cyclase type 5 virtually abolishes D1 receptor stimulation of adenylate cyclase activity while enhancing D1 agonist-stimulated locomotor activity *(141,142)*. Although interpretation of the results is complicated because D2 receptor signaling is also disrupted in the adenylate cyclase 5 null mutant mouse, one possible explanation is that a cAMP-independent signaling pathway mediates D1 receptor locomotor activation, and perhaps other behavioral effects of D1 receptor stimulation. An alternative pathway that has been proposed for D1-like receptor signaling is phospholipase C-mediated mobilization of intracellular calcium. There are at least two distinct mechanisms by which this might occur. Bergson and colleagues demonstrated that heterologously expressed D1 and D5 dopamine receptors, when coexpressed with calcyon, stimulate the release of calcium from intracellular stores following priming of the cells with a $G\alpha_q$-coupled receptor agonist *(157)*. Endogenous D1-like receptors in neocortical or hippocampal neurons, but not neostriatal neurons, display a similar priming-dependent ability to mobilize calcium *(158)*. The second mechanism invokes a novel SCH23390-binding D1-like receptor that is linked to phospholipase C via $G\alpha_q$. The regional distribution and pharmacological profile of this novel receptor differ from both D1 and D5 receptors *(159)*. Furthermore, this $G\alpha_q$-coupled receptor does not react with a D1 receptor antibody, is not a product of the *D1DR* gene, and may be encoded by mRNA of a different size from that encoding the D1 receptor *(121,160–162)*.

5.2.2. D2-Like Receptor Signaling

The first signaling pathway identified for D2-like receptors was inhibition of cAMP accumulation *(25,163)*. In the rodent neostriatum, this response is primarily mediated by adenylate cyclase type 5; genetic ablation of this adenylate cyclase abolishes D2 receptor-mediated inhibition of adenylate cyclase and also eliminates the locomotor inhibitory effects of D2 receptor-blocking antipsychotic drugs *(141)*. The lack of responsiveness to antipsychotic drugs is a phenotype also seen in D2 receptor *(164)* and DARPP-32 *(154)* null mutant mice, suggesting that this signaling pathway contributes to D2 receptor-stimulated locomotor activity. The D2 and D4 receptors both inhibit adenylate cyclase activity in a variety of tissues and cell lines *(42,143)*. Inhibition of adenylate cyclase by the D3 receptor is weaker and often undetectable although, interestingly, the D3 receptor robustly inhibits adenylate cyclase type 5 *(165,166)*, in contrast to several other adenylate cyclase subtypes including the closely related type 6. Whereas D2 and D4 receptors markedly increase the activity of the G protein $\beta\gamma$-stimulated type 2 adenylate cyclase, the D3 receptor has little or no effect *(165,167)*.

As is typical of $G\alpha_{i/o}$-coupled receptors, D2-like receptors modulate many signaling pathways in addition to adenylate cyclase, including phospholipases, ion channels, mitogen-activated protein (MAP) kinases, and the Na^+/H^+ exchanger *(143)*. Most if these pathways are regulated by G protein βγ subunits that are liberated by receptor activation of $G\alpha_{i/o}$ proteins. One such pathway is activation of the G protein-regulated inwardly rectifying potassium (GIRK or Kir3) channel, a channel that carries one of several potassium currents modulated by dopamine in midbrain dopamine neurons *(168,169)*. All of the D2-like receptors activate GIRK *(170)*, presumably via Gβγ *(171,172)*. The D3 receptor is approximately as efficient as the $D2_L$ receptor at coupling to homomeric GIRK2 *(173)*, the GIRK subtype predominantly expressed by dopamine neurons in the rat ventral mesencephalon *(174,175)*, and regulation of GIRK channels contributes to inhibition of secretion by the D3 receptor heterologously expressed in AtT-20 mouse pituitary cells *(176)*. D2 and D4 receptors both coprecipitate with GIRK channels in a heterologous expression system, and the rat neostriatal D2 receptor coprecipitates with GIRK2, suggesting the existence of a stable complex that forms during receptor/channel biosynthesis *(138)*. Evidence that dopamine release-regulating autoreceptors are coupled to potassium channels *(177)* rather than to inhibition of adenylate cyclase *(178)*, together with the robust regulation of GIRK currents by D2 receptors in substantia nigra dopamine neurons *(179)*, suggests that D2 receptor activation of GIRK currents contributes to D2 autoreceptor inhibition of dopamine release and dopamine neuronal activity. The hyperactivity and facilitation of D1 receptor signaling observed in GIRK2 null mutant mice *(180)* is also consistent with a loss of inhibitory autoreceptor function.

MAP kinases are components of parallel protein kinase cascades that transmit signals from a variety of extracellular stimuli to the cell nucleus, thus participating in cell proliferation, differentiation, and survival *(181)*. Many GPCRs, including those coupled to $G\alpha_{i/o}$, regulate the activity of MAP kinases *(181,182)*. Activation of the D2 receptor also stimulates MAP kinases, including extracellular signal-regulated kinase (ERK) 1 and 2 *(183–189)* and stress-activated protein kinase/Jun amino-terminal kinase (SAPK/JNK) *(185)*. D3 *(190)* and D4 *(189,191)* dopamine receptors also activate ERK1/2. D2-like receptors activate ERK1/2 in brain slices *(192,193)* and in the brain after administration of agonist in vivo *(194)*.

Although the pathway from D2-like receptors to activation of ERK1/2 has not been thoroughly described, and may differ depending on cell type, D2 receptor activation of ERK is frequently mediated by Gβγ *(183,187,188)*, phosphatidylinositol 3-kinase *(186,190)*, the small-molecular weight G protein Ras *(185,191)*, and the MAP kinase kinase MEK *(185,187,192,194)*. As for many other GPCRs, D2-like receptor signaling to MAP kinase pathways is in at least some cases mediated by transactivation of a receptor tyrosine kinase (RTK), thus recruiting the RTK signaling cascade in response to dopamine. Whereas the epidermal growth factor receptor has frequently been identified as an RTK that is transactivated by GPCRs *(195,196)*, transactivation of the platelet-derived growth factor receptor can be a necessary intermediate step in the activation of ERK1/2 by recombinant and endogenous D2 and D4 receptors *(189,197)*.

D2 receptor activation of ERK stimulates DNA synthesis and mitogenesis in many different cell types *(185,188,198,199)*. In postmitotic neurons, activation of MAP kinases is involved not only in cell survival and in synaptic plasticity *(200–202)*, but also in acute behavioral responses to dopamine receptor stimulation *(194)*. D2 receptor

signaling to ERK in pituitary lactotrophs may be more complicated; in both primary lactotrophs and a prolactin-secreting cell line, D2 receptors are reported to inhibit ERK1/2, leading to suppression of prolactin promoter function *(131)*. A conflicting report using a different prolactin-secreting cell line describes D2 receptor stimulation of ERK1/2 leading to inhibition of cell proliferation *(203)*.

Considerable data support D2-like receptor modulation of additional signaling pathways. D2 receptors in neostriatal large aspiny interneurons inhibit N-type Ca^{2+} channels by a membrane-delimited pathway that probably involves Gβγ, and that is postulated to mediate D2 receptor inhibition of acetylcholine release *(204)*. Voltage-dependent Ca^{2+} channels are also inhibited by D2 receptors in the anterior pituitary *(123)* and by the D3 receptor heterologously expressed in AtT-20 cells *(205)*; inhibition of Ca^{2+} channels in these cells would be expected to inhibit secretion of pituitary hormones. D2 receptors in neostriatal medium spiny neurons activate a cytosolic, Gβγ-stimulated form of phospholipase C, PLCβ1, causing calcium mobilization that activates calcium-dependent proteins, such as the protein phosphatase calcineurin *(206)*. The D2 receptor potentiates arachadonic acid release induced by calcium-mobilizing receptors in heterologous expression systems *(207,208)*, a response that is mediated by cytosolic phospholipase A_2 *(209)*. The D4 receptor also activates this pathway *(210)*. The D2 receptor stimulation of arachidonate has been reported to be insensitive to pertussis toxin and to be mediated by activation of protein kinase C *(207)*. These characteristics are shared by D2 receptor stimulation of phospholipase D, a response that may be mediated by interaction with a small–molecular weight G protein in the Rho family and activation of protein kinase Cε *(211)*. Heterologously expressed D2 *(212)*, D3 *(213,214)*, and D4 receptors *(210)* activate the Na^+/H^+ exchanger NHE1. Interestingly, this response, too, is insensitive to pertussis toxin in some cell lines *(212)*, as is the inhibition of Na^+/H^+ exchanger activity mediated by endogenous D2 receptors in primary lactotrophs *(215)*.

5.3. Modulation of Receptor Responsiveness

Altered dopamine receptor responsiveness has been implicated in the etiology, treatment, or treatment side effects of a variety of psychiatric, neurological, and endocrine disorders including schizophrenia, drug addiction, Parkinson's disease, Tourette syndrome, tardive dyskinesia, Huntington's chorea, and hyperprolactinemia, stimulating a tremendous amount of research on dopamine receptor regulation *(216)*. Although a comprehensive review of the topic is beyond the scope of this chapter, because of the importance of the phenomenon for the understanding of the role of dopamine in neuropsychiatric disorders, I will endeavor to provide a broad-brush treatment of the major characteristics of the regulation of dopamine receptor function and expression.

Most neurotransmitter receptors compensate for over- and understimulation with a reduction in responsiveness, or desensitization, and enhanced responsiveness, or supersensitivity, respectively *(217,218)*. In general, results from in vivo and in vitro studies of dopamine receptor regulation fit within this scheme. Denervation or chronic antagonism of D2-like dopamine receptors in vivo causes an increase in the density of the receptors, enhanced biochemical responsiveness, and behavioral supersensitivity to dopamine receptor agonists *(219–227)*. In vivo denervation or chronic antagonism also induces behavioral and biochemical supersensitivity of D1-like receptors and, in the case of

chronic antagonist treament, an increase in receptor number *(228–233)*, whereas the effect of denervation on D1 receptor density is more variable, with small decreases in receptor number being observed most frequently *(216)*. The lack of a consistent effect of denervation on D1 receptor density is one example of a broader mismatch between denervation-induced changes in dopamine receptor density and behavioral responsiveness. It is difficult to reconcile the unchanged or decreased density of D1 receptors and a 25–50% increase in the density of D2-like receptors with behavioral responsiveness to D1 or D2 receptor agonists that may be enhanced up to 40-fold after denervation *(234,235)*. One explanation for this discrepancy is that, rather than being a result of altered receptor density *per se*, most of the behavioral supersensitivity that is observed is due to a denervation- or antagonist-induced breakdown in the D1/D2 receptor synergism that, in the intact or untreated animal, requires stimulation of both receptor subtypes to obtain a functional response *(236)*.

Although treatment of intact rats with the dopamine precursor L-DOPA decreases D1 receptor-stimulated adenylate cyclase *(237)*, the effect of treatment with D1 receptor-selective agonists is less well understood. Chronic administration of the partial agonist SKF38393 has no effect on or increases the density of D1-like receptors in the intact animal, but decreases the density of receptors in a dopamine-depleted rat model *(238,239)*. The lack of a desensitization response in intact animals could be owing to the partial agonist nature of SKF38393; that treatment with a full D1 receptor agonist may cause behavioral tolerance *(240)* and internalization of D1 receptors *(241)* supports this hypothesis, although at least one study failed to find decreased receptor number after treatment with a full agonist *(233)*. Studies of the in vivo regulation of D2 receptors by agonists are also not in complete agreement. Two groups have described downregulation of neostriatal D2 receptors following chronic treatment with the D2 agonist quinpirole *(239,242)*, and some *(237,243)*, but not all *(244,245)*, have reported D2 receptor downregulation following repeated treatment with the partial agonist bromocriptine. Overall, the data suggest that agonist administration causes downregulation of D2 receptor expression in vivo *(216)*.

The D3 receptor represents an exception to the general model described above. Receptor expression in the basal forebrain is unaffected by D2-like receptor antagonist treatment, but is decreased by dopaminergic denervation *(246–248)*. Furthermore, chronic treatment with a D1-like agonist restores D3 receptor expression *(247,248)*, via increased striatal release of brain-derived neurotrophic factor (BDNF) *(249)*. BDNF regulates D3 receptor expression in the rat nucleus accumbens both during development and in adulthood *(249)*.

A variety of preparations have been used to demonstrate desensitization of D1 receptors in vitro *(216,250)*. Desensitization of D1-like receptors generally conforms to a model in which phosphorylation of the receptor (see subheading 3.2.3.) leads to rapid functional uncoupling of the receptor followed by β-arrestin-dependent sequestration or internalization and either dephosphorylation and resensitization or, after prolonged agonist treatment, downregulation and degradation of the receptors *(216)*. D1 receptor desensitization is mediated by both PKA and GRK2 *(75,251)*, with Thr268 in the third cytoplasmic loop being a site of phosphorylation by PKA *(76)* and Thr360 in the cytoplasmic tail a site of phosphorylation by GRK2 *(77)* (Fig. 1). The work of Jackson et al. *(252)* suggests that phosphorylation of residues distal to Thr360 in the cytoplasmic tail

also contributes to D1 receptor desensitization. The mechanisms of regulation of the D5 receptor appear to be similar to that of the D1 receptor *(253)*, except that the D5 receptor may normally exist in a partially desensitized condition as a result of the high constitutive activity of the receptor *(92)*.

Whereas downregulation of the D1 receptor is readily observed in cell lines, prolonged agonist treatment of cells expressing the D2 receptor generally does not decrease and often increases the density of receptors *(216,254)*. As for D1-like receptors, however, agonist activation of the D2 receptor leads to rapid phosphorylation of the receptor by GRK2 and/or GRK6, functional uncoupling including diminished inhibition of adenylate cyclase, sequestration of D2 receptors away from the surface of the membrane, and β-arrestin-dependent receptor internalization *(78,79,254–256)*. In contrast, the D3 receptor is only weakly phosphorylated and internalized *(78)*.

Functional desensitization of the D2 receptor, as measured by inhibition of adenylate cyclase, is typically modest and obscured by a more robust response that is a frequently described consequence of stimulation of $G\alpha_{i/o}$-coupled receptors: enhanced responsiveness of adenylate cyclase to activating stimuli, or heterologous sensitization *(257–259)*. Activation of D2 and D4 receptors, but not the D3 receptor, causes heterologous sensitization of adenylate cyclase *(213,258,260,261)*. D2 receptor mediated heterologous sensitization is detectable within minutes of stimulation by physiological concentrations of dopamine and other agonists and persists for some time after removing the agonist. In NS20Y neuroblastoma cells, D2 receptor-stimulated heterologous sensitization is mediated by $G\alpha_o$ *(127)*. As reviewed by Watts *(259)*, the pathway from $G\alpha_o$ to enhanced adenylate cyclase activity appears to involve $G\beta\gamma$ and a $G\alpha_s$-dependent facilitation of adenylate cyclase *(262,263)*. The characteristics of D2-like receptor-mediated heterologous sensitization suggest that it is likely to occur in vivo under conditions of prolonged overstimulation of the receptors, such as during cocaine binging, although whether heterologous sensitization of adenylate cyclase contributes to cocaine-induced behavioral sensitization is unknown.

6. DOPAMINE RECEPTOR PROTEIN–PROTEIN INTERACTIONS

6.1. Receptor Oligomerization

Evidence is accumulating that GPCRs exist as both homo- and hetero-oligomers of two or more individual GPCR monomers *(264,265)*. Several mechanisms of dimerization have been proposed, including domain swapping in which TM1-5, for example, from one GPCR monomer form a bundle with TM6-7 from another monomer, interreceptor disulfide bonds in the amino terminus, and interreceptor helix–helix interactions. There is also considerable disagreement on the function and regulation of receptor oligomers. There are data to support agonist-induced formation, agonist-induced dissociation, and constitutive existence of oligomers. Some of the disagreement is no doubt owing to differences in methods used, since each has weaknesses; for example, coprecipitation studies are subject to artefactual in vitro association of membrane proteins, whereas bioluminescence resonance energy transfer or fluorescence resonance enegy transfer studies may not be able to differentiate between association/dissociation of monomers and changes in receptor conformational states. Furthermore, there may be multiple mechanisms contributing to the formation of dimers and higher order multimers, and to the formation of homo- and hetero-oligomers, and it is likely that in some

cases apparent oligomerization reflects the interactions of two or more receptors with a scaffolding protein.

Considerable data indicate that at least some proportion of D1, D2, and D3 dopamine receptors exist as homo-oligomers *(69,266–273)*. Homodimerization has been proposed to alter the ligand binding characteristics of the D2 receptor *(266,268)*. Although the effect of TM6 and TM7 peptides on the presence of oligomers suggests a role for TM6-7 interhelix interactions in forming or stabilizing the D2 homo-oligomer *(266)*, recent cysteine cross-linking studies implicate the extracellular end of TM4 as the homodimer interface and also suggest that functional D2 receptors exist as constitutive dimers *(273)*. Similarly, that coexpression of nonfunctional mutant D2 receptors blocks the cell surface expression and function of the wildtype D2 receptor indicates that homodimerization is constitutive and necessary for expression of active receptor at the cell surface *(269)*. Hetero-oligomerization also occurs between the D3 receptor and its truncated splice variant D3nf *(267)*, with D3nf preventing trafficking of D3 to the cell membrane *(270)* or inhibiting ligand binding to the D3 receptor *(274)*, and between D2 and D3 receptors *(166)*. In the latter case, coexpression of D2 and D3 receptors in COS-7 cells with adenylate cyclase type 6 substantially increased the potency of 7-OH-DPAT for inhibition of cAMP accumulation, suggesting that the hetero-oligomer has increased potency for agonists and/or couples more efficiently to adenylate cyclase type 6.

Hetero-oligomers have also been described between dopamine receptors and other GPCRs, including the D2 receptor and the somatostatin receptor subtype SSTR5 *(275)*, the D2 and adenosine $A2_A$ receptors *(276)*, and the D1 and adenosine A1 receptors *(277)*, and between D1-like receptors and ion channel-coupled receptors *(278–280)*. The formation of hetero-oligomers is generally regulated by ligand binding, particularly agonists (but *see* ref. *280*), and typically serves to inhibit the function of at least one of the receptors in the complex (but *see* ref. *275*)

6.2. Receptor-Interacting Proteins

Another area of research that is rapidly expanding our view of how GPCRs function involves the identification and characterization of novel receptor-interacting proteins. GPCRs are defined by their interactions with heterotrimeric G proteins, and earlier I alluded to interactions of dopamine receptors with small-molecular weight G proteins, protein kinases, and β-arrestin, but it is now evident that many other GPCR–protein interactions regulate the trafficking and function of GPCRs *(281,282)*.

Interactions between the proximal cytoplasmic tail of the D1 receptor and the endoplasmic reticulum (ER) protein DRiP78 (*D*opamine *R*eceptor *i*nteracting *P*rotein of M_r *78*K) and γ-COP, a COPI golgi/ER-coated vesicle coatomer subunit, regulate transport of the receptor out of the ER *(283,284)*. DRiP78 binds to an FxxxFxxxF motif in the proximal C terminus that is shared by all dopamine receptor subtypes (Fig. 1) and many other GPCRs, whereas binding of γ-COP requires maintaining the hydrophobic face of the helix (helix 8) that is thought to run parallel to the membrane between the cytoplasmic end of TM7 and the palmitoylated cysteine residue (Fig. 1); thus, neither of these interactions is likely to be unique to the D1 receptor. The intermediate filament protein neurofilament-M binds to the third cytoplasmic loop of the D1 receptor. Overexpression of neurofilament-M in D1 receptor-expressing cells also causes the accumulation of D1

receptor in intracellular compartments, although it is not clear whether this is owing to reduced transport of newly synthesized receptor to the membrane or to constitutive internalization of functional membrane receptors. This interaction appears to be selective for D1-like receptors, as neurofilament-M binds weakly to the D5 receptor and not at all to D2, D3, or D4 receptors *(285)*. Association of the D1 receptor with protein phosphatase-1 may be involved in dephosphorylation and resensitization of the D1 receptor *(286)*, whereas binding of calcyon to residues 421–435 in the cytoplasmic tail of the D1 receptor promotes D1 receptor enhancement of $G\alpha_q$-coupled receptor-stimulated calcium mobilization, without altering the ability of the D1 receptor to stimulate cAMP accumulation *(157)* (*see* Subheading 5.2.1.).

D2 and D3 receptors, but not D1 or D4 receptors, bind the actin-binding protein filamin A, or ABP-280. Zhou and colleagues report that binding is to a segment in the carboxyl terminus of the third cytoplasmic loop, where both D2 and D3 receptors have a potential site of phosphorylation by PKC, and that D2 and D3 receptors expressed in cells that lack ABP-280 have diminished ability to inhibit adenylate cyclase *(287,288)*. Furthermore, PKC-catalyzed phosphorylation of the D2 receptor on Ser358 may inhibit binding of ABP-280, thus attenuating D2 receptor signaling *(287)*. In contrast, Lin et al. *(289)* report that ABP-280 binds to a segment toward the amino terminus of the third cytoplasmic loop, and that expression of ABP-280 is necessary for trafficking of D2 and D3 receptors to the cell surface *(289)*. The latter group has also described an interaction of D2 and D3 receptors with protein 4.1N and other members of the 4.1 family of cytoskeletal proteins; virtually the same binding site (amino terminus of the third cytoplasmic loop) and function (trafficking to the cell surface) has been attributed to the binding of 4.1N as to ABP-280/filamin A *(289,290)*. More recently, heart-type fatty acid binding protein (H-FABP) has been identified as a protein that binds to $D2_L$, but not $D2_S$, and thus selectively retains $D2_L$ in intracellular compartments in NG108-15 cells *(291)*.

In addition to the possible effect of ABP-280 binding on signaling to adenylate cyclase, other protein–protein interactions are likely to influence D2-like receptor signaling. The third cytoplasmic loop of the D2 receptor includes a binding site for spinophilin, a scaffolding protein that also binds and targets protein phosphatase-1 to dendritic spines *(292)*. Calmodulin binds in a calcium-dependent manner to the amino terminal end of the D2 receptor third cytoplasmic loop and inhibits D2 receptor activation of, but not binding to, $G\alpha_i$ *(293)*. Another EF-hand calcium-binding protein, neuronal calcium sensor-1 (NCS-1), binds to the proximal cytoplasmic tail of the D2 receptor to a region that overlaps the conserved DRiP78 and γ-COP binding sites identified in the D1 receptor *(294)*, although there is presumably no temporal overlap since the latter proteins bind during biosynthesis and transport, whereas NCS-1 interacts with the receptor at the cell surface. Overexpression of NCS-1 in D2 receptor-expressing cell lines attenuates agonist-induced internalization of the receptor *(294)*. NCS-1 also binds to D3 and D5 receptors, but not D1 or D4. Proteins, such as Nck, Grb2, and c-Src, that contain Src homology 3 (SH3) domains, a modular protein–protein interaction domain that is essential for the formation of functional signaling complexes, bind to the third cytoplasmic loop of the D4 receptor, which has multiple copies of the proline-rich SH3 binding motif *(295)*. Several SH3 domain-containing proteins also bind to the D3 receptor, although the site of binding has not been identified *(295,296)*. The functional role of SH3 protein binding to D2-like receptors is unknown, although mutation of the SH3 binding motifs in the D4

receptor causes constitutive internalization of the receptor *(296)*, and binding of the protein tyrosine kinase c-Src to other GPCRs has important consequences for receptor signaling and desensitization *(297,298)*. As discussed in Subheading 5.2.2., D2 and D4 receptors form stable complexes with GIRK potassium channels *(138)*. The formation of large multiprotein complexes that include GPCRs and their effectors may be a general characteristic of GPCR signaling *(299)*.

7. DOPAMINE RECEPTOR VARIANTS

There are numerous polymorphisms of the dopamine receptor genes that are in introns or otherwise outside the coding region, or that are synonymous single nucleotide polymorphisms *(27,300)*. Although such polymorphisms may affect gene transcription or message stability and translation *(301,302)*, and have been useful in exploring genetic relationships between neuropsychiatric disorders and dopamine receptors *(303,304)*, a review of this area is outside the scope of this chapter. Instead, I will provide a brief overview of structural variants that result from alternative RNA splicing (*see also* Chapter 2) or from nonsynonymous sequence polymorphisms within coding exons.

7.1. Splice Variants

The $D2_L$ and $D2_S$ splice variants of the D2 receptor, generated by alternative splicing of an 87-nucleotide exon that encodes 29 residues in the third cytoplasmic loop of $D2_L$, were the first GPCR splice variants to be identified *(28–31)*. Most tissues express both variants, with $D2_L$ being most abundant. Because of the location of the alternatively spliced insert in the third cytoplasmic loop, where a direct effect on the binding of ligands would not be expected, many comparisons of $D2_L$ and $D2_S$ have focused on identifying the G protein subtypes that are activated by each splice variant. As reviewed in detail elsewhere *(46,122)*, there is considerable evidence that $D2_L$ and $D2_S$ differ in the efficiency with which they bind to and activate different Gα subunits, but little agreement in the literature concerning the specific Gα subunits activated by each variant. Factors that could influence G protein selection to produce disparate results include the signaling pathway being examined, the relative abundance of Gα subtypes in a given tissue, the abundance of particular Gβγ subtypes, the presence of appropriate effectors *(137)*, and the choice of agonist used to activate the receptor *(128)*.

Recent studies of two independently generated lines of mice that express only $D2_S$ have provided intriguing evidence for functional differences between $D2_L$ and $D2_S$. In both lines of $D2_L$ null mutant mice, responses to D2 receptor agonists that are thought to be mediated by dopamine autoreceptors are spared or enhanced compared to wildtype mice. These autoreceptor-mediated responses include inhibition of locomotor activity by low doses of agonists, agonist inhibition of nigral cell firing, inhibition of dopamine release, and inhibition of tyrosine hydroxylase phosphorylation at Ser40 *(305–308)*. These studies show only that D2S *can* function as an autoreceptor, whereas if $D2_S$ null mutant mice are found to lack autoreceptor function that will be compelling support for the idea that $D2_S$ *normally* serves as the autoreceptor, but the latter hypothesis is supported by the observation that, in nonhuman primates, $D2_S$ is the predominant variant in dopaminergic neurons, whereas $D2_L$ is more abundant in neurons innervated by dopamine pathways *(309)*. Interestingly, $D2_L$ null mutant mice show deficits in behaviors mediated by postsynaptic D2 receptors: haloperidol-induced catalepsy and spontaneous

Table 3
DNA Sequence Polymorphisms of the Human Dopamine Receptors

Receptor	Polymorphism	Location	Reference
D2	Val96→Ala	TM2	*319*
	Pro310→Ser	IC3	*319*
	Ser311→Cys	IC3	*355*
D3	Ser9→Gly, creates *Bal*I/*Msc*I RFLP	NT	*322*
D4	Gly11→Arg	NT	*328*
	12-bp repeat in exon 1	NT	*327*
	21-bp deletion in exon 1	TM1	*329*
	13-bp deletion in exon 1	TM2	*328*
	Val194→Gly	TM5	*330*
	48 bp repeat in exon 3	IC3	*323–325*
D5	Leu88→Phe	TM2	*317*
	Ala269→Val	IC3	*316,317*
	Pro330→Gln	EC3	*316,317*
	Cys-335→stop	EC3	*316,317*
	Asn351→Asp	TM7	*316,317*
	Ser453→Cys	CT	*316,317*

or agonist-induced locomotor activity *(305,306)*. Furthermore, D2 receptor inhibition of D1 receptor-stimulated phosphorylation of DARPP-32, a response central to the postsynaptic actions of dopamine, is absent in $D2_L$ null mutant mice *(308)*. Not all nonautoreceptor-mediated responses require $D2_L$, however, because dopamine-dependent inhibition of neostriatal GABA transmission, lost in D_2-null mutant mice, is spared in the mice lacking only $D2_L$ *(310)*, as are certain quinpirole-induced stereotyped behaviors *(311)*.

Several variants of the human D3 receptor result from alternative splicing of exon 2 *(312,313)* or exon 3 *(313,314)*, as well as from cleavage of an atypical 3′ splice site, deleting a portion of exon 6 *(315)*. All are frame-shifted variants with D3 receptor sequence through the first two transmembrane segments, through the the first three transmembrane segments, or through the first five transmembrane segments, respectively; thus, none would be expected to function as a GPCR. Nevertheless, a protein-encoded by the latter variant, $D3_{nf}$, is expressed in brain *(315)*, and $D3_{nf}$ or any other truncated receptor variant could serve to regulate the expression of the full-length receptor *(267)*. No splice variants have been described for the D4 receptor. As they are encoded by genes that lack introns within the coding region, the D1 and D5 receptors also have no splice variants.

7.2. Allelic Variants

No DNA sequence polymorphisms have been identified that alter the coding sequence of the D1 receptor. The D5 receptor, however, has several nonsynonymous single nucleotide polymorphisms (SNPs) that are summarized in Table 3, including a nonsense change that would result in truncation of the protein between TM6 and TM7, the substitution of Asp for the highly conserved residue $Asn351^{7.45}$, and the substitution of Phe for

Leu88$^{2.51}$ *(316,317)*, adjacent to the highly conserved aspartic acid residue in TM2 that participates in a sodium-binding pocket in the D2 receptor *(318)*. Both of the missense changes in the transmembrane regions have modest effect on D5 receptor affinity for ligand *(317)*.

The human D2 receptor has three nonsynonymous SNPs: a substitution of Ala for Val96$^{2.66}$ and two adjacent substitutions in the third cytoplasmic loop *(319)*. Each of these substitutions has modest effects on ligand potency *(320)*. The two cytoplasmic loop substitutions also decrease the ability of the D2 receptor to inhibit cAMP accumulation *(321)*. The human D3 receptor has one nonsynonymous SNP in which a glycine residue replaces Ser9 in the amino terminus *(322)*.

The human D4 receptor has numerous allelic variants as a result of the presence of an imperfect tandem repeat of 48 nucleotides (16 amino acids) in the third cytoplasmic loop of the receptor *(323)*. At least 19 different repeat units (i.e., 19 different nucleotide sequences) encoding 10 different amino acid sequences have been identified. The order and number of copies of the repeat units can vary, so the potential number of alleles is large; 27 unique DNA sequence variants encoding 20 different amino acid sequences have been identified *(324,325)*. The functional significance of the allelic variants is still in question. When expressed in cells, differences among the allelic variants in terms of affinity for ligands, responsiveness to agonists, and coupling to G proteins are small or nonexistent *(139,261,325,326)*. As the SH3 binding region of the D4 receptor overlaps with the 48 bp repeats, so that the variants have differing numbers of SH3 binding motifs, it is possible that the variants will be found to participate in distinct SH3-dependent protein:protein interactions *(42)*. The D4 receptor also has a 12 bp sequence (Ala-Ser-Ala-Gly) in the amino terminus immediately extracellular to TM1 that is repeated perfectly in the most common variant of the receptor, but occurs only once in the rarer allele *(327)*. Two additional sequence polymorphisms consist of 21 and 13 bp deletions in TM1 and TM2, respectively (Table 3). The 21-bp deletion removes residues Ala36$^{1.34}$ to Val42$^{1.40}$ *(328)*. The 13-bp deletion interrupts TM2 at Ala99$^{2.48}$; because this frame-shifted variant has only one complete membrane-spanning domain it is predicted to be a null (nonfunctioning) allele *(329)*. Finally, one D4 variant has a Gly substitution for Val194$^{5.40}$ *(330)*. The Gly194 variant may also be a null allele, as it has reduced affinity for dopamine and a number of D2-like receptor antagonists and may be unable to inhibit cAMP accumulation *(331)*.

8. CONCLUSIONS

The aim of this chapter was to present background information on dopamine receptors that would provide a context within which the reader can evaluate the evidence for a contribution of dopamine to the neuropsychiatric disorders that are reviewed elsewhere in this volume. Because of this limited aim, and the space restrictions inherent in that aim, there are many important research areas, such as elucidating the structural basis of dopamine receptor function, characterizing dopamine receptor knockout mice, and determining the distinct functional roles of the dopamine receptor subtypes, that are described in only a narrow context or omitted entirely. In some areas where disagreement exists in the literature, it has not been feasible to give appropriate consideration to all points of view. In other research areas, work is advancing at such a pace that sections of this chapter are certain to be outdated by the time of publication. In particular, I predict

that a similar chapter written several years from now would have much more specific information about the mechanisms and function of protein–protein interactions involved in dopamine receptor function, from receptor oligomerization to interactions with G proteins to novel interactions with scaffolding and signaling proteins. Finally, and perhaps most relevant for the topic of this book, it seems likely that the insights gained from the confluence of work using increasingly selective drugs and transgenic and null mutant mice, including inducible and targeted mutations, will enhance our understanding of the behavioral roles of dopamine receptor subtypes and of how selectively manipulating the function of specific subtypes can be useful for the treatment of neuropsychiatric disorders

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