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Dopamine Receptors: From Structure to Function

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Missale, Cristina, S. Russel Nash, Susan W. Robinson, Mohamed Jaber, and Marc G. Caron. Dopamine Receptors: From Structure to Function. *Physiol. Rev.* 78: 189–225, 1998.—The diverse physiological actions of dopamine are mediated by at least five distinct G protein-coupled receptor subtypes. Two D_1-like receptor subtypes (D_1 and D_5) couple to the G protein G_s and activate adenylyl cyclase. The other receptor subtypes belong to the D_2-like subfamily (D_2, D_3, and D_4) and are prototypic of G protein-coupled receptors that inhibit adenylyl cyclase and activate K^+ channels. The genes for the D_1 and D_5 receptors are intronless, but pseudogenes of the D_5 exist. The D_2 and D_3 receptors vary in certain tissues and species as a result of alternative splicing, and the human D_4 receptor gene exhibits extensive polymorphic variation. In the central nervous system, dopamine receptors are widely expressed because they are involved in the control of locomotion, cognition, emotion, and affect as well as neuroendocrine secretion. In the periphery, dopamine receptors are present more prominently in kidney, vasculature, and pituitary, where they affect mainly sodium homeostasis, vascular tone, and hormone secretion. Numerous genetic linkage analysis studies have failed so far to reveal unequivocal evidence for the involvement of one of these receptors in the etiology of various central nervous system disorders. However, targeted deletion of several of these dopamine receptor genes in mice should provide valuable information about their physiological functions.

I. INTRODUCTION

Dopamine (DA) is the predominant catecholamine neurotransmitter in the mammalian brain, where it controls a variety of functions including locomotor activity, cognition, emotion, positive reinforcement, food intake, and endocrine regulation. This catecholamine also plays multiple roles in the periphery as a modulator of cardiovascular function, catecholamine release, hormone secretion, vascular tone, renal function, and gastrointestinal motility.

The dopaminergic systems have been the focus of much research over the past 30 years, mainly because several pathological conditions such as Parkinson's disease, schizophrenia, Tourette's syndrome, and hyperprolactinemia have been linked to a dysregulation of dopaminergic transmission. Dopamine receptor antagonists have been developed to block hallucinations and delusions that occur in schizophrenic patients, whereas DA receptor agonists are effective in alleviating the hypokinesia of Parkinson's disease. However, blockade of DA receptors can induce extrapyramidal effects similar to those resulting from DA depletion, and high doses of DA agonists can cause psychoses. The therapies of disorders resulting from DA imbalances are thus associated with severe side effects.

One of the challenges of the last 10 years has thus been to discover selective dopaminergic drugs devoid of adverse effects. This effort has led to the development of a number of new therapeutic agents that, although they have not resolved the etiology of the clinical problems, have contributed to increase our understanding of the dopaminergic system.

A new impetus to the search in the DA field came from the application of gene-cloning procedures to receptor biology one-half a decade ago, which revealed a higher degree of complexity within DA receptors than previously thought. The complementary DNAs of five distinct DA receptor subtypes (D_1-D_5) have been, in fact, isolated and characterized. This approach produced a wealth of information regarding the structure of these receptor proteins and provided the tools to precisely define their distribution in the central nervous system (CNS) and in the periphery, to express the receptors in host cells and characterize their pharmacology, and to evaluate the possible linkage of receptor genes to specific disorders. The application of in situ hybridization and polymerase chain reaction (PCR) with the newly cloned receptor probes made it possible to localize DA receptors to specific brain regions or peripheral tissues even where they had not been anticipated before. The function of many of these receptors, however, is still completely unknown, thus highlighting a serious gap between the molecular biology and the functional approaches.

A classical key requirement to elucidate the functional role of individual receptor subtypes is the identification of selective agonists and antagonists. Pharmacological manipulations have, in fact, partially clarified the role of D_1 and D_2 receptors in the control of various functions as well as the interaction of DA with other neurotransmitter systems. The specific structure-activity requirements necessary for compounds to be selectively active at each receptor subtype, on the other hand, are still unknown for the novel DA receptors so that drugs able to completely discriminate D_3, D_4, and D_5 receptor subtypes are not yet available. This drawback, together with the fact that the new receptor subtypes are expressed in lower amounts than the D_1 and D_2, has limited so far our possibility to understand their function.

Gene targeting using homologous recombination to inactivate a chosen gene has been developed in the last few years, and its application to DA receptor biology has provided an invaluable tool to investigate the function of each receptor subtype. This approach has been already used in the case of D_1 and D_2 DA receptors. Inactivation of these genes produced phenotypes in mice resembling those observed with specific pharmacological manipulations. Targeted inactivation of other members of the DA receptor family should thus be helpful, by overcoming the lack of specific ligands, to define their physiological functions.

In this paper, we review some features shared by the DA receptors, as well as those that make each unique. A special emphasis is given to their distribution, second messenger coupling, and function in the CNS and peripheral tissues. The pathological and therapeutic implications of DA receptor diversity are also analyzed.

II. CLASSIFICATION OF DOPAMINE RECEPTORS

The first evidence for the existence of DA receptors in the CNS came in 1972 from biochemical studies showing that DA was able to stimulate adenylyl cyclase (AC) (reviewed in Ref. 226). In 1978, DA receptors were first proposed, on the basis of pharmacological and biochemical evidence, to exist as two discrete populations, one positively coupled to AC and the other one independent of the adenosine 3′,5′-cyclic monophosphate (cAMP)-generating system (424). It was shown, in fact, that in the pituitary DA inhibited prolactin secretion but did not stimulate cAMP formation (59; reviewed in Ref. 226) and that although the antipsychotic drug sulpiride was a DA antagonist when tested in the anterior pituitary, it was not able to block the striatal DA-sensitive AC (reviewed in Refs. 226, 424). In 1979, Kebabian and Calne (226) summarized these observations and suggested to call D_1 the receptor that stimulated AC and D_2 the one that was not coupled to this effector.

Subsequent studies confirmed this classification scheme, and D_1 and D_2 receptors were clearly differentiated pharmacologically, biochemically, physiologically, and by their anatomic distribution.

Concurrently in the late 1970s, by means of functional tests such as renal blood flow and cardiac acceleration measurements in the dog, the existence of specific peripheral receptors for DA was demonstrated. These receptors were named DA_1 and DA_2 on the basis of some pharmacological properties distinguishing them from their central counterparts (reviewed in Ref. 166). This led to a long-standing controversy concerning the identity or nonidentity of peripheral versus central receptors. However, subsequent biochemical and molecular biology studies in peripheral tissues pointed to extensive similarities between central and peripheral DA receptors so that the DA_1/DA_2 classification has been dropped (reviewed in Refs. 7, 307, 326, 336).

For a decade, the dual receptor concept served as the foundation for the study of DA receptors. However, after the introduction of gene cloning procedures, three novel DA receptors subtypes have been characterized over the past five years. These have been called D_3 (420), D_4 (450), and D_5/D_{1b} (431, 441).

Detailed structural, pharmacological, and biochemical studies pointed out that all DA receptor subtypes fall into one of the two initially recognized receptor categories. The D_1 and D_5/D_{1b} receptors share, in fact, a very high homology in their transmembrane domains. Similarly, the transmembrane sequences are highly conserved among D_2, D_3, and D_4 receptors (reviewed in Refs. 78, 159, 217, 401, 421). Pharmacologically, although the profiles of D_1 and D_2 receptors are substantially different, the D_5/D_{1b} receptor exhibits the classical ligand-binding characteristics of D_1 receptors, and the D_3 and D_4 receptors bind the hallmark D_2-selective ligands with relatively high affinity (reviewed in Refs. 78, 159, 217, 401, 421). In addition, the initial distinction between D_1 and D_2 receptors in terms of signaling events, that is, positive and negative coupling to AC, appears to apply, in broad terms, also to the novel members of the DA receptor family, the D_5/D_{1b} receptor being coupled to stimulation of AC (95, 169, 431, 441) and the D_3 (75, 287, 360, 377) and D_4 receptors (74, 80, 287, 290, 438) to inhibition of cAMP formation.

The D_1/D_2 classification concept developed in the late 1970s thus is still valid, and D_1 and D_5/D_{1b} receptors are classified as D_1-like and D_2, D_3, and D_4 receptor subtypes as D_2-like. The mammalian D_{1b} receptor, originally named on the basis of its high homology with the D_1 receptor, is now commonly referred to as the D_5 receptor.

III. GENE STRUCTURE

The D_2 receptor cDNA was first isolated in 1988 (47) and subsequently, in 1989, the existence of splice variants of this receptor was demonstrated (91, 162, 315). The D_3 receptor was identified by screening a rat cDNA library with the D_2 receptor sequence followed by PCR extension and genomic library screening (420). The D_4 receptor was cloned by screening a library from the human neuroblastoma cell line SK-N-MC (450).

The D_1 receptor was cloned by using either low-stringency screening of libraries or PCR based on the sequence of the D_2 receptor (95, 314, 480). The second member of the D_1-like receptor family was isolated using the sequence of the D_1 receptor and was referred to as D_5 (431), D_{1b} (441) and $D_{1\beta}$ (464). It is now well established that the D_5 and D_{1b} are the human and rat equivalents of the same receptor.

The genomic organization of the DA receptors supports the concept that they derive from the divergence of two gene families that mainly differ in the absence or the presence of introns in their coding sequences. As summarized in Table 1, the D_1 and D_5 receptor genes do not contain introns in their coding regions (reviewed in Refs. 78, 159, 337), a characteristic shared with most G protein-coupled receptors (112). In contrast, and by analogy with the gene for rhodopsin (327), the genes encoding the D_2-like receptors are interrupted by introns (reviewed in Refs. 78, 159, 337). It appears likely that many of the genes in the G protein-coupled receptor family have arisen from a single primordial gene, suspected to be one of the opsin genes, that lost its introns by a gene-processing event (reviewed in Ref. 337). Two main evolutionary mechanisms may have created and amplified the molecular diversification within the two gene families: *1*) gene duplication mechanisms that gave rise to different, but nevertheless similar, sister genes encoding receptor subtypes or pseudogenes and *2*) speciation that originated species homologs and the development of genetic polymorphism that provided receptor variants found in individuals within the same species (reviewed in Ref. 452).

Analysis of the gene structure of D_2-like receptors revealed that the D_2 receptor coding region contains six introns (91, 162, 168, 315), the D_3 receptor coding region five (420), and the D_4 receptor three (450). Interestingly, the localization of introns is similar in the three receptor genes and in the opsin gene. The D_3 receptor lacks the fourth intron of the D_2, and the D_4 receptor lacks the third and fourth introns of the D_2. The third intron of the D_4 gene has an unusual intron/exon junction in which the conventional splice junction donor and acceptor sites are missing (450, 451).

The presence of introns within the coding region of D_2-like receptors allows the generation of receptor variants. Indeed, the D_2 receptor has two main variants, called D_{2S} and D_{2L}, which are generated by alternative splicing of a 87-bp exon between introns 4 and 5 (91, 162, 315; reviewed in Ref. 159). Splice variants of the D_3 receptor encoding nonfunctional proteins have been also identified

TABLE 1. *Molecular characteristics of dopamine receptors*

	D_1-Like		D_2-Like			
			D_2			
	D_1	D_5	D_{2S}	D_{2L}	D_3	D_4
Amino acids	446 (r)	475 (r)	415 (r)	444 (r)	446 (r)	387–515 (h)*
	446 (h)	477 (h)	414 (h)	443 (h)	400 (h)	385 (r)
Amino acids in 3rd cytoplasmic loop	57 (r)	50 (r)	135 (r)	444 (r)	166 (r)	101–261 (h)*
	57 (h)	50 (h)	134 (h)	443 (h)	120 (h)	106 (r)
Amino acids in COOH terminal	113 (r)	117 (r)	16 (r)		16 (r)	18 (r)
	113 (h)	116 (h)	16 (h)		16 (h)	18 (h)
Introns	0†	0†	6		5	3
Chromosomal localization	5q 35.1	4p 15.1–16.1	11q 22–23		3q 13.3	11p 15.5

r, Rat; h, human. * Number of amino acids in human D_4 receptor depends on number of repeats in 3rd intracellular loop. † An intrinsic sequence has been described in 5′-untranslated region of both D_1 and D_5 receptors.

(137, 161, 418). Analysis of the gene for the human D_4 receptor revealed the existence of polymorphic variations within the coding sequence. A 48-bp sequence in the third cytoplasmic loop exists either as a direct repeat sequence, as a fourfold repeat, or a sevenfold repeat. D_4 receptors containing up to 11 repeats have been found (451).

The D_5 receptor has two related pseudogenes on human chromosomes 1 and 2. They are 98% identical to each other and 95% identical to the human D_5 receptor and code for truncated, nonfunctional forms of the D_5 receptor (169, 464).

IV. STRUCTURE OF DOPAMINE RECEPTORS

Analysis of the primary structure of the cloned DA receptors revealed that they are members of the seven transmembrane (TM) domain G protein-coupled receptor family and share most of their structural characteristics (Fig. 1). Members of this family display considerable amino acid sequence conservation within TM domains (reviewed in Ref. 362).

Analysis of DA receptor structure pointed to similarities and dissimilarities between D_1-like and D_2-like receptors (78, 159, 217, 337). Members of the same family share considerable homology. The D_1 and D_5 receptors share a 80% identity in their TM domains. The D_2 and D_3 receptors have a 75% identity in their TM domains, and the D_2 and D_4 receptors share a 53% identity in the TM domains.

The NH_2-terminal stretch has a similar number of amino acids in all the receptor subtypes and carries a variable number of consensus *N*-glycosylation sites. The D_1 and D_5 receptors possess two such sites, one in the NH_2 terminal and the other one in the second extracellular loop. The D_2 receptor has four potential glycosylation sites, the D_3 has three, and the D_4 possesses only one (reviewed in Refs. 78, 159, 217, 337).

The COOH terminal is about seven times longer for the D_1-like receptors than for the D_2-like receptors, is rich in serine and threonine residues, and contains a cysteine residue that is conserved in all G protein-coupled receptors and that has been shown to be palmitoylated in the β-adrenergic receptors and in rhodopsin probably to anchor the cytoplasmic tail to the membrane (338, 347). In the D_1-like receptors, this cysteine residue is located near the beginning of the COOH terminus, whereas in the D_2-like receptors, the COOH terminus ends with this cysteine resi-

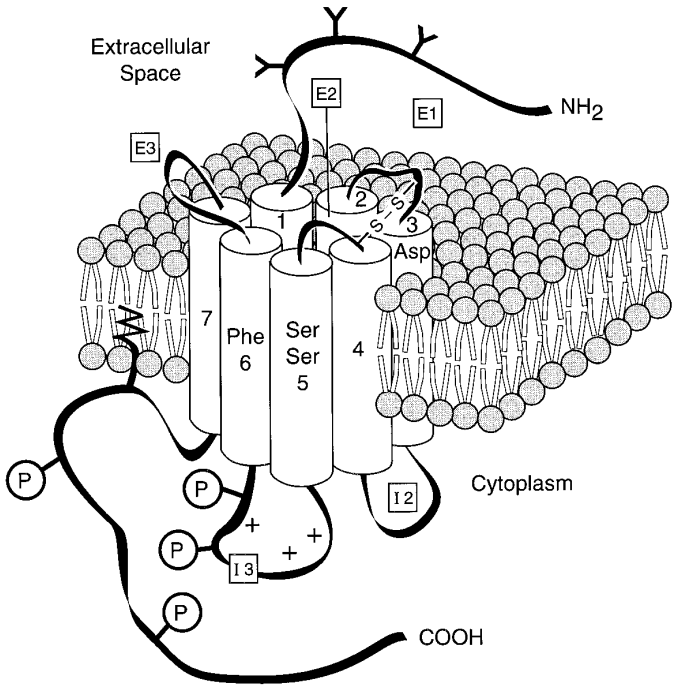

FIG. 1. Dopamine receptor structure. Structural features of D_1-like receptors are represented. D_2-like receptors are characterized by a shorter COOH-terminal tail and by a bigger 3rd intracellular loop. Residues involved in dopamine binding are highlighted in transmembrane domains. Potential phosphorylation sites are represented on 3rd intracellular loop (I3) and on COOH terminus. Potential glycosylation sites are represented on NH_2 terminal. E1-E3, extracellular loops; 1–7, transmembrane domains; I2-I3, intracellular loops.

due (Fig. 1). Likewise, as in all G protein-coupled receptors, DA receptors possess two cysteine residues in extracellular loops 2 and 3 (reviewed in Refs. 78, 159, 217, 337), which have been suggested to form an intramolecular disulfide bridge to stabilize the receptor structure (111, 142). The D_2-like receptors have a long third intracellular loop, a feature which is common to receptors interacting with G_i proteins to inhibit AC, whereas the D_1-like receptors are characterized by a short third loop as in many receptors coupled to G_s protein (reviewed in Refs. 78, 159, 337).

The D_1 and D_5 receptor third intracellular loop and the COOH terminus are similar in size but divergent in their sequence. In contrast, the small cytoplasmic loops 1 and 2 are highly conserved so that any difference in the biology of these receptors can be probably related to the third cytoplasmic loop and the COOH-terminal tail (reviewed in Refs. 78, 159, 337). The external loop between TM4 and TM5 is considerably different in the two receptor subtypes, being shorter (27 amino acids) in the D_1 receptor than in the D_5 receptor (41 amino acids). The amino acid sequence of this loop, in addition, is divergent in the D_5 and in its rat counterpart D_{1b} (431, 441).

Site-directed mutagenesis for catecholamine receptors (233, 426, 427) and protein modeling with the β_2-, α_2-, and D_2 receptors (189, 190, 443) suggested that the agonist binding likely occurs within the hydrophobic TM domains (Fig. 1). Highly conserved residues are present in the core of the protein and define a narrow binding pocket that most probably corresponds to the agonist binding site (190). In particular, an aspartate residue in TM3 is most probably involved in binding the amine group of the catecholamine side chain (190, 427). Two serine residues in TM5 have been shown to be hydrogen bond donors to bind the hydroxyl groups of the catechol moiety for the β_2- (426), α_2- (458), D_2 (85, 282), and D_1 (442) receptors. A phenylalanine in TM6 is highly conserved in all receptors interacting with catecholamine neurotransmitters and can make a stabilizing orthogonal interaction with the aromatic moiety of the ligand. A highly conserved aspartate residue in TM2 has been shown to play a crucial role in β_2-adrenergic (77, 190, 427), α_2-adrenergic (458), and D_1 (442) and D_2 dopaminergic (328) receptor activation and to affect agonist binding (190, 414, 442). It has been suggested that the interaction between this aspartate and the agonist is allosteric and can be modulated by Na^+ or H^+ (189, 196, 328). A number of cytoplasmic residues, such as the DRY sequence in the second intracellular loop or the alanine residue in the third intracellular loop of the α-adrenoceptor, also play a role in receptor activation (233, 427).

V. RECEPTOR VARIANTS

A. D_2 Receptor

The D_2 receptor exists as two alternatively spliced isoforms differing in the insertion of a stretch of 29 amino acids in the third intracellular loop (D_{2S} and D_{2L}) (91, 162, 315). Because this loop seems to play a central role in receptor coupling, the existence of a splicing mechanism at this level could imply functional diversity. However, in spite of the efforts of several groups, no obvious differences have emerged so far between the two D_2 receptor isoforms. Both variants share the same distribution pattern, with the shorter form less abundantly transcribed (91, 162, 315, 328). Both isoforms revealed the same pharmacological profile, even if a marginal difference in the affinity of some substituted benzamides has been reported (66, 278). When expressed in host cell lines, both isoforms inhibited AC (91, 162, 315). However, the D_{2S} receptor isoform displayed higher affinity than the D_{2L} in this effect (91, 317). Both isoforms mediate a phosphatidylinositol-linked mobilization of intracellular calcium in mouse Ltk^- fibroblasts. Protein kinase C (PKC), however, differentially modulates D_{2S}- and D_{2L}-activated transmembrane signaling in this system with a selective inhibitory effect on the D_{2S}-mediated response (265). Attempts to identify the preferred G protein α-subunit for D_{2S} and D_{2L} have led to conflicting results. One group suggested, in fact, that the 29-amino acid insertion in the D_{2L} receptor directs its interaction with $G_{i\text{-}2}\alpha$ (175, 318), whereas another report showed that in transfected cell lines the D_{2S} isoform signals preferentially through $G_{i\text{-}2}\alpha$ and the D_{2L} through $G_{i\text{-}3}\alpha$ (405). The two receptor variants, in addition, appear to differ in their mode of regulation (240, 283, 479).

B. D_3 Receptor

Splice variants of the D_3 receptor have also been identified. One transcript carries a 113-bp deletion in TM3 and a frame shift in the coding sequences generating a stop codon shortly after the deletion and encodes a 100-amino acid-long truncated form of the receptor (418). A second variant derives from a deletion of 54 bp between TM5 and TM6 of the D_3 receptor. Although this structure may be compatible with the occurrence of seven transmembrane domains, cell lines transfected with this cDNA failed to show any binding (161). Two alternatively spliced forms of the D_3 receptors have been identified in the mouse (137), but not in other species (161). These differ by a stretch of 21 amino acids in the third intracellular loop and are generated by a splicing mechanism that uses an internal acceptor site inside an exon, rather than a separate exon like the D_2 receptor. Both isoforms bind dopaminergic ligands with a D_3 pharmacological profile and have the same distribution pattern with the longer form predominant (137).

C. D_4 Receptor

Analysis of the deduced amino acid sequence of the D_4 receptor reveals that it is the most distantly related of

TABLE 2. *Pharmacological profile of dopamine receptors*

	D_1-Like		D_2-Like		
	D_1	D_5	D_2	D_3	D_4
Antagonists					
(+)-Butaclamol	+++	++	+++	ND	++
Chlorpromazine	+	+	+++	++	++
Clozapine	+	+	+	+	++
Eticlopride	−	−	++++	ND	+++
Haloperidol	+	+	++++	++	+++
Nafadotride	ND	ND	+++	++++	+/−
Nemonapride	ND	ND	++++	++++	++++
Raclopride	−	ND	+++	+++	+/−
SCH-23390	++++	++++	+/−	+/−	+/−
(−)-Sulpiride	−	−	++	++	++
Spiperone	+	+/−	++++	+++	++++
Agonists					
Apomorphine	+/−	+	+++	++	+++
Bromocriptine	+	+	+++	+++	+
Dopamine	+/−	+	+	++	++
Fenoldopam	+++	+++	++	ND	+
7-OH-DPAT	+/−	ND	++	+++	+/−
Quinpirole	−	ND	+/−	++	++
SKF-38393	+++	++++	+	+/−	+/−

++++, Inhibition constant (K_i) <0.5 nM; +++, 0.5 nM < K_i < 5 nM; ++, 5 nM < K_i < 50 nM; +, 50 nM < K_i < 500 nM; +/−, 500 nM < K_i < 5 μM; −, K_i >5 μM; ND, not determined; 7-OH-DPAT, 7-hydroxy-dipropylaminotetralin.

the D_2-like receptors. In human polymorphic variants, the D_4 receptor exists with different insertions in the third intracellular loop. This loop contains repeat sequences of 16 amino acids with the number of repeats differing in the different forms of the receptor. The four-repeat form ($D_{4.4}$) is the predominant in the human population (60%). The $D_{4.7}$ variant is present in 14% of the population and the $D_{4.2}$ in 10% (401, 451). Receptor forms with up to 10 repeats have also been identified but are much less frequent (401). The functional significance of these variants has not been elucidated. They display a slightly different affinity for the neuroleptic clozapine, but none of them has been related to an increased incidence of schizophrenia (401, 451).

VI. PHARMACOLOGICAL PROPERTIES OF DOPAMINE RECEPTORS

Although the pharmacological profiles of D_1-like and D_2-like receptors are substantially different, the main pharmacological differences described so far within each receptor subfamily are only represented by a variable shift in the affinity of certain agonists and antagonists (Table 2).

So far, it has not been possible to pharmacologically differentiate D_1 and D_5 receptors. The sensitivities of these two receptor subtypes to antagonists are similar. Nevertheless, these compounds generally show a slightly higher affinity for the D_1 than for the D_5, with (+)-butaclamol as the most discriminating (Table 2) (401, 441). The affinity of agonists at D_1 and D_5 receptors is almost identical. The most consistent difference is represented by DA itself, which has ~10 times higher affinity for the D_5 than the D_1 (Table 2) (431, 441). Cell lines expressing the D_5/D_{1b} receptor show a higher basal AC activity than those expressing the D_1 (440). This property, together with the observations that DA has a higher affinity for the D_5 than for the D_1 receptor and that some antagonists display negative efficacy at the D_5, but not at the D_1, make the D_5 receptor similar to various mutated G protein-coupled receptors that exhibit constitutive activity (250, 386). Functionally, whether the D_5 receptor represents a naturally occurring constitutively active counterpart of the D_1 receptor remains to be clarified.

Analysis of the pharmacological profiles of D_2-like receptors shows that there are no compounds that discriminate between the short and the long variants of the D_2 receptor. A marginal difference in the affinities of sulpiride and raclopride for the two isoforms has been described (66, 278). With respect to the D_3 and D_4 receptors, it has been shown that although they bind hallmark D_2-selective ligands with high affinity, nevertheless both of these receptors have distinguishing pharmacological characteristics (Table 2).

The pharmacological profile of the D_3 receptor reveals that some agonists and antagonists can distinguish it from the D_2. Dopamine itself has 20 times higher affinity at the D_3 than at the D_2 receptor (420), and this has been related in part to their sequence differences in the third intracellular loop (378). Among agonists, although apomorphine and bromocriptine display similar affinities for both receptors, TL-99, pergolide, quinpirole, and 7-hydroxy-dipropylaminotetralin (7-OH-DPAT) bind with higher affinity at the D_3 than at the D_2. Quinpirole and 7-OH-DPAT are the most discriminating compounds, with affinities 100 and 10 times higher than at the D_2, respectively (Table 2) (420). Most neuroleptics display nanomolar affinity at both receptors. However, haloperidol and spiperone show 10- to 20-fold higher affinity at the D_2 than at the D_3, whereas (−)-sulpiride, clozapine, and raclopride do not substantially discriminate between the two receptor subtypes (420). The antagonists UH-232 and AJ-76 have been shown to have three to four times higher affinity at the D_3 than at the D_2 (420). Antagonists with some selectivity for the D_3 receptor (10–30 times difference) were recently developed, such as nafadotride (reviewed in Ref. 421), S-14297 (371, 421), and U-99194A (460).

The pharmacological profile of the D_4 receptor closely resembles those of D_2 and D_3 receptors, but specific differences have emerged (450). The most important feature distinguishing the D_4 from D_2 and D_3 receptors is its higher affinity for clozapine (450). Raclopride, remoxi-

pride, and chlorpromazine, on the other hand, exhibit 10–20 times lower affinity at the D_4 than at the D_2 and D_3 (Table 2) (401, 450). The D_4 receptors have been indirectly measured in brain tissues using [^{3}H]nemonapride, which readily labels all three receptor subtypes, and [^{3}H]raclopride, which labels D_2 and D_3 but to a much lesser extent D_4 receptors. The difference in binding densities of these two ligands has been proposed to reflect specific D_4 receptor binding (400).

VII. SIGNAL TRANSDUCTION OF DOPAMINE RECEPTORS

The coupling of DA receptors to second messenger pathways has been a subject of intense interest ever since their existence was recognized. Originally, studies of this subject were carried out in preparations from brain or in some cases using purified reconstituted receptors. However, since DA receptor cloning, their coupling properties have been studied predominantly in cell lines transfected with each receptor cDNA. This gave the advantage of working with a pure population of receptor, whereas most brain regions express multiple DA receptor subtypes. However, heterologous expression systems have the disadvantage of mostly being fibroblast in nature, whereas the DA receptors are endogenously expressed primarily in neuronal cells. This raises the possibility of the receptors being expressed in an environment that may contain different complements of G proteins, effectors, and other molecules than they are in vivo. As a result, the use of different heterologous expression systems has often led to apparently conflicting results.

A. Adenylyl Cyclase

As early as the 1970s, it was recognized that DA receptors could influence the activity of AC (reviewed in Ref. 226). The existence of a D_1 receptor-stimulated AC was recognized in most dopaminergic brain regions, such as striatum, nucleus accumbens, and olfactory tubercle (299). After the cloning of the D_1 receptor in 1990, it was possible to examine its signaling properties in transfected cell lines. In a variety of cell culture lines, it was shown that the D_1 receptor robustly stimulated cAMP accumulation (95, 314, 480). Upon the cloning of the second D_1-like receptor, the D_5 was also found to be coupled to stimulation of AC, as was predicted from its structural similarity to the D_1 receptor (169, 431, 441, 464). Interestingly, the D_5 receptor appears to exhibit an increased agonist-independent activity when compared with the D_1 receptor in 293 cells (440) and raises the questions of whether this is a naturally occurring constitutively active receptor and whether this feature is of relevance to its physiological role. Recent cloning of two more nonmammalian D_1-like receptor subtypes has indicated that these subtypes also stimulate cAMP accumulation in COS-7 cells (101, 430). Thus activation of AC seems to be a general property of all D_1-like receptors.

It is generally assumed that the activation of AC by D_1-like receptors is mediated by the $G_s\alpha$ subunit of G proteins. However, it has also been shown that $G_{olf}\alpha$, which also stimulates AC, is expressed in caudate, nucleus accumbens, and olfactory tubercle and is more abundant in these tissues than $G_s\alpha$ (188). This suggests that the D_1 receptor in particular, which is highly expressed in these brain areas, may couple to AC by previously unappreciated mechanisms. Recent studies suggested that D_1-like receptors can also couple to G proteins different from $G_s\alpha$. In particular, striatal D_1 receptors appear to be associated with $G_i\alpha$ proteins when reconstituted in phospholipid vesicles (413). In transfected GH_4C_1 cells, D_1 receptors interact with an inhibitory $G_i\alpha/G_o\alpha$ protein that has not been better identified (229). In addition, immunoprecipitation with antibodies specific for different G protein subtypes revealed that the D_1 receptor coprecipitates with both $G_o\alpha$ (230) and $G_q\alpha$ (459), the latter coupling D_1 receptors to phosphoinositide metabolism (459, 477).

That the D_2 receptor can inhibit AC was shown in the early 1980s in the pituitary (99, 121, 289, 345) and in the CNS (344). As expected, the cloning of the D_2 receptor confirmed these observations (reviewed in Ref. 159).

Although not immediately apparent, the D_3 receptor has been shown to be coupled to inhibition of AC. Initially, it was reported that this receptor did not inhibit AC in cell lines and did not couple to G proteins as shown by the lack of a guanine nucleotide shift of agonist binding curves (420). Similarly, subsequent observations also indicated that the D_3 receptor did not inhibit cAMP accumulation in various cell lines (144, 274, 438). However, more recently it has been shown that the D_3 receptor does weakly inhibit AC in some cell lines (75, 287, 360, 377).

On the other hand, that the D_4 receptor can inhibit cAMP accumulation was reported in retina (80) and a variety of cell culture lines (74, 287, 290, 438). Thus inhibition of AC seems to be a general property of the D_2-like receptors.

B. Calcium Channels

The D_1-like receptors appear to modulate intracellular calcium levels by a variety of mechanisms. One mechanism is via the stimulation of phosphatidylinositol (PI) hydrolysis by phospholipase C (PLC), resulting in the production of inositol 1,4,5-trisphosphate, which mobilizes intracellular calcium stores. There have been conflicting reports as to whether D_1-like receptors are capable of stimulating PI hydrolysis. Upon the cloning of each of

the D_1-like receptors, it was reported that these receptors could not stimulate PI turnover in COS-7 cells (95, 101, 430, 441). In addition, Pedersen et al. (351) reported that neither D_1 nor D_5 receptors affected intracellular calcium concentration in Chinese hamster ovary (CHO) or baby hamster kidney cells. In contrast, it has been shown that D_1-like receptor agonists cause increases in PI metabolism in various brain regions (444, 445). However, it should be noted that greater than 100 μM agonist is required to see this effect, calling into question the physiological relevance of this response. Other results have suggested indirectly that D_1-like receptors activate PKC via a PLC-mediated mechanism. The D_1 agonists cause neurite retraction of catfish horizontal cells in culture, and this effect is mimicked by activators of PKC such as phorbol esters or diacylglycerol (379). In addition, the D_1 receptor stimulates PI hydrolysis in Ltk^- cells (266). In both of these cases, a significant effect was observed at 1 μM DA, suggesting that coupling to PLC may be a real mechanism of D_1-like receptor signaling, at least in some cases.

On the other hand, the D_1 receptor appears to stimulate release of intracellular calcium stores via a mechanism other than stimulation of PI turnover. D_1 receptor-induced increase in intracellular calcium levels in 293 cells (140, 263) is mimicked, in fact, by other means of increasing cAMP levels (263), and thus is probably the result of activation of protein kinase A (PKA).

Finally, the D_1 receptor appears to affect the activity of calcium channels. In both rat striatal neurons and D_1 receptor-transfected GH_4C_1 cells, D_1 agonists increase calcium currents by L-type calcium channels. In both cases, the effect is mimicked by cAMP analogs (266, 432) and blocked by PKA inhibitors (432), suggesting that it may be the result of phosphorylation of calcium channels by PKA. In addition, in rat striatal neurons, D_1 agonists reduce calcium currents carried by N- and P-type calcium channels. This activity of the D_1 receptor was also mimicked by cAMP analogs and blocked by PKA inhibitors as well as the phosphatase inhibitor okadaic acid (432). The proposed model is that D_1 receptors reduce these currents by PKA stimulation of a phosphatase which, in turn, dephosphorylates the channels leading to their inactivation. Thus the regulation of calcium by D_1-like receptors appears to be quite complex and occurs through a variety of mechanisms.

D_2-like receptors also mediate changes in intracellular calcium levels. In some transfected cell systems, the D_2 receptor produces an increase in intracellular calcium via stimulation of PI hydrolysis. This has been observed in Ltk^- cells (448) and in CCL1.3 cells (438). However, in many other cell lines, the D_2 receptor has been shown not to couple to this second messenger. In addition, D_2 receptors in the pituitary have been shown to inhibit PI metabolism (52, 122, 416). Neither D_3 nor D_4 receptors increase PI hydrolysis in any cell line tested. D_2 receptors have also been shown to cause release of intracellular calcium stores in NG108–15 cells, although the mechanism for this release has not been examined (64).

D_2-like receptors can also cause a decrease in intracellular calcium levels by inhibition of inward calcium currents. This is the case for the D_2 receptor in GH_4C_1 cells (396, 448), pituitary lactotrophs (268), melanotrophs (468), and differentiated NG108–15 cells (397). D_3 receptors also inhibit calcium currents in differentiated NG108–15 cells (395), whereas D_4 receptors have this effect in GH_4C_1 cells (396). Two mechanisms may be responsible for this effect: D_2-like receptor-induced activation of potassium currents leading to alterations in membrane potential (reviewed in Ref. 447) and activation of G proteins that directly inhibit some calcium channels. In both pituitary lactotrophs and GH_4C_1 cells, inactivation of $G_o\alpha$ subunits by antisense oligonucleotides abolishes inhibition of calcium currents by D_2 receptors (15, 267). In contrast, in pituitary cells, alterations in potassium currents by the D_2 receptor appear to be mediated via $G_{i\text{-}3}\alpha$ subunits (15, 268), suggesting that the D_2 modulation of calcium currents is independent of changes in potassium conductance. Thus, similar to the D_1-like receptors, the D_2 receptor seems to alter intracellular calcium levels through multiple mechanisms, whereas to date, the D_3 and D_4 receptors have only been shown to inhibit calcium currents.

C. Potassium Channels

Dopamine receptors have been shown to influence the activity of potassium channels. This has not been well documented in the case of the D_1-like receptors. D_1-like agonists were shown to increase potassium efflux from chick retinal cells via a cAMP-independent mechanism (243). In contrast, a D_1-like agonist inhibited a potassium current in rat striatal neurons (232).

The role of D_2-like receptors in modulating potassium currents has been more extensively studied. In many preparations, it has been shown that D_2-like receptors increase outward potassium currents, leading to cell hyperpolarization. Such effects have been observed in rat striatal and mesencephalic neurons as well as in anterior pituitary (65, 119, 172, 232, 264, 467). This activation of potassium currents appears to be modulated by G protein mechanisms. The effect of DA on potassium currents in melanotrophs is in fact abolished by pertussis toxin (PTX) treatment (264, 467). In addition, treatment of cells with G protein antibodies or antisense oligonucleotides blocks the D_2 receptor stimulation of potassium currents. In pituitary, activation of potassium currents appears to be mediated by $G_{i\text{-}3}\alpha$ (15, 268), whereas in rat mesencephalon cultures, by $G_o\alpha$ (264). Such discrepancies may be the result of varying G protein subunit expression between

different cells, or may reflect the modulation of different potassium conductances by D_2 receptors.

The functional significance of cell hyperpolarization appears to be the inhibition of DA release by autoreceptors in the brain and of prolactin secretion in the pituitary. Blockade of potassium channels with 4-aminopyridine (4-AP) or tetraethylammonium (TEA) abolished the inhibition of evoked DA release by D_2-like agonists in striatal slices or synaptosomes (39, 63). Furthermore, in transfected MN9D cells, D_2 or D_3 receptor-mediated inhibition of DA release was also blocked by 4-AP and TEA (439).

D. Arachidonic Acid

In 1991, several groups showed that in CHO cells, the D_2 receptor potentiates the release of arachidonic acid (AA) evoked by calcium (125, 227, 356). These results were confirmed later by Freedman et al. (144) and MacKenzie et al. (274). In addition, in primary striatal neuron cultures, D_2-like agonists also cause potentiation of calcium-evoked AA release (392). The D_3 receptor does not appear to have this effect in cultured cell lines, but the D_4 receptor does potentiate AA release in CHO cells (74). This pathway is sensitive to PTX (74, 356), suggesting that $G_i\alpha$ subunits are involved. The mechanism by which D_2-like receptors potentiate AA release is not clear. In some reports, this effect is not related to changes in cAMP levels that might be mediated by the D_2 or D_4 receptors (74, 225). Although Piomelli et al. (356) observed an enhancement of the D_2 receptor potentiation of AA release in the presence of a cAMP analog, PKC seems more likely to play a role in this signaling system. Downregulation of PKC by 24-h treatment of cells with phorbol 12-myristate 13-acetate blocks the D_2 and D_4 effect (74, 225) as does treatment with the PKC inhibitor staurosporine (125). In addition, activation of PKC increases the maximal AA release in the presence of D_2 agonists and calcium ionophore and increases the potency of agonist to elicit this response (109). This evidence suggests that potentiation of AA release is mediated by alterations in PKC activity.

There is little evidence that D_1-like receptors affect AA release. Piomelli et al. (356) reported that in CHO cells, the D_1 receptor did not affect calcium-evoked AA release. However, when D_1 and D_2 receptors were expressed simultaneously in CHO cells, a combination of D_1 and D_2 agonists caused a greater potentiation of AA release than D_2 agonists alone. In contrast, in primary cultures of striatal neurons, D_1-like agonists caused an inhibition of calcium-evoked AA release (392), an effect that was mimicked by forskolin, suggesting the involvement of PKA in this response.

E. Na^+/H^+ Exchange

Dopamine receptors also appear to affect the activity of amiloride-sensitive Na^+/H^+ exchangers, which are responsible for regulation of intracellular pH and cell volume. This exchanger is also the major player in sodium absorption in many epithelia (478). The activity of the Na^+/H^+ exchanger is regulated by multiple mechanisms, including phosphorylation-dependent and -independent events and direct regulation by the $G_{i\text{-}3}\alpha$ subunit (104, 478). In preparations of renal brush-border membrane vesicles, D_1 receptor agonists cause an inhibition of the activity of the Na^+/H^+ exchanger by both cAMP-dependent and cAMP-independent mechanisms (123, 125).

In contrast, the D_2 receptor activates a Na^+/H^+ exchanger in many cells. This has been observed in renal brush-border membrane vesicles (123) in transfected C6 glioma and Ltk^- cells (329) and in primary cultures of anterior pituitary cells (147). In these systems, the observed increase in extracellular acidification was not blocked by PTX, suggesting that a mechanism other than $G_i\alpha$ was involved. However, in CHO cells, D_2, D_3, and D_4 receptors all increase extracellular acidification rates in a PTX-sensitive manner (74). These conflicting reports are presumably the result of the existence of multiple subtypes of amiloride-sensitive Na^+/H^+ exchangers as well as multiple mechanisms for their regulation.

F. Na^+-K^+-ATPase

The Na^+-K^+-ATPase, which pumps sodium out of cells and potassium in, is essential for maintaining the electrochemical gradient that is responsible for the excitability of nerve and muscle cells and drives the transport of fluid and solutes across epithelial membranes. It has been known that DA receptors influence the activity of this ion pump. In this manner, DA regulates fluid absorption in the kidney and neuronal excitability in the brain. Most work has suggested that DA effects on the Na^+-K^+-ATPase are mediated through the D_1 receptor. However, some reports also suggested that activation of both D_1 and D_2 receptors may be required. In a preparation of dissociated striatal neurons, Bertorello et al. (34) found that inhibition of the Na^+-K^+-ATPase required the presence of DA or a combination of D_1 and D_2 agonists. However, other studies have suggested that D_1 receptors alone are sufficient to evoke an inhibition of the Na^+-K^+-ATPase. In the chick retina, DA inhibits Na^+-K^+-ATPase activity, and this has been suggested to be mediated by D_1 receptors (243). In addition, in renal proximal tubule preparations and the Madin-Darby canine kidney cell culture model of cortical collecting tubule, D_1-like agonists cause an inhibition of the Na^+-K^+-ATPase, whereas D_2-like agonists have no effect (70, 407). In the kidney, the effects of DA receptor activation on Na^+-K^+-ATPase activity appear to be the result of phosphorylation cascades involving both PKA and PKC. However, in Ltk^- fibroblast cells transfected with the D_1 receptor, D_1-like agonists inhibit

Na^+-K^+-ATPase activity in a PKA-dependent manner (195). Therefore, although in general it appears that D_1 receptors are responsible for regulation of the Na^+-K^+-ATPase, the mechanism may vary according to the tissue examined.

G. Additional Signal Transduction Pathways Involved in Mitogenesis

Recent evidence has suggested that in some cases D_2-like receptors are involved in mitogenesis and cell differentiation. The D_3 receptor stimulates [^{3}H]thymidine incorporation in NG108–15 cells (355), and both D_2 and D_3 receptors have this effect in CHO cells (75, 244, 434). This effect is blocked by PTX and appears to be independent of alterations in cAMP levels. Lajiness et al. (244) found that the D_2 mitogenic effect was accompanied by an increase in tyrosine phosphorylation levels and was blocked by the tyrosine kinase inhibitor genistein, suggesting that this receptor may cause the activation of the mitogen-activated protein kinase pathway.

In contrast to the above results, the D_2 receptor has also been shown to inhibit cell growth in some cell lines. GH_4C_1 cells transfected with the D_2 receptor respond to agonists with a decrease in [^{3}H]thymidine uptake. Florio et al. (138) found that this effect was abolished by PTX, was accompanied by an increase in phosphotyrosine phosphatase (PTP) activity, and was blocked by the PTP inhibitor vanadate. In contrast, another study found that in GH_4C_1, the D_2 receptor-mediated inhibition of [^{3}H]thymidine uptake was not blocked by PTX but was blocked by downregulation of PKC and by PKC inhibitors (406). Thus, although the mechanism of inhibition of mitogenesis by D_2 receptors in GH_4C_1 cells is not clear, it may result from PKC-mediated activation of a phosphatase. The effects of D_2 receptor activation on cell growth appear to highly depend on the cell type examined.

Finally, the D_2-like receptors may promote some aspects of cell differentiation. When D_2, D_3, or D_4 receptors were expressed in the mesencephalic cell line MN9D, agonists caused increases in neurite number and length as well as total neuritic extent (435). However, in a study using primary cultures of rat mesencephalon neurons, a D_2-like receptor agonist did not affect survival or differentiation of these cells (449). The role of D_2-like receptors in neuronal differentiation thus remains to be clarified.

In conclusion, much effort has gone into studying the signal transduction of the DA receptors during the last 20 years. Many second messengers for these receptors have been identified, including cAMP, calcium, potassium, and AA. In addition, these receptors modulate other "effectors" by more indirect means, including Na^+/H^+ exchangers, the Na^+-K^+-ATPase, and cell growth and differentiation pathways (Fig. 2). However, in many cases, there is conflicting evidence in the literature for the modulation of various messengers, or the mechanism by which an effector is modulated by the DA receptors. Many of these discrepancies probably arise from the use of different tissues or cell culture lines. It is now known that many of the components of signal transduction pathways have multiple isoforms, including receptors, G proteins, and effectors, and that these have differing patterns of expression and regulatory properties. Defining which of these specific signal transduction events is involved in the various physiological actions of DA may require the development of specific pharmacological agents or genetic animals models.

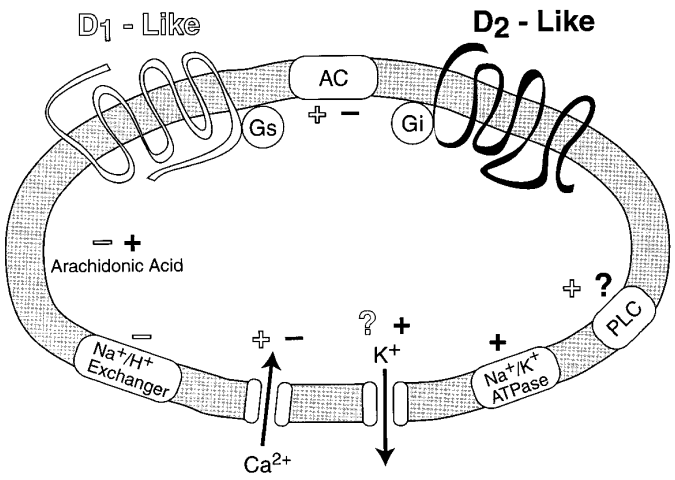

FIG. 2. Signal transduction of dopamine receptors. AC, adenylate cyclase; PLC, phospholipase C.

VIII. DOPAMINE RECEPTORS IN THE BRAIN

A. Distribution of Dopamine Receptors

Dopaminergic neurons in the substantia nigra pars compacta, the ventral tegmental area, and the hypothalamus give origin to three main pathways, the nigrostriatal, the mesolimbocortical, and the tuberoinfundibular. Because of the lack of ligands specific for each receptor subtype, in situ hybridization has been extensively used to study the distribution of DA receptor mRNAs in the brain.

The D_1 receptor is the most widespread DA receptor and is expressed at higher levels than any other DA receptor (95, 145, 463). D_1 mRNA has been found in the striatum, the nucleus accumbens, and the olfactory tubercle. In addition, D_1 receptors have been detected in the limbic system, hypothalamus, and thalamus. On the other hand, in other areas where the D_1 receptor protein is highly expressed such as the entopeducular nucleus and the sub-

stantia nigra pars reticulata (153, 255), no mRNA has been detected (95, 145, 463). This suggests that in these areas the D_1 receptor is mainly present in projections (95, 145, 463). As a matter of fact, D_1 receptors in the entopeduncular nucleus and in the substantia nigra pars reticulata are preferentially localized on striatal GABAergic neurons coexpressing substance P (153, 255).

The D_5 receptor is poorly expressed in rat brain when compared with the D_1 receptor. A distribution restricted to the hippocampus, the lateral mamillary nucleus, and the parafascicular nucleus of the thalamus, where the D_1 receptor is not significantly expressed, was originally reported (293, 441), with little or no message detected in the dorsal striatum, nucleus accumbens, and olfactory tubercle. Upon further examination, D_5 receptor mRNA has been found in several rostral forebrain regions including cerebral cortex, lateral thalamus, diagonal band area, striatum, and, to a lesser extent, substantia nigra, medial thalamus, and hippocampus (76, 203, 366).

The development of specific antibodies against DA receptor subtypes recently made it possible to define their cellular and subcellular localization in different regions of primate brain. Both D_1 and D_5 receptors are coexpressed in pyramidal neurons of prefrontal, premotor, cingulate and entorhinal cortex, the hippocampus, and the dentate gyrus (27, 28, 197, 417). Electron microscopy analysis demonstrated that in the prefrontal cortex and the hippocampus, D_1 and D_5 receptors have both pre- and postsynaptic localization, with the postsynaptic one more frequently observed. Ultrastructural analysis suggested that within individual pyramidal neurons, D_1 and D_5 receptors have a different localization with the D_1 concentrated in dentritic spines and the D_5 in dendritic shafts (28, 417). In the olfactor bulb D_1 receptors are restricted to the internal granular and plexiform layers and in the amygdala in the intercalated and basolateral nuclei (260). In the caudate nucleus, D_1 and D_5 receptors are mostly localized within medium-sized GABAergic neurons (28, 197, 417). D_5 but not D_1 receptors are present also in large cholinergic interneurons (28). Ultrastructural analysis suggested that D_1 receptors are present on spines postsynaptic to asymmetrical synapses, that both D_1 and D_5 receptors are at postsynaptic densities of small synapses characteristics of DA terminals, and that presynaptic D_1 and D_5 receptors are on axons forming asymmetrical synapses (28, 187, 260, 417). D_1 receptors have been localized in the entopeduncular nucleus and in the pars reticulata of the substantia nigra, where D_5 receptors are undetectable (28, 187, 260). This observation suggests that if D_1 and D_5 receptors are colocalized in medium-sized spiny neurons of caudate, only the D_1 receptor is transported to striatonigral terminals. These differences in the cellular and subcellular localization thus suggest that although D_1 and D_5 receptors exhibit similar pharmacology, they are not functionally redundant.

The D_2 receptor has been found mainly in the striatum, in the olfactory tubercle, in the core of nucleus accumbens (38; reviewed in Ref. 217), where it is expressed by GABAergic neurons coexpressing enkephalins (253, 256), and in the septal pole of the shell of the nucleus accumbens where it is expressed by neurotensin-containing neurons (105). D_2 receptor mRNA is also present in the prefrontal, cingulate, temporal, and enthorinal cortex, in the septal region, in the amygdala, and in the granule cells of the hippocampal formation (38; reviewed in Ref. 217). It is also found in the hypothalamus, in the substantia nigra pars compacta, and in the ventral tegmental area, where it is expressed by dopaminergic neurons (38, 292, 463). Immunohistochemical analysis with specific antibodies revealed that D_2 receptors are present in medium spiny neurons of the striatum where they are more concentrated in spiny dendrites and spine heads than in the somata. Colocalization with D_1 receptors is rare. D_2 immunoreactive terminals are frequently detectable, forming symmetrical, rather than asymmetrical, synapses (187, 260). The D_2 receptors are present in perikarya and dendrites within the substantia nigra pars compacta and are much more concentrated in the external segment of the globus pallidus than in other striatal projections (260). D_2 receptor immunoreactivity has been detected in the glomerular and internal plexiform layers of the olfactory nerve and in the central nucleus of the amygdala (260).

The D_3 receptor has a specific distribution to limbic areas (245, 246) such as the ventromedial shell of the nucleus accumbens (38) where it is expressed by substance P and neurotensin neurons projecting to the ventral pallidum (105, 106), the olfactory tubercle, and the islands of Calleja (38, 258). In contrast, it is poorly expressed in the dorsal striatum (38, 258, 420). The D_3 mRNA was also found in the substantia nigra pars compacta, in the ventral tegmental area, where it is expressed in a minority of dopaminergic neurons when compared with the D_2 receptors and in the cerebellum (105, 106). In the islands of Calleja, both D_3 receptor binding and mRNA are present in granule cells (106, 258), which are known to make sparse contacts with dopaminergic axons. Purkinje cells in lobules 9 and 10 of the archicerebellum express D_3 mRNA, whereas binding sites were detectable only in the molecular layer (106, 258). No dopaminergic projections are present in this area, suggesting that the D_3 receptor may respond to DA diffusing extrasynaptically (106). The D_3 receptor was also found at low expression levels in the hippocampus, in the septal area, and in various cortical layers and subregions of the medial-temporal lobe (38).

Low levels of the D_4 receptor mRNA have been found in the basal ganglia. In contrast, this receptor appears to be highly expressed in the frontal cortex, amygdala, hippocampus, hypothalamus, and mesencephalon (343,

450). Significant levels of D_4 mRNA were also found in the retina (80). Recently, a specific antibody directed against the D_4 receptor has been developed. Immunohistochemical and electron microscopy analysis revealed that in both the cerebral cortex and hippocampus, D_4 receptors are present in pyramidal and nonpyramidal neurons that have been identified as GABAergic interneurons (319). In the cerebral cortex and hippocampus, D_4 receptors thus modulate the GABAergic transmission. D_4 receptors have been also found in GABAergic neurons of both segments of globus pallidus and of the substantia nigra pars reticulata and in the reticular nucleus of the thalamus (319).

B. Function of Brain Dopamine Receptors

The behavioral effects of DA have been extensively reviewed (92, 217, 235, 469). Here we briefly summarize some of the functional effects of DA with particular attention to some behaviors where the role of the different DA receptor subtypes has been investigated.

The effects of DA on motor activity have been extensively investigated (reviewed in Refs. 79, 217, 456, 457). The degree of forward locomotion is primarily controlled by the ventral striatum through activation of D_1, D_2, and D_3 receptors. Activation of D_2 autoreceptors, which results in decreased DA release, has been shown to decrease locomotor activity (reviewed in Ref. 217), whereas activation of postsynaptic D_2 receptors slightly increases locomotion. Activation of D_1 receptors has little or no effect on locomotor activity (155; reviewed in Ref. 217). However, it is now clear that there is synergistic interaction between D_1 and D_2 receptors in determining forward locomotion so that concomitant stimulation of D_1 receptors is essential for D_2 agonists to produce maximal locomotor stimulation (41, 116; reviewed in Refs. 79, 217, 456, 457). As discussed in section VIII*D*, these pharmacological observations have been explicitly confirmed by targeted inactivation of the D_1 receptor gene in the mouse (471, 472).

The D_3 receptor, which has been shown to be mainly postsynaptically located in the nucleus accumbens (106), seems to play an inhibitory role on locomotion. D_3-preferring agonists inhibit, in fact, locomotor activity (93; reviewed in Ref. 421), whereas D_3-preferring antagonists evoke motor activation (reviewed in Refs. 421, 461). The opposing effects of D_2 and D_3 receptors on locomotor activity may find a neurochemical correlate in their opposite effects on neurotensin gene expression in the nucleus accumbens (105).

Mesolimbocortical DA is implicated in reward and reinforcement mechanisms as shown by the observation that administration of psychostimulants and drugs of abuse elicits an increase of DA release in the mesolimbic areas, whereas withdrawal of these drugs results in a reduction of dopaminergic transmission. A vast amount of literature has been written in this area (108, 252, 365, 404, 469). Various experimental models have been developed such as intracranial self-stimulation and drug self-administration. In the intracranial self-stimulation paradigm, rats work to obtain electrical stimulation that has rewarding properties and results in DA release in the prefrontal cortex and nucleus accumbens (reviewed in Ref. 217). Pharmacological studies clearly show that both D_1 and D_2 receptors are involved in this behavior, with agonists at both receptors stimulating and antagonists inhibiting the behavior (141, 234).

In the case of drug self-administration, it has been shown that both D_1 and D_2 receptors are involved in the reinforcing properties of different drugs of abuse, with D_2 receptors mediating the stimulant drug reinforcement and D_1 receptors playing a permissive role (25, 277, 354, 403). Stimulation of D_1 receptors by endogenous DA is thus required for the expression of D_2 receptor-mediated behaviors and gene regulation. A recent study suggested that although D_1-like and D_2-like receptor agonists are themselves reinforcing and can both substitute for cocaine in drug discrimination tests, they nevertheless may mediate qualitatively different aspects of the reinforcing stimulus produced by cocaine. In particular, activation of D_2-like receptors has been shown to mediate the incentive to seek further cocaine reinforcement in an animal model of cocaine-seeking behavior. In contrast, D_1-like receptors appear to mediate a reduction in the drive to seek further cocaine reinforcement (403). Agonists of D_1-like receptors may thus be evaluated as a possible therapy of cocaine addiction. Recently, it has been shown that D_3 receptor stimulation inhibits cocaine self-administration in the rat in a way indicating an enhancement of cocaine reinforcement (51, 349).

Although some inconsistencies are present in the literature, there is a general agreement that mesolimbocortical DA plays a role in learning and memory. In the monkey, DA neurons in the A10 area have been reported to be involved with transient changes of impulsive activity in basic attention and motivational processes underlying learning and cognitive behavior (394). Pharmacological studies have shown that both D_1 and D_2 receptors mediate the effects of DA on learning and memory. Activation of both D_1 and D_2 receptors in the hippocampus improves acquisition and retention of different working memory tasks in the rat (261, 348, 465, 466). In the monkey, activation of both D_1 and D_2 receptors in the prefrontal cortex has been reported to improve performance in a working memory task (12, 390, 391). Because of the lack of true agonists and antagonists discriminating among D_1-like and D_2-like receptors, the role of DA receptor subtypes in learning and memory has not been investigated. However, it is worth noting that although the D_1 receptor is poorly expressed in the hippocampal formation, the D_5 receptor

is highly expressed in this area so that the D_5, more than the D_1 receptor, is likely to mediate the effects of D_1 agonists on learning and memory. Similarly, D_3 and D_4 receptors are expressed in the hippocampus, and D_3 receptors are present in the septal area, suggesting a possible contribution of these receptor subtypes to the behavioral effects of D_2 agonists. In contrast, because of their distribution at the cortical level, a central role of D_1 and D_2 receptors can be proposed in the prefrontal cortex-mediated behaviors.

The role of D_3 and D_4 receptors in the physiology of dopaminergic system is still mostly unknown. They are specifically expressed in limbic and cortical regions involved in the control of cognition and emotion and, to a lesser extent in the dorsal striatum, and this makes them attractive and promising targets for new generations of antipsychotic drugs with low incidence of extrapyramidal side effects.

C. Dopamine Receptors and Regulation of Gene Expression

The study of receptor and peptide levels in the striatum after perturbation of DA transmission has been useful in better understanding the organization and regulation of the dopaminergic system. The paradigms used in these approaches have included consequences of blockade of DA receptors (as occurring after neuroleptic treatment), interruption of dopaminergic transmission (as occurring in Parkinson's disease), or after the hyperactivation of the DA system (observed after abuse of psychostimulants such as cocaine and amphetamine). Activation of DA receptors results in fact in modulation of both peptide and immediate early gene expression. On the other hand, expression of the genes encoding DA receptors is subject to modulation by DA itself and other signals.

1. Immediate early genes

Fos is the protein product of the immediate-early gene c-*fos* and is considered to be a marker of some neuronal activities. Fos appears to be required for long-lasting modifications of gene expression in response to acute stimuli and has been shown to be one of the final targets in the signaling cascade of DA receptors (374). Basal c-*fos* expression in the striatum is very low. However, administration of caffeine (322), haloperidol (330, 372), raclopride (102), cocaine, and amphetamine (171, 193, 213, 330) remarkably stimulates c-*fos* expression in the ventral and dorsal striatum with regional and cellular specificity depending on the drug used. Therefore, it has been proposed that Fos and Fos-related antigens may be used to map specific pathways involved in the response to modifications of the neuronal environment. Retrograde tracing studies suggested that cocaine and amphetamine preferentially increase Fos-like immunoreactivity in striatonigral neurons, whereas the stimulatory effects of neuroleptics are limited to striatopallidal neurons (67, 375). Both in the core and shell regions of nucleus accumbens, D_1 agonists increase *fos* expression in projections to the midbrain and the ventral pallidum. On the other hand, blockade of D_2 receptors results in a preferential increase of *fos* expression in the projections to the ventral pallidum (373).

Concomitant stimulation of D_1 and D_2 receptors appears to produce a synergistic effect on c-*fos* expression (242). Separate administration of selective D_1 or D_2 agonists induces an increase of Fos immunoreactivity in few neurons, whereas combined administration of D_1 and D_2 agonists produced patches of intensely stained immunoreactive nuclei in the striatum (350). In line with this, administration of SKF-38393 to DA-depleted rats increased the striatal expression of c-*fos*, whereas quinpirole did not significantly modify it (227). Combined administration of SKF-38393 and quinpirole, however, produced a higher extent of c-*fos* expression than SKF-38393 alone (227). Moreover, amphetamine and cocaine, which increase DA overflow, appear to be more effective in inducing c-*fos* expression than receptor-selective direct agonists.

These findings are in line with behavioral and electrophysiological evidence suggesting the existence of D_1 and D_2 synergism in the striatum (79, 116, 242, 375, 455). However, the anatomic basis of this synergism is still a matter of debate.

2. Neuropeptides

Anatomic, pharmacological, and molecular studies have given some insights in the mechanisms underlying D_1/D_2 synergism. Striatal efferent neurons are known to be under the influence of DA. As shown in Figure 3, two major types of neurons have been defined that are distinguished by their primary sites of axonal projections and neuropeptide synthesis (for a review, see Ref. 152). One population projects to the entopeduncular nucleus and the substantia nigra pars reticulata (striatonigral) and expresses the neuropeptides substance P (SP) and dynorphin (Dyn) (152, 255). The other projects to the external segment of the globus pallidus (striatopallidal) and contains enkephalin (152, 256). The striatonigral neurons preferentially express D_1 receptors that mediate the stimulatory effects of DA on SP and Dyn expression (153, 255), whereas the striatopallidal neurons mainly express D_2 receptors, inhibiting the expression of preproenkephalin A (PPA) (Fig. 3) (153, 256). A similar receptor organization was found in the nucleus accumbens with D_1 receptors mostly expressed in SP neurons (253), D_2 in enkephalin and neurotensin neurons (253), and D_3 receptors in SP and neurotensin neurons (105, 106).

In the ventral shell of the nucleus accumbens, D_3 recep-

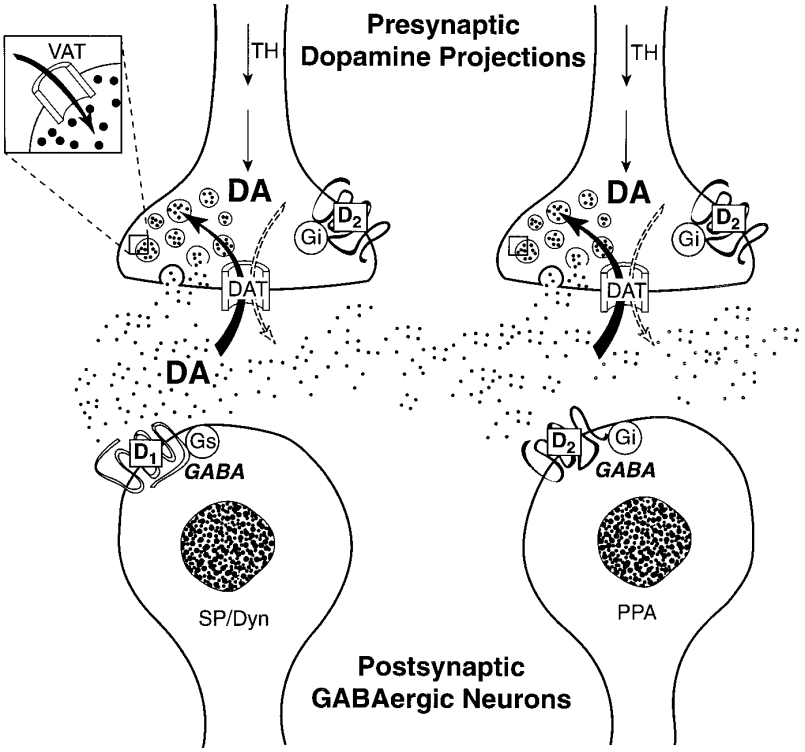

FIG. 3 Organization of striatal dopaminergic synapses. D_1 receptors are preferentially expressed by γ-aminobutyric acid (GABA)ergic neurons coexpressing substance P (SP) and dynorphin (Dyn) and projecting to entopeduncular nucleus and substantia nigra, whereas D_2 receptors are segregated on GABAergic neurons containing enkephalin and projecting to globus pallidus. D_2-like autoreceptors are present on dopaminergic terminals. PPA, preproenkephalin A; DAT, dopamine transporter; VAT, vesicular transporter; TH, tyrosine hydroxylase.

tors tonically activate neurotensin gene expression (105), whereas D_2 receptors in the septal pole of the nucleus accumbens inhibit neurotensin gene expression (105).

Although some controversy arose concerning colocalization or segregation of D_1 and D_2 receptors in the different neuronal populations, there is now a general agreement that D_1 and D_2 receptors are segregated in SP and enkephalin neurons, respectively, with a small percentage of neurons coexpressing both receptor genes. This was clearly demonstrated in in situ hybridization studies showing that striatal D_1 receptors are coexpressed with SP and D_2 receptor with PPA (90, 153, 253, 255, 256).

On the other hand, other studies suggested that D_1 and D_2 receptors are mostly colocalized in the same neurons (11, 257, 433). However, immunohistochemistry studies with D_1 and D_2 antibodies recently confirmed that D_1 and D_2 receptor are indeed segregated in distinct neurons of the dorsal striatum (187).

In line with these observations, pharmacological studies have shown that DA agonists and antagonists as well as disruption of dopaminergic transmission by either 6-hydroxydopamine (6-OHDA) or reserpine modulate striatal peptide gene expression in a way that confirms the concept of receptor segregation. Chronic administration of haloperidol and sulpiride increases the mRNA level of PPA, which is under the inhibitory control of D_2 receptors (29, 45, 216, 333), whereas SP and Dyn are not modified by these treatments. Dopamine receptor stimulation, on the other hand, resulted in increases of both SP and Dyn levels (178, 179). Disruption of dopaminergic transmission by 6-OHDA treatment resulted in an increase of striatal PPA mRNA, an effect which was reversible upon chronic treatment with quinpirole but not with the D_1 agonist SKF-38393 (153). In the same model, SP mRNA was decreased, and this effect was reversed by SKF-38393 but not by quinpirole (153). A decrease in SP and Dyn precursor mRNAs was also observed after DA depletion by reserpine treatment (42, 49, 214, 215). On the other hand, in mutant mice having a constitutively hyperactive dopaminergic transmission, due to targeted inactivation of the DA transporter gene, the mRNA levels of Dyn precursor are greatly increased and those of PPA significantly decreased (160).

At present, the data thus seem to converge to support the concept that, for the most part, D_1 and D_2 receptors are segregated with only a small population of neurons, showing coexpression of D_1/D_2. Taken together, these observations imply that the D_1/D_2 synergistic effects observed at molecular, electrophysiological, and behavioral levels may occur by interneuronal interactions. A D_2-mediated suppression of striatopallidal neurons might in fact relieve a tonic inhibitory influence of enkephalin or GABA on striatonigral neurons, thus increasing D_1-mediated responses (227). On the other hand, in vitro studies suggested D_1/D_2 synergism to take place at the single-cell level (34, 356, 433). On this basis, the possibility should be considered that D_1 and D_2 synergism may occur by the coexpression of D_1-like and D_2-like receptors in the same neurons (60). In this case, the same neurons would ex-

press $D_1/D_3/D_4$ or D_2/D_5 receptors. Supporting this hypothesis, a recent report by Bergson et al. (28) documents that in the primate brain the D_5 receptor is expressed by large spiny neurons in the striatum, known to be cholinergic interneurons expressing the D_2 receptor. Similarly, D_1 and D_3 receptors were found to be colocalized in the granule cells of the islands of Calleja, in some medium spiny neurons in the nucleus accumbens, and in the ventral striatum, suggesting that, in this last region, D_1/D_2-like synergism may occur at a single neuronal level in a significant proportion of SP/dynorphin neurons (90, 106, 254).

3. Dopamine receptor gene expression

An indication of the importance of DA receptors in the regulation of gene expression is the modulation of the expression of the genes encoding the DA receptors themselves. Chronic treatment with neuroleptic drugs such as haloperidol and sulpiride increases the mRNA level of D_2, but not D_1, receptors in the striatum (29, 45, 216, 333). Disruption of nigrostriatal dopaminergic neurons by 6-OHDA results in an increase in D_2 mRNA and a decrease in D_1 mRNA expression, both effects being reversed by treatment with quinpirole or SKF-38393, respectively (42, 153). The 6-OHDA-induced increases in the mRNA and protein levels of the D_2 receptors are maintained for weeks (153), suggesting that an increased rate of receptor synthesis is required to sustain an increased number of receptors even in the absence of the natural agonist. On the other hand, mutant mice lacking the DA transporter and thus having a constitutively hyperactive dopaminergic transmission clearly have a remarkable downregulation of both D_1 and D_2 mRNAs in the striatum (160).

D_3 receptors have been shown to be regulated opposite from the D_2 receptors. Denervation leads to D_3 receptor downregulation. This paradoxical effect seems to be unrelated to deprivation of either DA or one of its cotransmitters and has been proposed to be dependent on a yet unidentified putative messenger released from dopaminergic neurons (259).

Factors other than DA or dopaminergic drugs have also been shown to modulate DA receptor gene expression. Treatment of Y79 human retinoblastoma cells with dibutyryl cAMP results in the expression of D_2 receptors (313), and exposure of the GH_3 cell line to epidermal growth factor (EGF) results in a remarkable increase in the levels of both D_{2S} and D_{2L} mRNAs (302). In addition, EGF as well as basic fibroblast growth factor and neurotrophins have been shown to exert a differentiative and trophic effect on central dopaminergic neurons (22, 61, 62, 136, 428). These observations suggest that specific factors originating from surrounding cells such as glial cells or from afferent neurons or by the dopaminergic neurons themselves may regulate DA receptor gene expression during development and adaptation to abnormal stimuli or pharmacological treatments.

D. Development of Transgenic Animals in the Study of Dopamine Receptor Physiology

Although there has been a general consensus regarding the general role and function of D_1 and D_2 DA receptors in the basal ganglia, there are still many questions that remain unanswered. The specific participation of each of these receptors in behavioral paradigms and regulation of gene expression is still a matter of debate, as discussed in section VIII*B*.

Gene targeting using homologous recombination to inactivate a chosen gene has been used for D_1 and D_2 DA receptors (18, 114, 471, 472).

Disruption of the D_1 receptor gene has been independently reported by two groups (114, 472). One group showed locomotor hyperactivity in mutant mice compared with wild type, an effect likely due to compensatory mechanisms activated by the lack of D_1 receptors (472), whereas the other group did not detect any significant change in the locomotor activity of mutant mice (114). D_1 mutant mice showed no increase in their locomotor activity in response to cocaine, thus explicitly confirming that in the absence of D_1 receptors psychomotor stimulation mediated by D_2 receptors cannot occur (471). The finding that high doses of cocaine inhibit locomotor activity in mutant mice (471) could suggest that removal of D_1 receptor may have enhanced D_3 receptor-mediated locomotor suppression. On the other hand, a role of the serotoninergic system in this response to cocaine has not been excluded (158, 471). The study of gene expression modifications in mice lacking the D_1 receptor showed that, correlating with the distribution of DA receptors at neuronal level, SP mRNA was decreased in mutant mice, whereas PPA mRNA levels were unchanged (114). These molecular changes demonstrate that these mice exhibit selective functional changes in striatal neurons with a direct output pathway to the substantia nigra.

Inactivation of the D_2 gene produced almost the opposite phenotype in the mutant mice. Animals lacking D_2 receptors are akinetic and bradykinetic, with significantly reduced spontaneous movement (18). This mouse phenotype resembles that obtained with D_2 antagonist administration and is reminiscent of the extrapyramidal symptoms of Parkinson's disease. At the molecular level, PPA mRNA, which is under the inhibitory control of DA via the D_2 receptors, is increased by 40% in the mutant mice (18).

On the basis of these results, inactivation of the other members of the DA receptor family could provide valuable information about their physiological functions. The drawback of this approach, however, is that inactivation of specific receptor genes in the mouse germ line produces animal phenotypes where possible developmental alterations and compensatory changes are superimposed on the true effects of receptor removal, so that behavioral

alterations in the mutant mice should be interpreted with some caution. Development of spatially and temporally targeted inactivation of specific receptor genes could be helpful to overcome this problem and to produce a clearer picture of the function of DA receptors in adult animals as opposed to their role in development.

E. Clinical and Pharmacological Implications of Multiple Dopamine Receptors

The hypothesis that the dopaminergic system is overactive in schizophrenia is based on the observation that neuroleptics, which are used in the management of the major symptoms of this disorder, selectively block DA receptors (223, 286, 368, 415). The DA hypothesis was further strengthened by the fact that amphetamine induces psychotic states resembling those observed in the positive symptoms of schizophrenia (euphoria, auditory hallucinations, and akathisia or the inability to remain inactive).

Treatment with neuroleptics has the major drawback that most of patients under medication suffer from extreme movement disorders known as extrapyramidal syndrome. The symptoms include muscular rigidity and akinesia that are sometimes difficult to distinguish from the negative symptoms of schizophrenia. Moreover, prolonged treatment invariably leads to irreversible tardive dyskinesia. It is believed that the antipsychotic effects of neuroleptics are due to their action on the dopaminergic receptors in the mesolimbic system, whereas the extrapyramidal side effects are thought to result from blockade of D_2 receptors in the striatum (reviewed in Refs. 103, 297, 415). From this perspective, the discovery of multiple DA receptors with differential expression in the brain and with different affinities for antipsychotic drugs is of great interest.

The high overall sequence homology between DA receptors of the same subfamily has made it extremely laborious to develop specific ligands that do not interact with related receptors. Of particular interest is the high affinity of "atypical" neuroleptics, such as sulpiride and its derivatives and clozapine, for D_3 and D_4 receptors, respectively (154, 399, 420). The low level of expression of the D_3 and D_4 receptors in the striatum and their relatively high expression in limbic and cortical areas led to the suggestion that the antipsychotic actions of neuroleptics may be mainly mediated through D_3 and D_4 receptors, whereas the side effects may be mediated through D_2 receptors. This hypothesis is further strengthened by the observation that administration of clozapine is associated with a very low incidence of extrapyramidal side effects. However, clozapine at therapeutic doses also blocks many other types of receptors, in addition to the D_4 receptor, so that it is difficult to draw conclusions on the mechanism of action of its antipsychotic effects (296, 401). There were recent claims that D_4 receptors, measured by indirect binding, may be increased in the brain of schizophrenic patients (402, 400). Additional work will be required to confirm these findings, since many of these observations came from indirect measurements with partially selective ligands. The development of specific antipsychotics targeting a single DA receptor subtype should shed more light on the role of each of the DA receptors in schizophrenia.

1. *Genetic linkage of dopamine receptors to pathophysiologies*

The cloning and characterization of the human genes for the five DA receptors have initiated studies of their genetic relationship with neuropsychiatric disorders associated with the DA system. These include bipolar disorder (96, 228, 411), schizophrenia (83, 324, 367, 429), manic depression (220), Parkinson's disease (325), and Tourette's syndrome (151). For all of these conditions, there is strong evidence against linkage of any of the five DA receptors. For example, chromosome 11 has long been suspected to harbor a gene causing predisposition to bipolar disorder. It has been extensively studied for genetic linkage with genes coding for tyrosine hydroxylase, tyrosinase, and D_2 and D_4 DA receptors, all of which can be found on human chromosome 11 (96, 228, 411). All studies conducted to date exclude any possible association between these markers and the pathogenesis of bipolar disorder at least in the pedigrees examined.

Because the implication of the dopaminergic system in the etiology of schizophrenia is strong, the alleles coding for five DA receptors have been investigated and all systematically excluded in many pedigrees including Japanese, Swedish, Italian, Irish Californian, and Amish (83, 324, 367, 429). Crocq et al. (86), however, detected a small but significant increase in the risk of schizophrenia in two French and British populations associated with homozygosity at D_3. These findings, however, need to be confirmed. None of the various alleles of the D_4 receptor seems to be associated with an increased risk of schizophrenia (273, 312, 325).

The situation is not clear regarding appetite and addictive behaviors such as alcoholism. Indeed, early reports did indicate that the A1 allele of the *Taq* I restriction fragment length polymorphism containing the D_2 DA receptor gene may confer susceptibility to alcoholism. This claim has proved to be controversial, with three reports confirming the original findings and two others excluding the existence of a possible linkage (reviewed in Refs. 82, 167). The possibility that a remote regulatory element controlling the expression of a candidate gene could be involved in the disorder investigated should also be taken into consideration.

IX. DOPAMINE RECEPTORS IN THE PITUITARY

In the late 1970s, with the use of the radioligand binding assay, it was first directly shown that D_2 receptors are present in the anterior and intermediate lobes of the pituitary gland (reviewed in Refs. 26, 59, 320) where they mediate the tonic inhibitory control of hypothalamic DA on prolactin (Prl) (26, 121, 298) and α-melanocyte-stimulating hormone (84, 425) secretion.

The genes encoding the D_2 receptor have been later found in the pituitary (47, 91, 162, 292, 315). In particular, D_{2S} and D_{2L} receptor isoforms are expressed in both melanotroph (47, 91; 292) and lactotroph cells, where the longer form is predominant (91, 162, 292, 315). Interestingly, subpopulations of lactotrophs have been identified that express different D_{2L}/D_{2S} mRNA ratios. Gonadal steroids have been shown to influence this ratio in vitro, providing a possible basis for variation in the density of pituitary D_2 receptors during the estrous cycle (240).

The D_4 receptor and in particular its $D_{4.4}$ variant is also expressed in the anterior pituitary (451). Its role in the physiology of the gland, however, has not been examined yet.

Multiple transduction mechanisms are activated by D_2 receptors in the pituitary. In addition to inhibition of AC (121, 289, 298, 344), pituitary D_2 receptors inhibit PI metabolism (52, 122, 416), activate voltage-activated potassium channels (I_A and I_K currents) (65, 212, 269, 270), and decrease voltage-activated L-type and T-type calcium currents (269, 270, 447). All these effects are mediated by G proteins, with $G_o\alpha$ mostly involved in the inhibition of calcium currents and $G_{i\text{-}3}\alpha$ in the activation of voltage-dependent potassium channels (268, 302).

In addition, the recent findings that the expression of the POU/Pit1 transcription factor, which activates growth hormone (GH) and Prl gene expression (210, 454), is inhibited by activation of D_2 receptors in transfected cell lines (120, 262) suggest the existence of a dopaminergic control on Prl gene expression.

The presence of D_2 receptors inhibiting Prl secretion in the anterior pituitary leads to a major therapeutic application in the treatment of hyperprolactinemia either due to functional hypothalamus-pituitary defects or to the presence of Prl-secreting tumors. D_2 receptor agonists, such as bromocriptine, are in fact the most effective pharmacological tool to normalize plasma Prl levels in these patients (reviewed in Ref. 89).

These observations stimulated the study of D_2 receptor pharmacology, biochemistry, and functional properties as well as the mechanisms regulating its expression in the pituitary. Primary cultures from the anterior pituitary, however, have the limitation of being nonhomogeneous cell systems. The GH_3 cell line, derived from a rat anterior pituitary tumor, is the most widely used model to study the regulation of Prl secretion. The recent findings that different neurotrophic factors, such as EGF (149, 302, 306) and nerve growth factor (NGF) (305), can induce the expression of D_2 receptors in this cell line made it an excellent model to study D_2 receptor regulation. These observations also suggest that neurotrophic factors may be operative in the anterior pituitary to regulate the expression of D_2 receptors during development (135, 303, 359) or in particular pathophysiological conditions.

The clinical relevance of these findings concerns the therapy of those Prl-secreting tumors that do not respond to the conventional pharmacological treatment with bromocriptine and require neurosurgical intervention (89). The major biochemical defect contributing to DA agonist resistance in those prolactinomas is, in fact, decreased density (352) or absence (304) of D_2 receptors. The observation that short-term exposure of resistant prolactinomas to NGF, both in vitro and in vivo, results in the expression of D_2 receptors (304) may open the way to a new therapy for these patients. Nerve growth factor treatment, by inducing the expression of D_2 receptors in the tumor, restores the molecular target for subsequent therapy with bromocriptine. Therefore, sequential therapy with NGF and bromocriptine appears to be a potential alternative to neurosurgical intervention for patients with DA-resistant prolactinomas (310).

X. PERIPHERAL DOPAMINE RECEPTORS

Dopamine receptors in the cardiovascular system were originally characterized by physiological evaluation of changes in blood flow in response to the administration of catecholaminergic agonists and antagonists. Two distinct patterns of responsiveness were observed, and these were classified as DA_1 and DA_2 (reviewed in Ref. 166) in a scheme that paralleled the D_1/D_2 classification of Kebabian and Calne (226).

The cloning and molecular characterization of DA receptors later indicated that the same molecular species are present in the CNS and in some peripheral tissues. The existence of different D_1-like and D_2-like receptors in the cardiovascular system, however, has not been systematically investigated. It has been shown that all the cloned DA receptors are present in the kidney (148, 285, 326, 420, 473) and that D_4 receptors are present in the heart (343). However, little is known to date about the molecular nature of DA receptors in blood vessels, in postganglionic sympathetic nerve terminals, and in the adrenal cortex, so their function and classification in these regions are largely based on pharmacological data. The distribution and function of peripheral DA receptors are summarized in Table 3.

A. Dopamine Receptors in Blood Vessels

Initial screening for D_1 and D_2 activities was conducted in the anesthetized dog with simultaneous re-

TABLE 3. *Distribution and function of peripheral dopamine receptors*

Tissue	Receptor Type	Function
Blood vessels		
Adventitia	D_2-like	Inhibition of NE release
Media	D_1-like	Vasodilatation
Intima	D_2-like	Unknown
Adrenal gland		
Glomerulosa	D_1-like	Unknown
	D_2-like	Inhibition of aldosterone secretion
Medulla	D_1-like	Stimulation of E/NE release
	D_2-like	Inhibition of E/NE release
Kidney		
Glomerulus	D_1-like	Increase of filtration rate
Juxtaglomerular apparatus	D_1-like	Stimulation of renin secretion
Proximal tubule	D_1-like	Inhibition of Na^+ reabsorption
Ascending limb of loop of Henle	D_1-like	Inhibition of Na^+ reabsorption
Cortical collecting duct	D_1-like	Inhibition of Na^+ reabsorption
	D_2-like	Inhibition of vasopressin action
Sympathetic ganglia/ endings	D_2-like	Inhibition of NE release
Heart	D_4	Unknown

NE, norepinephrine; E, epinephrine.

cordings of cardiac contractility, heart rate, arterial blood pressure, and renal and femoral blood flows (reviewed in Ref. 166). The results of these studies led to the current paradigm that postjunctional D_1 receptors producing direct vasodilatation are present in the renal artery and that prejunctional D_2 receptors on postganglionic sympathetic nerve terminals inhibit norepinephrine release to indirectly induce vasodilatation in the femoral artery and decrease of cardiac contractility (166).

Subsequent studies using either radioligand binding combined with autoradiography or measurement of AC activity confirmed and extended the results of physiological studies. D_1 receptors associated with stimulation of AC have been identified in the renal, mesenteric, and splenic arteries (307) and were shown to be concentrated in the medial layer and to be insensitive to chemical sympathectomy (5), thus confirming their preferential postjunctional localization.

D_2 receptors were shown to be localized in the adventitial as well as the adventitial-medial border and intimal layer of renal, mesenteric, and splenic arteries (4) and to be associated with inhibition of AC (307). Chemical sympathectomy remarkably reduced the density of D_2 receptors in the adventitial and adventitial-medial layers, but not in the intimal layer (4), thus suggesting that both prejunctional and postjunctional D_2 receptors are present in arterial vessels. In addition, chemical sympathectomy did not modify the extent of inhibition of AC by D_2 agonists, suggesting that postjunctional D_2 receptors are associated with inhibition of cAMP formation, whereas prejunctional D_2 receptors are not (307). The role of postjunctional D_2 receptors in arterial physiology has yet to be revealed.

The pharmacological profiles of D_1 and D_2 receptors in blood vessels are very similar to those of D_1 and D_2 receptors in the CNS. It should be noted, however, that the compounds shown to partially discriminate among different DA receptor subtypes have not been tested on these tissues and that the existence of the mRNAs for D_1-like and D_2-like receptors in the vasculature has not been investigated to date. Thus, although the definition of DA receptors in the arteries as D_1 and D_2 is generally accepted, further studies are necessary to definitely ascertain their molecular identity.

B. Dopamine Receptors Controlling the Renin-Angiotensin-Aldosterone System

1. *Effects of dopamine on renin secretion*

The physiological role of a direct dopaminergic mechanism in the regulation of renin secretion is still a matter of controversy. The wide range of activity of DA in the cardiovascular system makes the results of in vivo studies difficult to interpret. The effects of DA on blood pressure, cardiac output, and regional blood flow distribution may in fact indirectly influence renin secretion.

In vivo studies in conscious and anesthetized dogs have shown that intrarenal infusions of DA either increases renin secretion, an effect associated with renal vasodilatation, or does not affect plasma renin activity (PRA) (reviewed in Ref. 309). In most studies in humans, no consistent effects of intravenous infusion of DA on renin secretion were observed (54, 53, 115, 334, 423). Fragmentary observations reported that infusion of low doses of DA or administration of gludopa decreased PRA, whereas high, pressor doses of DA increased PRA in healthy subjects (reviewed in Ref. 309). Administration of either bromocriptine to normal subjects in sodium balance (56) or dihydroergotoxine to hypertensive patients kept on both normal and low sodium intake (271) does not modify PRA. On the other hand, it has been shown that D_1 agonists can stimulate renin secretion from renal cortical slices (9, 241) and that D_1 receptors are present on renin-containing vesicles within the juxtaglomerular apparatus (336). Thus the major effect of DA on renin secretion is stimulatory and is mediated by D_1 receptors.

2. *Dopaminergic mechanisms controlling aldosterone production*

The first evidence for a role of DA in the control of aldosterone secretion came from in vivo studies in both humans and experimental animals.

Administration of the D_2 antagonist metoclopramide

to both rats and humans was shown to increase plasma aldosterone levels without modifying any of the known stimulators of the hormone release, an effect that was blocked by intravenous infusion of DA (56, 334, 422). Administration of DA and of DA agonists such as bromocriptine, however, did not modify basal plasma aldosterone levels (37, 53, 56, 57, 470). These observations thus suggested that aldosterone production is under maximum tonic dopaminergic inhibition.

Subsequent studies confirmed this hypothesis and pointed to the sodium balance state as being crucial for the effects of exogenous DA on aldosterone secretion. During sodium depletion, DA excretion is decreased, circulating aldosterone is increased, and plasma aldosterone responsiveness to angiotensin II is increased (57, 191). Reciprocal findings were reported in the sodium-replete state (2). According to these concepts, it has been shown that the increase in plasma aldosterone levels induced by angiotensin II infusion and by upright posture was remarkably inhibited by both DA and D_2 agonists in normal subjects in metabolic balance at low sodium intake, but not in sodium-repleted subjects (58, 115, 276). Similarly, the D_2 agonist dihydroergotoxine remarkably reduced plasma aldosterone levels in hypertensive patients kept on a low-sodium diet (271). The effects of DA on aldosterone secretion have been demonstrated to be mediated by D_2 receptors located on adrenal glomerulosa cells.

3. Dopamine receptors in the adrenal cortex

In vitro binding studies indicated that saturable and stereospecific binding sites labeled by [^{3}H]spiperone, ^{3}H-labeled 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN), and (−)-[^{3}H]sulpiride are present in bovine and rat adrenal cortex. The pharmacological characterization of the binding sites made it possible to classify DA receptors in the adrenal cortex as D_1 and D_2 (reviewed in Ref. 309). Autoradiographic analysis of [^{3}H]spiperone binding revealed that the majority of adrenocortical D_2 receptors are concentrated in the zona glomerulosa and, to a lesser extent, in the zona reticularis. The same pattern of D_2 receptor distribution has been found in the human adrenal cortex (3). No information is available to date concerning the presence of the other D_2-like and D_1-like receptors in the adrenal cortex.

Analysis of the transduction pathways activated by DA receptors in glomerulosa cells revealed that D_1 receptors are associated with stimulation of AC (308). D_2 receptors have been shown to inhibit both cAMP formation (308) and T-type voltage-dependent calcium channels in this tissue (146, 346).

In vitro studies with isolated adrenal glomerulosa cells demonstrated that activation of D_2 receptors resulted in a remarkable inhibition of angiotensin II-induced aldosterone secretion but did not modify the hormone release under basal conditions or after stimulation by adrenocorticotropic hormone (311). Consistent with this, it has also been shown that activation of D_2 receptors inhibits cAMP formation and Ca^{2+} influx, both induced by angiotensin II (146, 309). These data thus indicated that the effects of DA on aldosterone secretion are mediated by D_2 receptors in adrenal glomerulosa cells and pointed to a selective, functional interaction between DA and angiotensin II in the regulation of the production of aldosterone.

One issue that is still open concerns the origin of DA in this system. In particular, whether D_2 receptors in glomerulosa cells are the target of circulating DA or whether a dopaminergic innervation is present in the adrenal cortex is still matter of investigation. No evidence for the presence of dopaminergic terminals in the adrenal cortex has been reported so far. However, it has been shown that noradrenergic varicosities surrounding the zona glomerulosa are able to accumulate DA from the circulation and to release it in response to neural activity or to convert it into norepinephrine (358, 453), thus providing the possibility of a fine tuning of local circulation and glomerulosa cell activity.

C. Dopamine Receptors Controlling Catecholamine Release

The presence of DA-containing cells in sympathetic ganglia, i.e., small intensely fluorescent (SIF) cells, has been known for a long time. In vivo studies on anesthetized dogs and in vitro studies on arterial preparations pointed to the existence of D_2 receptors on sympathetic nerve endings inhibiting norepinephrine release (4, 166, 307). Subsequent studies identified D_2 receptors and D_2 receptor mRNA in adrenal medulla and in isolated chromaffin cell preparations (272, 361). Functional studies in the anesthetized dog reported that activation of adrenomedullary D_2 receptors by quinpirole inhibited epinephrine release induced by splanchnic nerve stimulation, whereas blockade of these receptors by domperidone potentiated the adrenal response to nerve stimulation (139). Similarly, stimulation of D_2 receptors reduced epinephrine and norepinephrine content in rat adrenal gland (316). These effects have been suggested to be mediated through inhibition of slowly inactivating, voltage-gated calcium channels by D_2 receptors (35, 36).

In line with these data are the results of studies in humans showing that blockade of D_2 receptors by domperidone induces a greater norepinephrine and epinephrine release in response to physical exercise (281) and to glucagon (280). Similarly, activation of D_2 receptors by bromocriptine produced a significant decrease in plasma norepinephrine both in the supine and in the upright posture (280).

Studies with radiolabeled ligands did not reveal the presence of D_1 receptors in the adrenal medulla. However, the development of fluorescent ligands for DA receptors made it possible to prove the previously unappreciated existence of D_1 receptors in adrenal chromaffin cells by fluorescence microscopy (14). Stimulation of these receptors activates the facilitation 27-pS dihydropyridine-sensitive calcium channels in the absence of predepolarizations or repetitive activity (14). Facilitation calcium channels in unstimulated bovine chromaffin cells are normally quiescent and are activated by large predepolarizations or by repetitive depolarizations, such as increased nerve splanchnic activity. This activation resulting in a twofold increase in calcium current suggests a physiological role for these channels in stimulating rapid catecholamine secretion in response to danger or stress (14). The recruitment of these channels by D_1 receptor stimulation may thus be the basis of a positive-feedback loop mechanism for catecholamine secretion mediated by DA (14).

In conclusion, DA seems to have a dual effect on catecholamine release, a tonic inhibitory activity mediated by D_2 receptors on sympathetic nerve endings and on chromaffin cells, and a stimulatory action mediated by D_1 receptors on chromaffin cells that can be activated in response to stressful situations.

D. Dopamine Receptors in the Kidney

Dopamine has been shown to act at specific dopaminergic receptors in the renal vasculature and renal parenchyma to produce changes in renal function (reviewed in Ref. 166). Although regulation of calcium (284) and phosphate (88, 97, 163, 211, 224) excretion by DA have also been described, the bulk of recent investigations have focused on the regulation of sodium homeostasis, and the effects of renal dopaminergic regulation of sodium handling have been found to be most pronounced under conditions of mild sodium excess (46, 72, 177, 363).

Intravascular administration of DA causes increases in renal blood flow and in sodium and water excretion in human subjects (2, 87, 164, 288) and experimental animals (19, 291, 353). At low doses, which do not affect systemic hemodynamics, DA produces renal vasodilation, diuresis, and natriuresis (50, 300), and these effects have led to the clinical use of low-dose DA infusion in certain pathological conditions (165, 251, 364). Either high dietary salt intake or volume expansion with normal saline causes a rise in urinary excretion of DA with a concomitant natriuresis and diuresis (183, 335) that can be blocked by administration of dopaminergic antagonists (143, 237).

Within the kidney, DA is formed in renal nerves and in the epithelial cells of certain nephron regions. Dopaminergic nerve endings have been detected in proximity to the vascular pole/juxtaglomerular apparatus of renal cortical glomeruli (23, 110), and neural input appears to be important for regulation of the renal hemodynamic responses to volume expansion with saline (185). Dopamine formed within the renal tubular epithelium also acts as an intrarenal paracrine or autocrine hormone to regulate the reabsorption of sodium ions within the nephron (24, 130, 198, 222, 247, 249). Furthermore, D_1 dopaminergic agonists stimulate the secretion of renin (9, 241), and interactions of dopaminergic signal transduction with signaling by other renal hormones such as angiotensin II (71), atrial natriuretic peptide (182, 462), and antidiuretic hormone (321) have been described.

Interestingly, some patients with hypertension and animal models of essential hypertension exhibit abnormal dopaminergic responses to saline loading or inefficient dopaminergic signal transduction through renal DA receptors. It is possible that molecular characterization of the DA receptor subtypes and mechanisms of dopaminergic signal transduction within the kidney will lead to the identification of potential targets for new antihypertensive agents.

1. *Pharmacology and signal transduction of renal dopamine receptors*

A) D_1-LIKE RECEPTORS. Studies of D_1-like receptor binding on membranes prepared from homogenates of renal cortex (131, 200, 323, 412), purified renal proximal tubules (127), kidney-derived established cell lines (20), and primary cultures (44) have shown that the pharmacological profiles of renal DA receptors are very similar to those of central DA receptors (44). Dissociation constants for D_1-selective ligands are higher in homogenates of renal tissue than in membrane preparations from the brain (412). However, the dissociation constants for binding of D_1-selective ligands to the opossum kidney (OK) cell D_1 receptor are higher when the receptor is expressed endogenously in OK cell membranes than when the receptor is transfected into COS cells, although comparison reveals a linear relationship between the two data sets (20, 326). This suggests that some factor independent of the primary sequence of the protein might be responsible for the lower affinities of drugs for renal receptors.

Adenylate cyclase is stimulated by DA or dopaminergic agonists in renal preparations (124, 410) with an order of agonist potency that resembles the DA-stimulated AC in striatal membranes, although the efficacy of all agonists appears to be reduced two- to fivefold in renal membranes in comparison with brain preparations (130). Dopamine and D_1-specific agonists also stimulate PI hydrolysis in proximal tubules by a cAMP-independent mechanism (124, 126). Both the human and goldfish D_1 receptors have been found to increase intracellular calcium when expressed in HEK 293 cells by a cAMP-dependent mechanism (263).

B) D_2-LIKE RECEPTORS. Radioligand binding identified high-affinity and low-affinity haloperidol binding sites in homogenates of renal cortex and high-affinity spiroperidol sites in purified proximal tubule cells. The high-affinity site shows a pharmacological profile very similar to central D_2 receptors (21, 127, 323). Radioligand autoradiography of rat renal slices with [^{3}H]spiperone has been used to characterize a D_2-like receptor that has been termed the D_{2K} (207). The pharmacological profile of this receptor appears unique to the kidney; however, there are insufficient data for a satisfactory comparison with the cloned D_3 and D_4 receptors (401).

Dopamine inhibits AC in isolated glomeruli (129) and rat renal cortical membranes (369). In inner medullary collecting duct cells, the putative D_{2K} receptor has been linked to the production of prostaglandin (PG) E_2 by phospholipase A_2 and to the mobilization of intracellular calcium via a PTX-sensitive G protein (204, 206).

2. Dopaminergic sites of action within the kidney

A) GLOMERULUS. At the vascular pole of the glomerulus, DA has been shown to exert a dose-dependent relaxation of both efferent and afferent glomerular arterioles (117) that is mimicked by D_1 agonists fenoldopam or SKF-87516 and blocked by a D_1 antagonist (118). In the rat, DA released from intrarenal nerve endings plays a role in the increased glomerular filtration rate that is part of the dopaminergic response to volume expansion with saline or increased dietary intake of salt (16). Although the importance of dopaminergic neurotransmission is controversial (40, 107), DA has been shown to regulate the release of norepinephrine through D_2 receptors located on nerve endings (381). Dopamine receptors within the vascular elements adjacent to the renal glomeruli, or D_1-like receptors in mesangial cells, may be at least in part responsible for DA-induced changes in glomerular filtration rate.

D_1-like receptors have been identified within the juxtaglomerular apparatus by the ability of fenoldopam to stimulate the secretion of renin from renal cortical tissue slices (9, 241). Electron microscopic immunocytochemical experiments have recently demonstrated the presence of D_1 receptors on renin-containing granules within the juxtaglomerular apparatus (336).

Experiments with isolated glomeruli demonstrated a weak inhibition of adenylyl cyclase at high concentrations of DA, which may indicate the presence of D_2-like receptors (129), although autoradiography using the D_2-selective radioligand [^{3}H]spiroperidol failed to detect any specific binding within the glomeruli (369). Binding experiments with D_1-selective radioligands are inconclusive, since some groups (199, 437), but not others (131, 205), report the presence of specific binding within the glomeruli. Immunohistochemistry also failed to detect the presence of the D_1 receptors in rat glomeruli (336). On the other hand, primary cultures of rat glomerular mesangial cells express a D_1-like receptor that has been well characterized pharmacologically (43, 44).

B) PROXIMAL TUBULE. The proximal tubule is the site of reabsorption for two-thirds of the water and sodium present in the glomerular filtrate as well as for virtually all important metabolic products (e.g., amino acids and glucose) (279, 382). Membranes prepared from isolated proximal tubules contain both D_1-like and D_2-like receptors (127). Thus the proximal tubule is likely to play an important role in the natriuretic and diuretic responses to renal DA.

The proximal tubule also is the major site of DA synthesis within the kidney due to a high concentration of L-aromatic amino acid decarboxylase at the apical pole of the tubular epithelium (33). The vast majority of urinary DA is derived from L-dopa that is decarboxylated at this epithelial site (481). The regulation of intrarenal DA synthesis is still not well understood; however, plasma sodium concentration is thought to act at several levels to increase the effective concentration of DA (reviewed in Ref. 419). First, the uptake of L-dopa is sodium dependent; thus higher sodium concentrations yield a higher rate of substrate delivery (419). Additionally, an increase in sodium concentration inhibits the oxidation/inactivation of DA by monoamine oxidases in tissues slices (419). In the intact animal, however, a simple increase in the concentration of sodium within the renal tubules is not sufficient to trigger the dopaminergic response associated with increased dietary salt intake or volume expansion with isotonic saline (184).

Tubular DA acts to inhibit the reabsorption of sodium within the proximal tubule and possibly at more distal sites along the nephron (202, 382). Dopamine inhibits the apical Na^+/H^+ antiporter in proximal tubule cells (156) via activation of D_1-like receptors (218) by both cAMP-dependent (125) and cAMP-independent (123) mechanisms. This protein is responsible for the vast majority of sodium uptake from the glomerular filtrate. Additionally, the reuptake of sodium is dependent on the maintenance of a gradient in sodium concentration across the cellular membrane that is produced by the action of Na^+-K^+-ATPase located on the basolateral membrane of the epithelial cell. Dopamine has been found to inhibit the action of Na^+-K^+-ATPase (17) by a mechanism that requires activation of both D_1-like and D_2-like receptors. Selective agonists, in fact, have no effect, whereas combined treatment with D_1 and D_2 agonists mimic the effects of DA (31, 388, 437), suggesting the existence of D_1/D_2 synergism at this level. The mechanism by which DA acts to inhibit Na^+-K^+-ATPase is still not well understood. In experiments using isolated proximal tubules, DA inhibition of Na^+-K^+-ATPase was shown to be dependent on activation of PKC (36, 388). In vitro studies demonstrate that phosphoryla-

tion of the catalytic subunit of Na^+-K^+-ATPase with either PKA or PKC is sufficient to inhibit pump activity (32, 195). However, within the proximal tubule, PKA does not appear to be responsible for Na^+-K^+-ATPase inhibition (388). Furthermore, the straightforward mechanism of a direct interaction of Na^+-K^+-ATPase with PKC leading to an inhibition of the pump does not readily account for the requirement of both D_1-like and D_2-like receptor activation (70). The inhibition of Na^+-K^+-ATPase by DA has been shown to be sensitive to mepacrine, an inhibitor of phospholipase A_2 (388). Although further investigations are warranted, the fact that activation of D_1 and D_2 subtype DA receptors coexpressed in CHO cells leads to a synergistic enhancement of AA release (356) supplies further evidence for a role of arachidonate pathways in dopaminergic inhibition of Na^+-K^+-ATPase.

Dopamine in the proximal tubule inhibits sodium-coupled transport of phosphate (211). This effect has also been demonstrated in OK cells (163), an established cell line model of the proximal tubule epithelium that expresses only the D_1 receptor (326). This result suggests that activation of this subtype is sufficient for phosphate transport inhibition.

C) DISTAL TUBULE SEGMENTS. Studies of sodium reabsorption during DA infusion have demonstrated that DA-induced natriuresis is due to increased delivery of sodium from the proximal tubule, which is inadequately compensated for by the distal nephron segments (342). Because the distal nephron is, in general, theoretically capable of compensation for increases in sodium delivery, the poor compensation observed during DA infusion may arise from the action of DA at sites along the distal nephron. In line with this assumption, specific DA binding sites have been detected in all cortical and outer medullary nephron segments with the highest density present in the proximal tubule (186, 437). The presence of D_1-like receptors in the medullary thick ascending limb of the loop of Henle had been strengthened by the presence of DA-sensitive Na^+-K^+-ATPase and by the expression of DA- and cAMP-regulated phosphoprotein (DARPP-32) (294). In the outer renal medulla, the presence of D_1-like receptors has been supported by the presence of a DA-sensitive AC (6). D_1-like receptors in the thick ascending limb inhibit Na^+-K^+-ATPase by a cAMP-dependent mechanism that appears to involve DARPP-32 (294), and thus different from the mechanism of inhibition in the proximal tubule. Additionally, D_1-like receptor binding and AC stimulation are present in the cortical collecting duct (CCD) (339, 436). In the CCD, DA-stimulated increases in intracellular cAMP inhibit Na^+-K^+-ATPase by a mechanism that involves phospholipase A_2 (387). The dopaminergic blockade of the action of vasopressin (236, 321) is also thought to occur in the distal nephron. The mechanism of this effect is unclear, but no inhibition of the vasopressin-stimulated AC was observed in microdissected CCD after treatment with fenoldopam (339). The antagonism of vasopressin signaling observed physiologically is hypothesized to involve D_2-like receptors (339). The intramedullary collecting duct has been demonstrated to express the so-called D_{2K} receptor (204, 206, 207). The specific role of this receptor in the dopaminergic control of renal function remains unclear, although PGE_2 is an inhibitor of sodium transport (181) and of Na^+-K^+-ATPase (81, 389), and DA-sensitive release of PGE_2 has been demonstrated to increase during salt loading (475).

3. *Identification of cloned dopamine receptor subtypes within the kidney*

A) D_1-LIKE RECEPTORS. The mRNA for both D_1 and D_5 receptors has been detected by ribonuclease protection in mammalian kidney (326, 473), and the D_1 has also been detected by PCR and in situ hybridization in the rat kidney (295, 473). The D_1 subtype is also endogenously expressed in both the OK cell and LLC-PK_1 cell lines (20, 173, 174, 326). Immunohistochemistry with D_1-specific antibodies has localized this receptor within the renal artery, intrarenal vasculature, juxtaglomerular apparatus, proximal tubule, and CCD (336). No D_1 immunoreactivity was observed in the glomeruli. Within the proximal tubule epithelium, D_1 immunoreactivity was observed in both basolateral and apical membranes (336).

B) D_2-LIKE RECEPTORS. Expression of mRNA from all of the cloned D_2-like receptor genes has been detected in mammalian kidney by PCR, including the D_{2L} in rat (148), the D_3 in rat (420), and the D_4 in human kidney (285). Autoradiography with [^{3}H]spiroperidol demonstrated D_2-like binding in cortical tubules from both proximal and distal nephron segments, medullary collecting tubules, and intrarenal arteries (4, 370). However, no further information is presently available concerning the intrarenal localizations and putative functions of these receptor subtypes.

C) UNCLONED RECEPTOR SUBTYPES. Several arguments have been proposed for the existence of additional uncloned DA receptors in the kidney. One is that the question of whether the cloned D_1-like receptors are able to couple to PI hydrolysis remains unanswered. Renal D_1-like receptors have been shown to be associated to PI turnover. The report of D_1 receptors-coupled PI turnover in the striatum (275), however, is controversial (380). On the other hand, coupling of D_1 receptors to PI hydrolysis has been reported (263). Another argument is that the low levels of D_1-like receptor mRNAs detected in the kidney do not account for the relatively high levels of D_1 ligand binding in renal tissue (336). Finally, some experiments have revealed biphasic binding curves with D_1-selective ligands (most notably with SCH-23390) in renal cortical membranes (131, 200, 205) or kidney-derived cell lines (20), and the lower affinity site has been suggested to

potentially represent an unidentified subtype (20, 198). This lower affinity site has been demonstrated, however, to lack stereoselectivity and most likely represents binding to a nonreceptor site (192). With respect to potential novel D_2-like subtypes, a fair argument can be made that the D_{2K} binding site described in inner medullary collecting duct is pharmacologically different from the cloned D_2 receptor (204, 206, 207). However, insufficient data are available to allow a satisfactory comparison of the D_{2K} binding site with the pharmacological properties of the cloned D_3 and D_4 DA receptor subtypes (401). Because the current understanding of the localizations and functions of the cloned DA receptor subtypes within the kidney remains fragmentary, the suggestion of the existence of novel receptor subtypes in renal tissue remains highly speculative.

XI. DOPAMINERGIC SIGNAL TRANSDUCTION AND HYPERTENSION

A. Human Hypertension

Several lines of evidence suggest that defects in the renal dopaminergic system may underlie some forms of essential (idiopathic) hypertension. Several groups of patients with high blood pressure have been found to have either high (238, 383) or low (10, 208, 209) levels of urinary DA excretion, suggesting a heterogeneity of underlying defects (238). Although normal subjects demonstrate a rise in urinary DA excretion after salt loading (335), some hypertensive patients display a paradoxical fall in urinary DA excretion (180). Furthermore, some hypertensive patients have been shown to respond with an exaggerated level of natriuresis and diuresis to the administration of DA (8), fenoldopam (55), or a dopaminergic prodrug (gludopa, Ref. 248). Comparison of normotensive subjects with or without a family history of hypertension revealed abnormal levels of DA excretion before the development of high blood pressure, suggesting that the dopaminergic abnormalities are not a secondary effect (208, 384, 409).

B. Animal Models of Hypertension

Two rat models of genetic hypertension, the Dahl salt-sensitive strain and the spontaneously hypertensive rat (SHR) Okamoto-Aoki strain, display abnormalities in renal DA production or signal transduction (133, 221, 239). After introduction of a high-salt diet, DA production decreased in the Dahl strain (100, 239, 474) reminiscent of the response of low renin essential hypertension patients (239). The Dahl strain also shows an impaired natriuretic and diuretic response to volume expansion with isotonic saline (385). Examination of isolated proximal tubules from these animals revealed a decreased ability of dopaminergic agonists to stimulate production of cAMP (340) and a loss of the dopaminergic regulation of Na^+-K^+-ATPase (331, 332).

In contrast, 4-wk-old SHR have higher urinary DA levels than control rats (475), and maintenance on a high-salt diet increased DA production in a manner similar to the response of some groups of essential hypertension patients (238, 239, 408). This strain also possesses a blunted natriuretic response to administration of D_1 agonists (134) despite a similar DA D_1-like receptor density to Wistar-Kyoto rats (WKY), the normotensive counterpart of SHR (231, 414). Comparison of the receptor density of both D_1-like and D_2-like receptors in the proximal tubules of both the SHR and WKY strains revealed no interstrain differences up to the age of 75 wk (48). However, stimulation of AC by D_1 agonists is defective in isolated proximal tubules, although stimulation of AC by parathyroid hormone or forskolin is intact (231). This defect in signal transduction is specific to this nephron segment, since AC was stimulated normally by the D_1 receptor in cortical collecting duct (341) and striatum (123). Activation of PLC by D_1 agonists is also defective (73). Competition binding of D_1 agonists for the DA receptor in the proximal tubule reveals only a low-affinity site that is insensitive to nonhydrolyzable GTP analogs, and this abnormality of the ligand binding site persists after solubilization of the receptor (414). In comparison with tissue from WKY, there is a relative inability of dopaminergic agonists but not antagonists to protect the binding site from photoaffinity labeling (446). The loss of high-affinity agonist binding suggests a defect in G protein coupling that is reinforced by the observation that coadministration of G protein activators (e.g., NaF) and fenoldopam yields a synergistic inhibition of angiotensin II-induced vasoconstriction (68).

Isolated proximal tubules from SHR show a decrease in dopaminergic inhibition of Na^+/H^+ antiporter activity (157, 194). Although Na^+-K^+-ATPase activity is increased in the proximal tubule of the SHR strain through the age of 5 wk (150, 176), dopaminergic inhibition of Na^+-K^+-ATPase is also impaired (69). Investigation of the effect of cholera and PTXs on DA inhibition of Na^+-K^+-ATPase in SHR demonstrated that this effect could be partially recovered after treatment of proximal tubule preparation with PTX (176). Interestingly, the regulation of sodium-coupled phosphate transport appears to function normally in these animals (98). Amplification of a region of the D_1 gene by PCR from the genomic DNA of SHR revealed no mutations within the third intracellular loop, a region which is important for G protein coupling, although other receptor regions were not examined (473). Defects may also be present in downstream components of the dopaminergic signal transduction pathway, since the Na^+/H^+ exchange activity within the proximal tubule was inhibited by exogenously added

8-chlorophenylthio-cAMP in 3- to 4-wk old rats, but this inhibition was lost in adults (194).

Although it is not at all clear that the underlying defects in these animal models correspond to those underlying human pathology, it would seem clear that the study of DA receptors and dopaminergic signal transduction in the kidney holds the promise of providing a better understanding of the pathophysiology of human hypertension and will perhaps also lead to the identification of new molecular targets for therapeutic intervention and new pharmacological agents.

In conclusion, the distribution and function of receptors for DA within the cardiovascular system is such that DA agonists, by acting at different levels, may induce changes that synergistically operate to reduce blood pressure, thus making them the potential target for a new class of antihypertensive drugs. In particular, the dilatation of splanchnic vascular beds, the reduction of circulating catecholamines, the inhibition of norepinephrine release at synaptic terminals, the inhibition of stimulated aldosterone secretion, and the increase of sodium excretion are involved in the hypotensive effects of DA.

Similarly, the property of DA of reducing afterload through D_1 receptor-mediated vasodilatation, of increasing renal blood flow and improving renal function, and of decreasing aldosterone secretion and norepinephrine release together with its positive inotropic effect provide beneficial hemodynamic effects that have potential applications in the treatment of congestive heart failure (165).

XII. CONCLUDING REMARKS

The development of the recombinant DNA technologies made it possible to identify new DA receptor subtypes and provided valuable information about the structure of the receptor proteins. The use of site-directed mutagenesis and receptor chimeras allowed us to find the determinants of ligand binding and of coupling to specific G proteins. The use of PCR and in situ hybridization with the cloned DA receptor probes made it possible to define the localization of DA receptor subtypes even in brain areas where they were undetectable with more classical methods. The progress made in the study of signal transduction has played a critical role in providing a molecular basis to understand how activation of DA receptors translates in changes in neuronal and peripheral cell function. On the other hand, two major issues are still open: *1*) pharmacological agents selective for each receptor subtype are not yet available, and *2*) the physiological function of the newly cloned DA receptor subtypes is still mostly unknown. Thus, if the structural and transductional properties of each DA receptor subtype have now been largely elucidated, defining their physiological functions and finding selective potential therapeutic agents remain the challenges of the next years.

There are indications that the diversity in DA receptors will not be limited to the five subtypes already characterized. Biochemical, pharmacological, and molecular studies suggested the existence of further heterogeneity within D_2 receptors in the pituitary. Although the majority of DA agonists can activate with the same efficiency both inhibition of AC and opening of potassium channels in pituitary lactotrophs (65, 212, 269, 270, 298), the benzazepine derivative BHT-920 does not inhibit cAMP formation, while activating potassium channels (357). This observation may suggest that two distinct D_2-like receptor subtypes may exist with different affinities for BHT-920 and be individually coupled to one or the other signaling pathway. Consistent with this idea are the results of binding studies in the anterior pituitary and in the striatum, unraveling the existence of an extra D_2 site with low affinity for spiperone (398) and in GH_3 cells that express a D_2-like receptor with an unusual low affinity for haloperidol in response to NGF (305). Similarly, studies with the kidney pointed to the existence of a unique renal D_2-like receptor (D_{2K}) and suggested the existence of heterogeneity within D_1-like receptors as well.

Behavioral studies also suggested the existence of D_1-like receptors that either display unique affinities for some D_1-selective compounds or are not defined as AC coupled (13, 94, 113, 301). In addition, evidence showing differential order of potencies and efficacies for a series of benzazepine compounds in stimulating phosphoinositide hydrolysis and in activating AC in brain tissues suggests that the D_1 receptor that is linked to PLC differs from that coupled to AC (445). In line with this, it has been shown that when rat striatal mRNA is fractionated and then expressed in *Xenopus* oocytes, the mRNA fraction that demonstrates a PLC-coupled DA receptor is prominently different in size from AC-coupled D_1 receptor mRNA (275). The recent cloning and characterization of a novel D_1-like receptor subtype, named D_{1C}, from *Xenopus laevis* (430) and of another unique subtype, named D_{1D}, from *Gallus domesticus* (101) may hint to the existence of a further heterogeneity within mammalian D_1-like receptors.

In spite of this evidence, however, cloning by homology has not identified any new DA receptor in mammals since 1991. However, the possibility should not be excluded that, as is the case for other neurotransmitters, DA receptors structurally divergent from the ones that have been already cloned still remain to be identified and characterized.

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