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The D_3 Dopamine Receptor: Neurobiology and Potential Clinical Relevance

BETH LEVANT[a]

Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, Kansas City, Kansas

I. Introduction

Dopamine is a major neurotransmitter in the central nervous system. Receptors for this catecholamine are of considerable interest, as they are the principal target of drugs employed in the treatment of neuropsychiatric disorders such as schizophrenia and Parkinson's disease. Before 1990, the dopamine receptor population in brain and periphery was believed to consist of two subtypes, D_1 and D_2 (Seeman and Grigoriadis, 1987; Vallar and Meldolesi, 1989; Levant, 1996). These receptors have been extensively studied by using a variety of methodologies including behavioral, physiological, neurochemical, pharmacological, and, more recently, molecular approaches in vivo and in vitro. The D_1 receptor is located postsynaptically, has low-nanomolar affinity for dopamine, and stimulates adenylyl cyclase activity. The D_2 receptor has nanomolar affinity for dopamine and is

[a] Address for correspondence: Beth Levant, Ph.D., Department of Pharmacology, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160-7417.

located both pre- and postsynaptically. The D_2 site is negatively coupled to adenylyl cyclase and is also associated with other signal transduction systems such as a potassium channel and the phosphoinositide cascade. Both D_1 and D_2 receptors exist in high- and low-affinity states for dopamine agonists. Conversion between the high- and low-affinity conformations appears to be mediated by sodium ions and guanyl nucleotides. Likewise, both dopamine receptor subtypes are distributed heterogeneously throughout the central nervous system with highest densities in the striatum, nucleus accumbens, olfactory tubercles, and substantia nigra pars compacta.

We now know that the D_1 and D_2 subtypes represent families of dopamine receptors. After the cloning of the D_1 and D_2 receptors (Bunzow et al., 1988; Monsma et al., 1990; Zhou et al., 1990), several additional low-abundance dopamine receptors were identified. These novel subtypes include the D_3 and D_4 receptors, which are similar to D_2, and the D_5 receptor, which is similar to D_1 (Sokoloff et al., 1990; Van Tol et al., 1991; Sunahara et al., 1991). The D_3 receptor was initially cloned from a rat complementary DNA library by Sokoloff and colleagues (1990) by using probes derived from the D_2 dopamine receptor sequence. The cloning of the human D_3 receptor was reported shortly thereafter (Giros et al., 1990), followed by the murine D_3 receptor (Fishburn et al., 1993). This receptor has been of particular interest because of its hypothesized role as a therapeutic target in the treatment of schizophrenia and drug abuse.

Although still in the early stages, considerable progress has been made in the study of the D_3 receptor. As with the other recently identified receptors, the tools initially available to investigate the D_3 receptor were molecular rather than pharmacological. These powerful tools enabled the selective study of the receptors in vitro by transfection in cells that do not normally express dopamine receptors. Molecular methods also allowed the study of receptor messenger ribonucleic acid (mRNA[b]) in brain. However, only in the last few years have putatively selective pharmacological agents and other tools been identified. These tools have enabled the study of the D_3 receptor protein in brain. This article reviews the progress made to date in assessing the neurobiological role of this novel receptor. Its relevance in disease and as a potential therapeutic target is also discussed.

II. Molecular Biology

A. Receptor Taxonomy

Based on amino acid sequence and gene organization, the D_3 receptor has been classified as a member of the family of D_2-like dopamine receptors (Sibley et al., 1993) (fig. 1). Unlike genes for the D_1-like receptors that do not contain introns, the D_2, D_3, and D_4 receptor genes contain intervening sequences. The D_2-like receptors are also characterized by relatively long 3rd intracellular domains and short carboxy termini relative to the D_1-like receptors. The D_2-like receptors possess moderate sequence homology with the D_1-like receptors. For example, the rat D_1 and D_2 receptors possess only 41% homology in the transmembrane domains (Monsma et al., 1990). In contrast, the rat D_3 receptor possesses 52% homology with the rat D_2 receptor, with 75% homology in the transmembrane domains (Sokoloff et al., 1990). The D_2 and D_3 receptors exhibit 39% and 41% overall homology with the D_4 receptor, respectively (Van Tol et al., 1991).

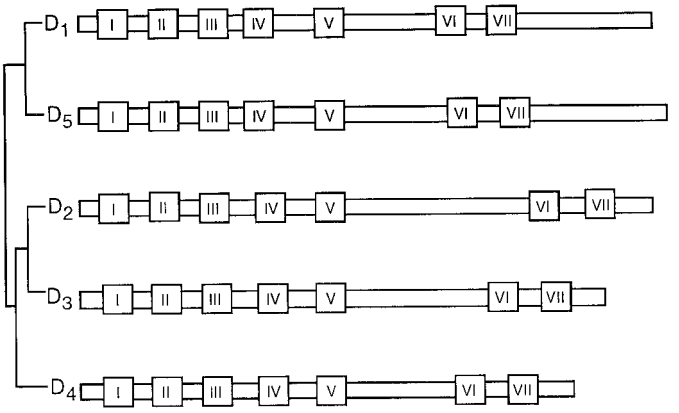

FIG. 1. Dendrogram of the family of dopamine receptors. The D_1 and D_5 receptors are characterized by a short third intracellular loop and long intracellular carboxy termini. The D_2, D_3, and D_4 receptors possess a long third intracellular loop and a short intracellular carboxy termini. The rat D_3 and D_4 receptors exhibit 52 and 41% homology with the D_2 receptor, respectively. The D_3 and D_4 receptors share 39% homology. Proposed receptor topography is presented schematically. Boxes represent transmembrane domains I–VII.

B. Gene Organization and Receptor Synthesis

The rat D_3 gene encodes a primary transcript initially reported to contain six exons and five introns (Sokoloff et al., 1990). Similarly, the human D_3 receptor gene, localized on chromosome 3, band 3q13.3 (Le Coniat et al., 1991), encodes a primary mRNA of more than 53,000 base pairs with six exons and five introns (Griffon et al., 1996) (fig. 2). The translated human protein exhibits 78% homology with the rat D_3 receptor but differs in that there is a deletion of 46 residues in the 3rd intracellular loop (Giros et al., 1990). The primary transcripts for the rat and human D_3 receptor mRNA appear to differ from that of the D_2 receptor in which both rat and human receptor primary transcripts contain seven exons and six introns. The additional exon in the D_2 receptor gene, located in the region encoding the 3rd intracellular domain, allows the formation of two functional alternate splice variants, D_{2L} and D_{2S}, which vary in the length of 3rd intracellular loop (Dal Toso et al., 1989; Giros et al., 1989). The apparent lack of an analogous

[b] Abbreviations: CHO, Chinese hamster ovary; mRNA, messenger ribonucleic acid; 7-OH-DPAT, 7-hydroxy-dipropylaminotetralin; 7-OH-PIPAT, [^{125}I](R)-*trans*-7-hydroxy-2-[*N*-propyl-*N*-]3′-iodo-2′-propenyl)amino]tetralin.

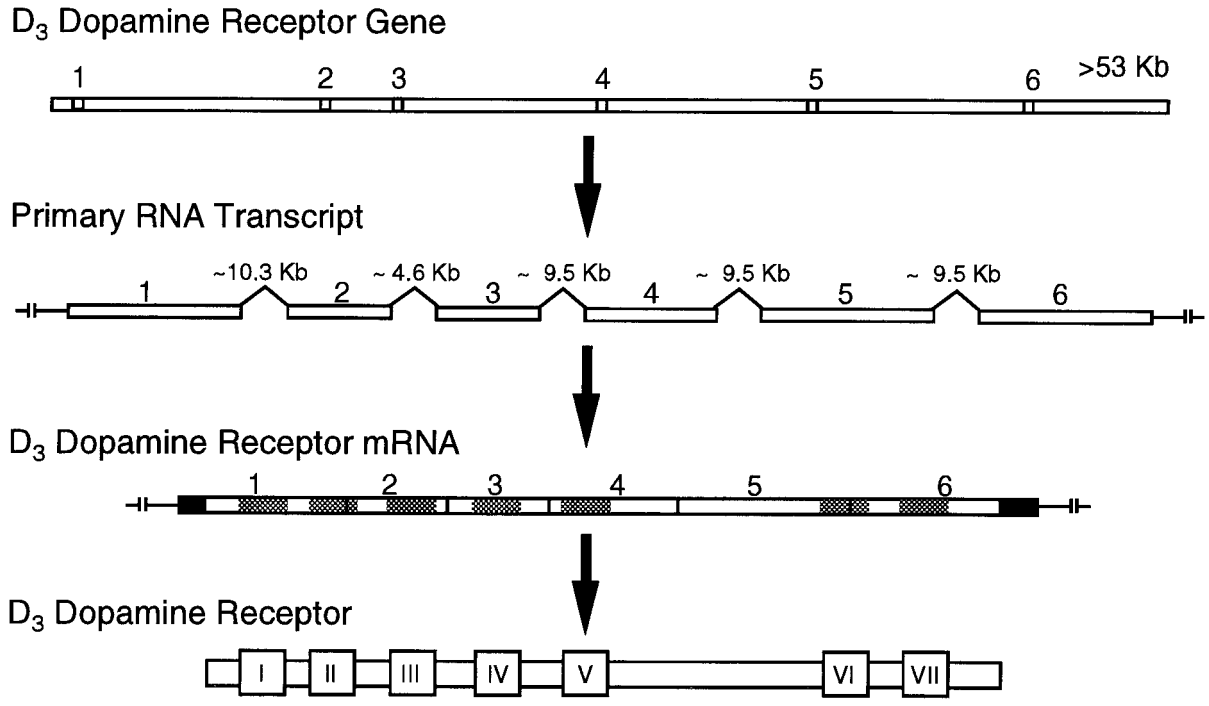

FIG. 2. Organization of the human D_3 receptor gene, primary ribonucleic acid (RNA) transcript, receptor messenger RNA (mRNA), and receptor. Regions of deoxyribonucleic acid (DNA), primary and mature RNA corresponding to exons are numbered 1–6. Shaded areas of the mature D_3 receptor mRNA denote regions encoding transmembrane domains; black regions are noncoding. Transmembrane domains of the D_3 receptor are represented by boxes.

exon in the rat and human D_3 receptor primary transcript suggests that a similar alternate splicing event does not occur (Sokoloff et al., 1990; Giros et al., 1990).

In contrast, primary mRNA for the murine D_3 receptor is reported to contain a 6th intron located in the 3rd intracellular domain (Fu et al., 1995; Park et al., 1995). Two murine mRNA splice variants of the D_3 receptor that vary in the length of the 3rd intracellular domain, similar to D_{2L} and D_{2S}, have been identified. The long form encodes a receptor with 94% homology with the rat D_3 receptor. The short form contains a 63 base pair deletion in the 3rd intracellular loop but retains binding activity and D_3-like pharmacological profile (Fishburn et al., 1993; Fu et al., 1995). Fu et al. (1995) also report the presence of a 6th intron in the rat D_3 receptor primary transcript. The presence of this additional intron could enable the generation of long and short forms of the rat D_3 receptor; however, mRNA encoding the short variant of the receptor was not detected in either rat or human brain.

C. Receptor Isoforms

As discussed above, two splice variants of the murine D_3 receptor mRNA that vary in the length of the 3rd intracellular domain have been identified (Fishburn et al., 1993; Fu et al., 1995). Although alternate splice variants of the 3rd intracellular loop have yet to be detected in the rat and human, several truncated isoforms of the D_3 receptor have been reported. These proteins arise from alternate splicing events or exchange of cassette exons that result in a large deletion or a change in reading frame. In some instances, this establishes a premature stop codon. In the rat, two truncated D_3 receptor variants have been identified. One variant arises from the deletion of the 3rd transmembrane domain resulting in translation of only the first two transmembrane domains (Giros et al., 1991; Snyder et al., 1991); the 2nd from the deletion of 119 base pairs coding for part of the 2nd intracellular loop and 5th transmembrane domain (Giros et al., 1991). A truncated D_3 receptor variant resulting from deletion of the 3rd transmembrane domain has also been identified in humans (Snyder et al., 1991; Griffon et al., 1996). Additional variants arise from deletion of 143 base pairs primarily encoding transmembrane domain IV resulting in translation of only the first three transmembrane domains (Nagai et al., 1993; Griffon et al., 1996) or from an 84 base pair insertion encoding a stop codon in the 1st intracellular domain (Pagliusi et al., 1993). A human variant, D_{3nf}, with a 98 base pair deletion in the C-terminal region of the 3rd intracellular loop that results in a frame shift has also been identified. Whereas mRNA subsequent to the deletion appears to be translated, the resulting amino acid sequence differs significantly from the wild-type receptor (Schmauss et al., 1993). A final splice variant, identified in humans, results from the deletion of the 3rd transmembrane domain resulting in the translation of only the 1st, 2nd, and 4th transmembrane domains (Griffon et al., 1996).

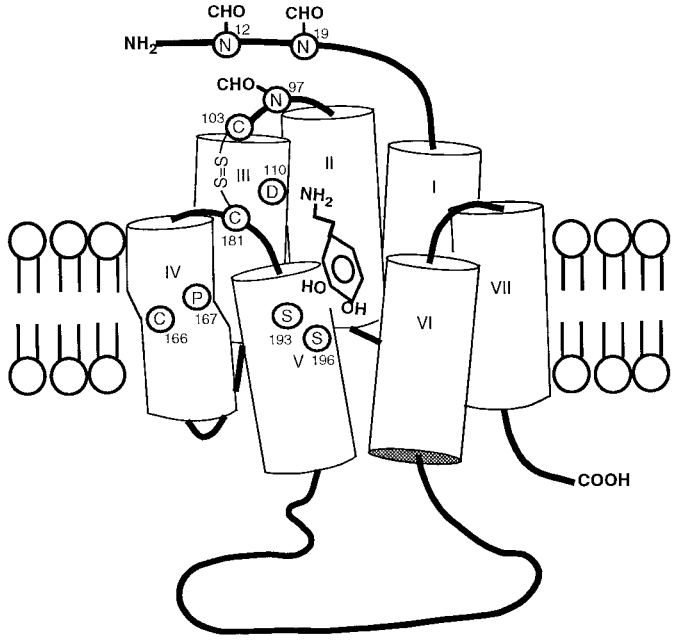

FIG. 3. Schematic representation of the proposed topography of the D_3 dopamine receptor. Hypothetically important amino acid residues include Ser (193) and Ser (196) (transmembrane domain V) which are believed to form H-bonds with the hydroxyl groups of catechols. Asp (110) (transmembrane domain III) may participate in salt-linking with the amine group of monoamines. The Cys (166)-Pro (167) bond of transmembrane domain IV is believed to introduce a bend in this α-helical region. Cys (103) and Cys (181) may form a disulfide bond. Asparagine (Asn) (12), Asn (19), and Asn (97) represent probable sites of posttranslational glycosylation. S, Ser; C, Cys.

To date, the functional properties of only some of the truncated D_3 receptor variants have been assessed. Both truncated rat D_3 receptor variants identified by Giros et al. (1991) have been shown to lack binding activity in transfected cell lines. The D_{3nf} variant identified by Schmauss et al. (1993) has also been shown to lack high-affinity agonist binding. It is likely that the other truncated forms are also nonfunctional.

Another question concerning the truncated variants is whether these proteins are transcribed and inserted in the membrane. Immunoreactivity for the D_{3nf} protein has been observed in brain (Liu et al., 1994b). Whether the other truncated variants of the D_3 receptor are translated remains to be determined. Likewise, the physiological role of these receptor variants is also unclear. It is speculated that the truncated receptors could be expressed under certain circumstances as a mechanism for controlling the density of functional D_3 sites or might occur in certain disease states (Giros et al., 1991) (See Section VIII.B.).

D. Protein Structure

The D_3 receptor contains 446 amino acids and is synthesized as a 35 to 37 kDa protein that undergoes posttranslational glycosylation (Sokoloff et al., 1990; David et al., 1993). Although biochemical evidence for the secondary structure of this receptor has yet to be generated, hydrophobicity analysis indicates that the most probable structure of the D_3 receptor is consistent with those of the seven transmembrane-spanning, G-protein–coupled receptors (fig. 3). In computer models, the spatial orientation of conserved amino acids is nearly identical with those of the D_2 receptors (Livingstone et al., 1992). The seven transmembrane domains of the D_3 site conform to idealized α-helices, with the exception of transmembrane domain IV in which the Cys (166)-Pro (167) bond may introduce a bend in the α-helix (Livingstone et al., 1992). This sort of proline-induced deviation has been hypothesized to play a role in the conformational changes that occur upon agonist binding (Lefkowitz and Caron, 1988; Hulme et al., 1990).

Computer modeling studies suggest several amino acid residues with potential functional importance. For example, Cys (103) and Cys (181) may form an extracellular disulfide bond (Sokoloff et al., 1990). Other important residues are located in the binding-site crevice. These include Ser (193) and Ser (196), which are located in transmembrane domain V and are likely to be involved in the formation of H-bonds with the two hydroxyl groups of catechols (Sokoloff et al., 1990; Malmberg et al., 1994). Asp (110) may participate in salt-linking with the amine groups of monoamines (Sokoloff et al., 1990). In addition, the location and orientation of Ser (193) and Asp (110) appear to allow for optimal bonds with oxygenated 2-aminotetralins, such as 7-hydroxy-dipropylaminotetralin (7-OH-DPAT), which may confer the higher affinity of these compounds at the D_3 receptor than the D_2 (Malmberg et al., 1994).

Because of the high degree of homology between the D_2 and D_3 receptors, it is not surprising that these receptors exhibit similar pharmacological and other properties. Chimeric D_2/D_3 receptors have been used as one approach to determine whether certain attributes of the receptor are determined by specific domains of the receptor protein. For example, the D_3 receptor appears to possess higher affinity for some agonists and lower affinity for certain antagonists than the D_2 receptor. In one study, chimeric receptors were constructed in which the D_2 receptor contained the 3rd intracellular loop of the D_3 receptor. The chimeric receptors exhibited higher affinity for agonists than the wild-type D_2 receptor (Robinson et al., 1994). Conversely, a D_3 receptor containing the 3rd intracellular loop of the D_2 receptor exhibited lower affinity for agonists, implicating this region in conferring agonist binding properties (Robinson et al., 1994). Similar experiments suggest a role for transmembrane domains VI and VII in the determination of antagonist affinity (Norman and Naylor, 1994). Other studies using chimeric receptors, however, indicate that D_3 receptors containing the 3rd intracellular loop of the D_2 receptor exhibit binding and coupling attributes identical with D_3 or intermediate between D_2 and D_3 (McAllister et al., 1993; Van Leeuwen et al., 1995).

III. Cellular Signaling Mechanisms

A. Signal Transduction in Expression Systems

Because of the similar pharmacological profiles of the D_3 and other D_2-like dopamine receptors, the primary means for initial studies of the functional properties of this novel receptor required the expression of the receptor in transfected cell lines. Because the host cells may not express the same cellular components, e.g., G-proteins, as the native tissue, receptors may display different functional properties in various expression systems (Kenakin, 1996). Accordingly, it is not surprising that reports on the coupling of the D_3 receptor to signal transduction systems have varied considerably. The initial cloning report indicated that the D_3 receptor expressed in Chinese hamster ovary (CHO) cells did not exhibit a decrease in affinity for agonists in the presence of guanyl nucleotides, or G-shift, as would be expected for a G-protein-coupled receptor (Sokoloff et al., 1990). This suggested that the D_3 receptor might not be functionally coupled to G-proteins. Other groups studying the receptor expressed in other cell lines including neuronal mesencephalic MN9D cells, neuroblastoma NG108–15 cells, and insect Sf21 cells observed a similar lack of G-shift in D_3 binding (Freedman et al., 1994b; Tang et al., 1994a; Woodcock et al., 1995). G-shifts in D_3 receptor binding, however, were observed in several studies by using a variety of other cell lines. Interestingly, the magnitude of the decrease in agonist affinity observed in the presence of guanyl nucleotides ranged from 5 to 10-fold (Seabrook et al., 1992; Sokoloff et al., 1992; Chio et al., 1994; MacKenzie et al., 1994) to 50 to 100-fold, similar to the roughly 100-fold shifts observed for the D_2 receptor (Castro and Strange, 1993; Pilon et al., 1994; Grigoriadis and Seeman, 1985).

Observations on the coupling of the D_3 receptor in expression systems to specific signal transduction cascades have also varied. In some systems, a G-shift in D_3 binding was observed but alterations in second-messengers such as cyclic adenosine monophosphate, phosphoinositides, or arachidonic acid were not detected (Seabrook et al., 1992; MacKenzie et al., 1994). Other groups observed a variety of D_3-initiated signaling events including stimulation or inhibition of adenylyl cyclase, increased extracellular acidification, alterations in Ca^{2+} and K^+ currents, and induction of c-Fos expression (Chio et al., 1994; Cox et al., 1995; Pilon et al., 1994; Potenza et al., 1994; Seabrook et al., 1994; Liu et al., 1996; Werner et al., 1996). D_3 receptors have also been shown to induce aggregation in melanocytes and to stimulate mitogenesis in CHO cells (Chio et al., 1994; Pilon et al., 1994; Potenza et al., 1994). Several of the D_3-mediated signaling events, including stimulation of adenylyl cyclase, mitogenesis, alterations in Ca^{2+} and K^+ currents, and increases rate of extracellular acidification were blocked by pertussis toxin suggesting coupling to a G_i or G_o isoform (Pilon et al., 1994; Potenza et al., 1994; Seabrook et al., 1994; Chio et al., 1994; Liu et al., 1996; Werner et al., 1996). In another study, however, D_3-induced increases in the rate of extracellular acidification were not blocked by pertussis toxin (Cox et al., 1995). Thus, these studies demonstrate functional coupling of the D_3 receptor to a variety of signaling cascades in some expression systems. The cellular signaling pathways affected, however, vary depending on the host cell and may not necessarily reflect the signaling pathways associated with the receptor in brain.

B. Coupling in Brain

Whereas coupling of the D_3 receptor has been shown in some expression systems, the demonstration of functional coupling in brain has been a more formidable task. Although all of the D_3-selective radioligands identified to date, such as [^{3}H]7-OH-DPAT, [^{3}H]PD 128907, and [^{125}I](R)-*trans*-7-hydroxy-2-[*N*-propyl-*N*-(3′-iodo-2′-propenyl)amino]tetralin (7-OH-PIPAT), have been agonists, which presumably label the high-affinity state of a G-protein coupled receptor, most studies indicate that the binding of these ligands at putative D_3 sites is insensitive to guanyl nucleotides (Lévesque et al., 1992; Burris et al., 1994; Kung et al., 1994; Bancroft et al., 1997). In fact, the binding of several D_2-like receptor agonists remaining in the presence of guanyl nucleotides has been suggested to represent labeling of D_3 sites in autoradiographic studies (Gehlert, 1992; Levant et al., 1993; Kung et al., 1994). One study, however, has reported the inhibition of [^{3}H]7-OH-DPAT by guanyl nucleotides and the sulfhydryl alkylating agent N-ethylmaleimide indicating G-protein coupling (Liu et al., 1994c). This observation, however, is most likely the result of the nonselective labeling of both D_2 and D_3 sites due to the presence of Mg^{2+} in the assay buffer.

Although these findings may suggest that D_3 receptor in brain may lack functional G-protein coupling, there are other possible explanations. Whereas the high-affinity state of the D_2 receptor exhibits approximately 100-fold higher affinity for agonists than the low-affinity state, the high-affinity conformation of the cloned D_3 receptor in expression systems has been most often reported to exhibit only approximately 5 to10-fold higher affinity for agonists than the low-affinity state. Thus, whereas agonist radioligands are presumed to preferentially label the high-affinity state conformation of G-protein coupled receptors, the putative D_3 binding observed in brain, albeit of nanomolar affinity, may be to receptors in the low-affinity state. As such, the binding of either agonist or antagonist ligands to these sites would be unaltered in the presence of guanyl nucleotides.

There are several possible reasons why the observed D_3 binding in brain tissue may represent receptors in the low-affinity state. The first and simplest explanation is that the affinity state of these sites is a function of the in vitro assay conditions used to obtain putatively selec-

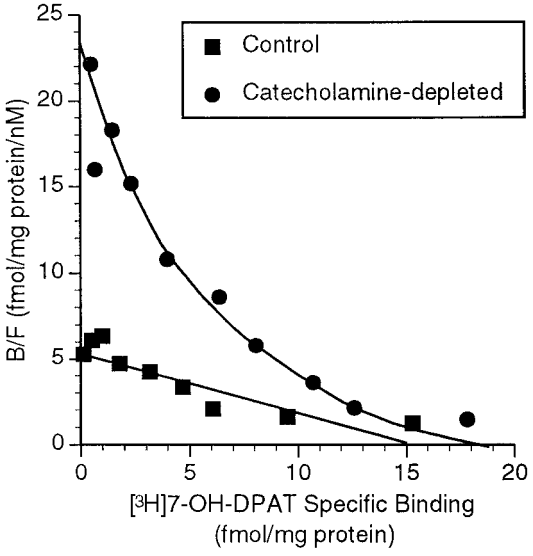

FIG. 4. D_3 receptor binding in catecholamine-depleted rats. Rats were treated with reserpine and α-methyl-tyrosine to produce >90% depletion of striatal dopamine. Putative D_3 receptor binding was assessed ex vivo by saturation analysis using [^{3}H]7-OH-DPAT. Binding parameters for this experiment were: Control, K_D = 2.6 nM, B_{max} = 15 fmol/mg protein; Depleted, $K_{D(high)}$ = 0.12 nM, $B_{max(high)}$ = 1.9 fmol/mg protein, $K_{D(low)}$ = 1.5 nM, $B_{max(low)}$ = 13 fmol/mg protein. B/F, bound/free ratio. Reprinted from Brain Research, vol. 698, Beth Levant, "Differential sensitivity of [^{3}H]7-OH-DPAT-labeled binding sites in rat brain to inactivation by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline," pp. 146–154, 1995, with kind permission from Elsevier Science - NL, Sara Burgerhartstraat, 1055 KV Amsterdam, The Netherlands.

tive labeling of D_3 sites. Specifically, obtaining selective labeling of the D_3 site with the radioligands currently available appears to be dependent on the use of assay conditions that disfavor agonist binding at the D_2 site. The greatest D_3/D_2 selectivity for these ligands has been obtained in the absence of Mg^{2+} and the presence of ethylenediamine-tetraacetic acid (Lévesque et al., 1992; Akunne et al., 1995) in concordance with previous studies indicating that the high-affinity state of D_2-like receptors is not favored in the absence of Mg^{2+} (Sibley and Creese, 1983). Although these conditions may also affect the affinity state of the D_3 receptor, the low-affinity conformation of the D_3 site exhibits much higher affinity for agonists than the low-affinity state of the D_2 receptor. As such, selective labeling of D_3 sites occurs.

Alternatively, D_3 sites in rat brain may exist predominantly in the low-affinity state under basal conditions as has been suggested for the D_1 receptor (Richfield et al., 1989). Although "D_3-selective" radioligands, such as [^{3}H]7-OH-DPAT, label a single site in rat brain (Lévesque et al., 1992; Akunne et al., 1995; Levant, 1995), depletion of endogenous catecholamines resulted in the detection of an additional [^{3}H]7-OH-DPAT binding site ex vivo (fig. 4). This additional binding site exhibited roughly ten-fold higher affinity than the single binding site detected in control animals without a significant increase in the total number of sites (Levant, 1995). Although the higher affinity sites may have been occupied, and thus masked, by endogenous dopamine in control animals (Schotte et al., 1992), preincubation and extensive washing of membranes from control animals to remove any residual dopamine failed to alter binding of [^{3}H]7-OH-DPAT (Levant, 1995). These observations suggest that in the absence of dopamine, some D_3 sites, which under normal conditions are predominantly in the low-affinity state, assume a high-affinity conformation. This hypothesis is supported by the observation that the high-affinity state component of [^{3}H]7-OH-DPAT binding in catecholamine-depleted rats is inactivated by the alkylating agent 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, whereas the low-affinity component is not–a difference that might well be conferred by a conformational change. In fact, when catecholamine-depleted rats are treated with 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, only low-affinity sites remain and the density of these sites is reduced by roughly the same amount as the density of high-affinity state sites present in the catecholamine-depleted animals (Levant, 1995).

Although the current lack of evidence of cellular signaling mechanisms for the D_3 receptor in brain is puzzling, it need not imply a lack of function. In fact, several presumably D_3-mediated behavioral, neurochemical, and electrophysiological effects have been reported (See Section VI.). Likewise, the D_3-preferring antagonist U99194A has been reported to induce expression of c-fos mRNA in brain (Merchant et al., 1996). Clearly, further study must address the issues of the cellular signaling mechanism(s) associated with the D_3 receptor in brain as well as those related to the affinity state of these sites under basal conditions.

IV. Pharmacology

A. Radioligand Binding Studies

Considering the extensive homology between the D_2 and D_3 sites, it is not unexpected that the pharmacological profile of the D_3 receptor is generally similar to that of the D_2 receptor. As such, the D_3 receptor exhibits high affinity for nonselective and D_2-selective agonists, such as dopamine, quinpirole, and apomorphine, and significantly lower affinity for the D_1-selective agonist SKF 38393 (Sokoloff et al., 1990). The D_3 site also possess significantly higher affinity for D_2-selective antagonists, such as spiperone and haloperidol, than the D_1-selective antagonist SCH 23390 (Freedman et al., 1994b). Likewise, the D_3 receptor exhibits stereospecificity with higher affinity for (+)-butaclamol than (−)-butaclamol and (−)-sulpiride than (+)-sulpiride (Freedman et al., 1994b; Kula et al., 1994; MacKenzie et al., 1994).

What is perhaps of greater interest than the pharmacological profile of the D_3 receptor is the relative affinities of compounds for the D_2-related subtypes. Several studies have examined the relative affinities of dopaminergic compounds for D_2 and D_3 receptors in various

TABLE 1

Affinities of dopaminergic compounds at D_3 and D_2 dopamine receptors in in vitro radioligand binding assays

Compound	Ligand	D_2 source	D_3 source	K_i (nM)		$K_{i(D_2)}/K_{i(D_3)}$	Reference
				D_2	D_3		
Agonists							
Dopamine	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	474	25	19	Sokoloff et al. (1990)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	710	29	24	Freedman et al. (1994)
	[^{3}H]YM-09151-2	rStriatum	hD_3/CCL1.3	710	15	46	Kula et al. (1994)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	540	23	23	Sautel et al. (1995a)
	[^{125}I]NCQ-298	hD_{2I}/HEK 293	rD_3/HEK 293	1908	44	43	Burris et al. (1995)
	[^{125}I]7-OH-PIPAT	hD_{2I}/HEK 293	rD_3/HEK 293	5.8	5.6	1.0	Burris et al. (1995)
	[^{3}H]N-0437	hD_{2I}/CHO-K1	hD_3/CHO-K1	31	11	2.8	Pugsley et al. (1995)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	8.5	4.8	1.8	Flietstra and Levant (1996)
Bromocriptine	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	5.3	7.4	0.72	Sokoloff et al. (1990)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	33	49	0.67	Levant and DeSouza (1993)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	0.62	2.1	0.30	Freedman et al. (1994b)
	[^{3}H]YM-09151-2	rStriatum	hD_3/CCL1.3	0.067	0.20	0.34	Kula et al. (1994)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	5.3	7.4	0.72	Sautel et al. (1995a)
	[^{3}H]pramipexole	hD_{2I}/HEK 293	hD_3/DHO dhfr-	2.5	12.2	0.21	Mierau et al. (1995)
Apomorphine	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	24	20	1.2	Sokoloff et al. (1990)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	63	73	0.86	Sokoloff et al. (1992)
	[^{3}H]spiperone	hD_2/CHO-K1	hD_3/CHO-K1	24	9.3	2.6	MacKenzie et al. (1994)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	30	16	1.9	Freedman et al. (1994)
	[^{3}H]YM-09151-2	rStriatum	hD_3/CCL1.3	34	23	1.5	Kula et al. (1994)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	63	73	0.86	Sautel et al. (1995a)
	[^{125}I]NCQ-298	hD_{2I}/HEK 293	rD_3/HEK 293	168	31	5.4	Burris et al. (1995)
	[^{125}I]7-OH-PIPAT	hD_{2I}/HEK 293	rD_3/HEK 293	4.9	14	0.35	Burris et al. (1995)
	[^{3}H]N-0437	hD_{2I}/CHO-K1	hD_3/CHO-K1	2.9	8.9	0.33	Pugsley et al. (1995)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	47	23	2.0	Millan et al. (1995b)
Quinpirole	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	576	5.1	113	Sokoloff et al. (1990)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	1402	39	36	Sokoloff et al. (1992)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	3.7	3.6	1.0	Levant and De Souza (1993)
	[^{3}H]spiperone	hD_2/CHO-K1	hD_3/CHO-K1	193	5.3	36	MacKenzie et al. (1994)
	[^{3}H]spiperone	rD_{2I}/CCL1.3	hD_3/CCL1.3	15	19	0.80	Tang et al. (1994a)
	[^{3}H]YM-09151-2	rStriatum	hD_3/CCL1.3	1920	32	60	Kula et al. (1994)
	[^{125}I]NCQ-298	hD_{2I}/HEK 293	rD_3/HEK 293	1065	8.0	133	Burris et al. (1995)
	[^{125}I]7-OH-PIPAT	hD_{SI}/HEK 293	rD_3/HEK 293	6.4	1.7	3.8	Burris et al. (1995)
	[^{125}I]iodosulpiride[a]	rStriatum	rCerebellar lob.X	157[b]	28[b]	5.6	Levant et al. (1995)
	[^{3}H]pramipexole	hD_{2I}/HEK 293	hD_3/DHO dhfr-	1.8	0.96	1.9	Mierau et al. (1995)
	[^{3}H]N-0437	hD_{2I}/CHO-K1	hD_3/CHO-K1	82	9.3	8.8	Pugsley et al. (1995)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	911	43	21	Millan et al. (1995)
Quinelorane	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	341	3.6	95	Sokoloff et al. (1992)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	265	6.1	43	Millan et al. (1995)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	5.7	3.4	1.7	Fliestra and Levant (1996)
7-OH-DPAT	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	61	0.78	78	Lévesque et al. (1992)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	30	5.8	5.2	Levant and De Souza (1993)
	[^{3}H]spiperone	hD_2/CHO-K1	hD_3/CHO-K1	156	1.6	98	MacKenzie et al. (1994)
	[^{3}H]spiperone	hD_2/CCL1.3	hD_3/CCL1.3	223	7.1	31	MacKenzie et al. (1994)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	60	1.6	38	Freedman et al. (1994)
	[^{3}H]YM-09151-2	rStriatum	hD_3/CCL1.3	160	3.8	42	Kula et al. (1994)
	[^{125}I]7-OH-PIPAT	hD_2/sf9	hD_3/sf9	142	2.9	49	Chumpradit et al. (1994)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	103	2.1	49	Sautel et al. (1995a)
	[^{125}I]NCQ-298	hD_{2I}/HEK 293	rD_3/HEK 293	165	1.2	138	Burris et al. (1995)
	[^{125}I]7-OH-PIPAT	hD_{2I}/HEK 293	rD_3/HEK 293	2.6	0.4	6.5	Burris et al. (1995)
	[^{125}I]iodosulpiride[a]	rStriatum	rCerebellar lob.X	99[b]	4.2[b]	24	Levant et al. (1995)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	103	2.2	47	Millan et al. (1995)
(−)-N-prophynor-apomorphine	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	0.12	0.21	0.57	Freedman et al. (1994)
	[^{3}H]YM-09151-2	rStriatum	hD_3/CCL1.3	3.4	0.27	13	Kula et al. (1994)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	2.9	0.36	8.1	Sautel et al. (1995a)

[a] Autoradiographic study.
[b] IC_{50} value.
r, rat; h, human; K_i, inhibition constant; lob., lobe.

TABLE 1
(Continued)

Compound	Ligand	D_2 source	D_3 source	K_i (nM)		$K_{i(D_2)}/K_{i(D_3)}$	Reference
				D_2	D_3		
Pramipexole	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	790	4.1	193	Sautel et al. (1995a)
	[^{3}H]pramipexole	hD_{2L}/HEK 293	hD_3/CHO dhfr-	3.9	0.5	7.8	Mierau et al. (1995)
PD 128907	[^{3}H]N-0437	hD_{2L}/CHO-K1	hD_3/CHO-K1	42	2.3	18	Pugsley et al. (1995)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	389	1.8	216	Sautel et al. (1995a)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	109	18	6.1	Flietstra and Levant (1996)
7-trans-OH-PIPAT	[^{125}I]7-OH-PIPAT	hD_2/sf9	hD_3/sf9	265	1.9	143	Chumpradit et al. (1994)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	20	47	0.43	Flietstra and Levant (1996)
Antagonists							
Domperidone	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	0.30	9.5	0.03	Sokoloff et al. (1990)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	1.3	7.5	0.17	Sokoloff et al. (1992)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	0.58	2.9	0.20	Freedman et al. (1994)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	0.5	3.5	0.14	Millan et al. (1995)
	[^{125}I]iodosulpiride[a]	rStriatum	rCerebellar lob.X	4.5[b]	83[b]	0.05	Levant et al. (1995)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	3.4	125	0.027	Flietstra and Levant (1996)
Haloperidol	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	0.45	9.8	0.05	Sokoloff et al. (1990)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	0.6	2.9	0.21	Sokoloff et al. (1992)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	17	1020	0.017	Levant and De Souza (1993)
	[^{3}H]raclopride	hD_{2L}/Ltk-	hD_3/Ltk-	0.67	2.74	0.24	Malmberg et al. (1993)
	[^{3}H]spiperone	hD_2/CHO-K1	hD_3/CHO-K1	0.3	1.0	0.30	MacKenzie et al. (1994)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	2.6	1.5	1.73	Freedman et al. (1994)
	[^{3}H]YM-09151-2	rStriatum	hD_3/CCL1.3	0.90	1.91	0.47	Kula et al. (1994)
	[^{125}I]iodosulpiride[a]	rStriatum	rCerebellar lob.X	6.3[b]	23[b]	0.27	Levant et al. (1995)
	[^{3}H]pramipexole	hD_{2L}/HEK 293	hD_3/DHO dhfr-	0.17	2.9	0.059	Mierau et al. (1995)
	[^{3}H]N-0437	hD_{2L}/CHO-K1	hD_3/CHO-K1	0.27	2.8	0.10	Pugsley et al. (1995)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	0.45	2.4	0.19	Millan et al. (1995)
Spiperone	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	0.069	0.61	0.11	Sokoloff et al. (1990)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	0.35	28	0.013	Levant and De Souza (1993)
	[^{3}H]spiperone	hD_2/CHO-K1	hD_3/CHO-K1	0.2	0.3	0.67	MacKenzie et al. (1994)
	[^{3}H]spiperone	hD_2/CCL1.3	hD_3/CCL1.3	0.37	0.32	1.16	MacKenzie et al. (1994) Tang et al. (1994)
	[^{3}H]spiperone	rD_{2L}/MN9D	hD_3/MN9D	0.28	0.71	0.39	Tang et al. (1994)
	[^{3}H]YM-09151-2	rStriatum	hD_3/CCL1.3	0.017	0.030	0.57	Kula et al. (1994)
	[^{125}I]iodosulpiride[a]	rStriatum	rCerebellar lob.X	2.1[b]	3.4[b]	0.62	Levant et al. (1995)
	[^{3}H]N-0437	hD_{2L}/CHO-K1	hD_3/CHO-K1	0.10	0.4	0.25	Pugsley et al. (1995)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	0.06	0.25	0.24	Millan et al. (1995)
Clozapine	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	56	180	0.31	Sokoloff et al. (1990)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	69	479	0.14	Sokoloff et al. (1992)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	1575	9633	0.16	Levant and De Souza (1993)
	[^{3}H]raclopride	hD_{2L}/Ltk-	hD_3Ltk-	60	83	0.72	Malmberg et al. (1993)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	38	88	0.43	Freedman et al. (1994)
	[^{3}H]spiperone	hD_2/CHO-K1	hD_3/CHO-K1	17	264	0.064	MacKenzie et al. (1994)
	[^{3}H]spiperone	hD_2/CCL1.3	hD_3/CCL1.3	143	620	0.23	MacKenzie et al. (1994) Tang et al. (1994)
	[^{3}H]siperone	rD_{2L}/MN9D	hD_3/MN9D	170	480	0.35	Tang et al. (1994)
	[^{3}H]YM-09151-2	rStriatum	hD_3/CCL1.3	125	158	0.79	Kula et al. (1994)
(−)-Sulpiride	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	9.2	25	0.37	Sokoloff et al. (1990)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	10	20	0.50	Sokoloff et al. (1992)
	[^{3}H]raclopride	hD_{2L}/Ltk-	hD_3/Ltk-	7.4	8.0	0.93	Malmberg et al. (1993)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	6.0	8.0	0.75	Freedman et al. (1994)
	[^{3}H]spiperone	hD_2/CCL1.3	hD_3/CCL1.3	72	570	0.13	MacKenzie et al. (1994)
	[^{3}H]spiperone	rD_{2L}/MN9D	hD_3/MN9D	57	207	0.28	Tang et al. (1994)
	[^{125}I]NCQ-298	hD_{2L}/HEK 293	rD_3/HEK 293	12	14	0.86	Burris et al. (1995)
	[^{125}I]7-OH-PIPAT	hD_{2L}/HEK 293	rD_3/HEK 293	60	142	0.42	Burris et al. (1995)
	[^{125}I]iodosulpiride[a]	rStriatum	rCerebellar lob.X	11[b]	6.3[b]	1.8	Levant et al. (1995)

TABLE 1
(Continued)

Compound	Ligand	D_2 source	D_3 source	K_i (nM)		$K_{i(D_2)}/K_{i(D_3)}$	Reference
				D_2	D_3		
Amisulpiride	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	1.7	3.8	0.45	Sokoloff et al. (1990)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	1.3	2.4	0.54	Sokoloff et al. (1992)
	[^{3}H]raclopride	hD_{2L}/Ltk-	hD_3/Ltk-	0.97	3.0	0.32	Malmberg et al. (1993)
Chlorpromazine	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	2.8	6.1	0.46	Sokoloff et al. (1990)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	2.3	5.9	0.39	Sokoloff et al. (1992)
	[^{3}H]raclopride	hD_{2L}/Ltk-	hD_3/Ltk-	1.14	1.16	0.98	Malmberg et al. (1993)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	8.0	3.0	2.7	Freedman et al. (1994)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	29	114	0.25	Flietstra and Levant (1996)
Raclopride	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	1.8	3.5	0.51	Sokoloff et al. (1990)
	[^{3}H]raclopride	hD_{2L}/Ltk-	hD_3/Ltk-	2.3	1.8	1.28	Malmberg et al. (1993)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	1.1	1.4	0.79	Millan et al. (1995)
Pimozide	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	2.4	3.7	0.65	Sokoloff et al. (1990)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	9.8	11	0.89	Sokoloff et al. (1992)
	[^{3}H]raclopride	hD_{2L}/Ltk-	hD_3/Ltk-	0.72	0.53	1.4	Malmberg et al. (1993)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	0.39	0.39	1.0	Freedman et al. (1994)
(+)-AJ76	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	270	91	3.0	Sokoloff et al. (1990)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	311	139	2.2	Sokoloff et al. (1992)
	[^{3}H]raclopride	hD_{2L}/Ltk-	hD_3/Ltk-	80	35	2.3	Malmberg et al. (1993)
	[^{125}I]iodosulpiride	rStriatum	rCerebellar lob.X	388[b]	143[b]	2.4	Levant et al. (1995)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	154	70	2.2	Millan et al. (1995)
(+)-UH232	[^{125}I]iodosulpiride	rD_2/CHO	rD_3/CHO	40	9.2	4.3	Sokoloff et al. (1990)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	36	11	3.3	Sokoloff et al. (1990)
	[^{3}H]raclopride	hD_{2L}/Ltk-	hD_3/Ltk-	14	2.9	4.8	Malmberg et al. (1993)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	9.0	4.9	1.8	Freedman et al. (1994)
	[^{125}I]iodosulpiride[a]	rStriatum	rCerebellar lob.X	56[b]	23[b]	2.4	Levant et al. (1995)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	125	215	0.58	Flietstra and Levant (1996)
(+)-Butaclamol	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	22	245	0.090	Levant and De Souza (1993)
	[^{125}I]iodosulpiride	hD_{2S}/CHO	hD_3/CHO	0.44	2.1	0.21	Freedman et al. (1993)
	[^{3}H]spiperone	hD_2/CHO-K1	hD_3/CHO-K1	3.0	4.0	0.75	MacKenzie et al. (1994)
	[^{3}H]spiperone	hD_2/CCL1.3	hD_3/CCL1.3	0.69	11	0.063	MacKenzie et al. (1994) Tang et al. (1994)
	[^{3}H]spiperone	rD_{2L}/MN9D	hD_3/MN9D	2.6	4.1	0.63	Tang et al. (1994)
	[^{3}H]YM-09151-2	rStriatum	hD_3/CCL1.3	0.63	0.22	2.9	Kula et al. (1994)
	[^{125}I]NCQ-298	hD_{2L}/HEK 293	rD_3/HEK 293	0.20	3.2	0.063	Burris et al. (1995)
	[^{125}I]7-OH-PIPAT	hD_{2L}/HEK 293	rD_3/HEK 293	0.69	5.0	0.14	Burris et al. (1995)
	[^{3}H]N-0437	hD_{2L}/CHO-K1	hD_3/CHO-K1	0.42	1.0	0.42	Pugsley et al. (1995)
Eticlopride	[^{3}H]spiperone	hD_2/CCL1.3	hD_3/CCL1.3	0.07	0.16	0.44	MacKenzie et al. (1994) Tang et al. (1994)
	[^{3}H]spiperone	rD_{2L}/MN9D	hD_3/MN9D	0.029	0.46	0.063	Tang et al. (1994)
	[^{3}H]YM-09151-2	rStriatum	hD_3/CCL1.3	0.062	0.043	1.4	Kula et al. (1994)
YM-09151-2	[^{3}H]spiperone	hD_2/CCL1.3	hD_3/CCL1.3	0.02	0.06	0.33	MacKenzie et al. (1994) Tang et al. (1994)
	[^{3}H]spiperone	rD_{2L}/MN9D	hD_3/MN9D	0.03	0.05	0.60	Tang et al. (1994)
Risperidone	[^{3}H]raclopride	hD_{2L}/Ltk-	hD_3/Ltk-	1.7	6.7	0.25	Malmberg et al. (1993)
	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	3.6	11	0.33	Millan et al. (1995)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	3.3	103	0.032	Flietstra and Levant (1996)
1-Nafadotride	[^{125}I]iodosulpiride	hD_{2L}/CHO	hD_3/CHO	3.0	0.31	9.7	Sautel et al. (1995b)
	[^{3}H]quinpirole[a]	rStriatum	rCerebellar lob.X	7.0	3.0	2.3	Fliestra and Levant (1996)
(+)-S 14297	[^{125}I]iodosulpiride	hD_2/CHO	hD_3/CHO	297	13	23	Millan et al. (1995)

expression systems and in brain. These studies suggest that some dopaminergic agonists, such as dopamine and quinpirole possess higher affinity for the D_3 site whereas antagonists, such as haloperidol, spiperone, and domperidone, have higher affinity for D_2 (Sokoloff et al., 1990). However, as summarized in table 1, results of these studies vary considerably, depending, at least in part, on the expression system or tissue, the radioligand, and the in vitro assay conditions used (Tang et al., 1994a; Burris et al., 1995; Levant et al., 1995). For example, quinpirole was found to have more than 100-fold higher affinity for the D_3 receptor than the D_2 receptor in some assay systems (Sokoloff et al., 1990; Lévesque et al., 1992; Burris et al., 1995) but roughly equal affinity for these sites in others (Levant and DeSouza, 1993; Tang et al., 1994a; Burris et al., 1995). In fact, the high-affinity state of the D_2 receptor appears to have similar affinity for agonists as the D_3 site (Burris et al., 1995). As such, the observed D_3-selectivity of many agonists may have resulted from the use of in vitro conditions that disfavor the high-affinity conformation of the D_2 receptor such as the inclusion of Na^+ in in vitro assay systems used for benzamide radioligands (Burris et al., 1995; Levant et al., 1995; Grigoriadis and Seeman, 1985). What is clear from these studies is that under certain conditions, several compounds exhibit significant selectivity between the D_2 and D_3 dopamine receptors. This information is likely to be of considerable utility in the design and interpretation of in vitro studies, particularly for the determination of the localization and density of D_3 sites. On the other hand, the attribution of in vivo pharmacological effects of these drugs to specific receptor subtypes based on these data is, in most instances, premature.

B. Functional Assays

Several functional assays have established the agonist or antagonist activity of a variety of dopaminergic compounds at the D_3 receptor. D_2 agonists, such as dopamine, quinpirole, and bromocriptine, have been shown to possess agonist activity at the D_3 receptor as assessed by the induction of CHO cell mitogenesis, melanocyte aggregation, or extracellular acidification (Chio et al., 1994; Pilon et al., 1994; Potenza et al., 1994; Sautel et al., 1995a; Boyfield et al., 1996). The putatively D_3-selective compounds 7-OH-DPAT and PD 128907 also exhibit agonist activity in the mitogenesis test (Chio et al., 1994; Pilon et al., 1994; Potenza et al., 1994; Sautel et al., 1995a; Pugsley et al., 1995). In contrast, antagonists, such as spiperone, (±)-sulpiride, and nafadotride, block agonist-induced activity in these tests (Potenza et al., 1994; Sautel et al., 1995b). The D_2/D_3 ligand (+)-UH 232 has been shown to be a partial agonist at the D_3 receptor in the mitogenesis assay (Griffon et al., 1995).

In addition to elucidating the agonist or antagonist activity of compounds at the D_3 receptor, the assays described above are also useful in determining the D_2/D_3-selectivity of drugs in a functional test. In contrast to the significant D_3-selectivity reported in some binding studies, the agonists tested, including dopamine, quinpirole, and 7-OH-DPAT, exhibited only modest, if any, D_3-selectivity in the mitogenesis, melanocyte aggregation, or extracellular acidification assays (table 2) (Chio et al., 1994; Pilon et al., 1994; Potenza et al., 1994; Sautel et al., 1995a; Boyfield et al., 1996). In contrast, the antagonists spiperone and (±)-sulpiride were roughly 65-fold more potent in inhibiting agonist-induced melanocyte aggregation at D_2 receptors than D_3 (Potenza et al., 1994). These observations further underscore the need for caution in the use of in vitro binding data in the interpretation of in vivo or in vitro functional studies.

V. Localization of D_3 Receptors in Brain

A variety of approaches may be employed to study the localization of the D_3 receptor including molecular, pharmacological, and immunological methods. Much of what is known about the distribution of the D_3 receptor, and other novel dopamine subtypes, for which selective pharmacological tools have only recently been identified and have not been extensively validated, is based on the localization of receptor mRNA. Whereas the detection of mRNA with appropriate probes can be presumed to be specific for the receptor of interest, the distribution and relative abundance of mRNA does not necessarily parallel the distribution and density of the receptor it encodes.

Several means of selectively visualizing D_3 sites have also been developed. These methods include the use of a putatively selective D_3 ligand such as [^{3}H]7-OH-DPAT (Lévesque et al., 1992), [^{3}H]PD 128907 (Akunne et al., 1995), or [^{125}I]trans-7-OH-PIPAT (Kung et al., 1994), in radioligand binding and autoradiographic studies. Alternatively, a ligand that labels both D_2 and D_3 receptors such as [^{3}H]quinpirole, [^{3}H]CV 205 502, [^{125}I]iodosulpiride, or [^{125}I]epidepride may be used in the presence of an unlabeled ligand selective for D_2 receptors (Murray et al., 1992; Schotte et al., 1992; Landwehrmeyer et al., 1993a; Levant and DeSouza, 1993). Antibodies for the D_3 receptor have also been developed and used in immunocytochemical studies. It must be noted, however, whereas these radioligands and antibodies generally identify a similar, apparently homogeneous population of dopaminergic sites that differ from the classical D_2 site in several respects, in vitro assay conditions appear to significantly influence the activities of these ligands (Lévesque et al., 1992). For this reason, and perhaps others, controversy has arisen over the D_3/D_2-selectivity of radioligands such as [^{3}H]7-OH-DPAT (Gonzales and Sibley, 1995). Interaction of [^{3}H]7-OH-DPAT with the *sigma* site has also been reported (Schoemaker, 1993; Wallace and Booze, 1995). Hence,

TABLE 2
Potencies of dopaminergic agonists at D_3 and D_2 dopamine receptors in in vitro functional assays

Compound	Assay	D_2 Source	D_3 Source	EC_{50} (nM)		$\frac{EC_{50(D_2)}}{EC_{50(D_3)}}$	Reference
				D_2	D_3		
Dopamine	inhibition of adenylyl cyclase	rD_{2L}/CHO 10001	rD_3/CHO 10001	13.0	16	0.81	Chio et al. (1994)
	mitogenesis	rD_{2L}/CHO 10001	rD_3/CHO 10001	5.4	2.2	2.5	Chio et al. (1994)
	mitogenesis	hD_{2S}/CHO	hD_3/NG108-15	20	1.4	15	Sautel et al. (1995a)
	melanocyte aggregation	hD_2/Xenopus melanocytes	hD_3/Xenopus melanocytes	154	295	0.52	Potenza et al. (1994)
	extracellular acidifcation	hD_{2L}/CHO	hD_3/CHO	174	30	5.8	Boyfield et al. (1996)
Bromocriptine	mitogenesis	hD_{2S}/CHO	hD_3/NG108-15	1.8	12	0.15	Sautel et al. (1995)
	melanocyte aggregation	hD_2/Xenopus melanocytes	hD_3/Xenopus melanocytes	24.5	43.5	0.56	Potenza et al. (1994)
Apomorphine	inhibition of adenylyl cyclase	rD_{2L}/CHO 10001	rD_3/CHO 10001	46	79	0.58	Chio et al. (1994)
	mitogenesis	rD_{2L}/CHO 10001	rD_3/CHO 10001	0.40	1.1	0.36	Chio et al. (1994)
	mitogenesis	hD_{2S}/CHO	hD_3/NG108-15	2.3	2.2	1.1	Sautel et al. (1995)
Quinpirole	inhibition of adenylyl cyclase	rD_{2L}/CHO 10001	rD_3/CHO 10001	6.0	3.7	1.6	Chio et al. (1994)
	mitogenesis	rD_{2L}/CHO 10001	rD_3/CHO 10001	2.2	1.7	1.3	Chio et al. (1994)
	mitogenesis	hD_{2S}/CHO	hD_3/NG108-15	2.8	0.86	3.3	Sautel et al. (1995)
	mitogenesis	hD_{2L}/CHO-P5	hD_3/CHO-P5	7.1	2.8	2.5	Pugsley et al. (1995)
	melanocyte aggregation	hD_2/Xenopus melanocytes	hD_3/Xenopus melanocytes	10.9	15.4	0.71	Potenza et al. (1994)
	extracellular acidification	hD_{2L}/CHO	hD_3/CHO	52	2.09	25	Boyfield et al. (1996)
7-OH-DPAT	inhibition of adenylyl cyclase	rD_{2L}/CHO 10001	rD_3/CHO 10001	1.1	0.08	14	Chio et al. (1994)
	mitogenesis	rD_{2L}/CHO 10001	rD_3/CHO 10001	1.1	0.30	3.7	Chio et al. (1994)
	mitogenesis	hD_{2S}/CHO	hD_3/NG108-15	2.7	0.39	7.0	Sautel et al. (1995)
	melanocyte aggregation	hD_2/Xenopus melanocytes	hD_3/Xenopus melanocytes	56.2	113	0.50	Potenza et al. (1994)
	extracellular acidification	hD_{2L}/CHO	hD_3/CHO	8.31	1.10	7.5	Boyfield et al. (1996)
(−)-3-PPP	inhibition of adenylyl cyclase	rD_{2L}/CHO 10001	rD_3/CHO 10001	9.7	3.9	2.5	Chio et al. (1994)
	mitogenesis	rD_{2L}/CHO 10001	rD_3/CHO 10001	9.5	23	0.41	Chio et al. (1994)
	mitogenesis	hD_{2S}/CHO	hD_3/NG108-15	9.1	4.4	2.1	Sautel et al. (1995)
	melanocyte aggregation	hD_2/Xenopus melanocytes	hD_3/Xenopus melanocytes	1103	1102	1.0	Potenza et al. (1994)
PD128907	mitogenesis	hD_{2L}/CHO-P5	hD_3/CHO-P5	10	1.58	6.3	Pugsley et al. (1995)

r, rat; h, human.

sites identified by using these tools are referred to as "putative" D_3 sites.

A. Distribution of D_3 Receptor Messenger Ribonucleic Acid

1. Distribution in rat brain. Although present in significantly lower levels than D_1 or D_2 receptor mRNAs, in situ hybridization studies in rat brain demonstrate that mRNA for the D_3 receptor appears to be expressed preferentially in limbic brain regions. Highest density is reported in the islands of Calleja, in which D_3 mRNA is expressed by granule cells (Diaz et al., 1995). High levels of D_3 mRNA are also observed in the nucleus accumbens and olfactory tubercle (Sokoloff et al., 1990; Bouthenet et al., 1991; Mengod et al., 1992; Landwehrmeyer et al., 1993a; Diaz et al., 1995). Within the nucleus accumbens, D_3 receptor mRNA is often colocalized with cells expressing proneurotensin or prodynorphin mRNAs (Curran and Watson, 1995; Diaz et al., 1995)

Additional brain regions also exhibit dense expression of D_3 mRNA in rat. These regions include the medial division of the bed nucleus of the stria terminalis, the nucleus of the vertical limb of the diagonal band of Broca, the paracentral thalamic nucleus, the medial and ventral lateral geniculate nuclei, the magnocellular preoptic nucleus, mammillary nucleus, the lateral part of the substantia nigra pars compacta, the dorsal cochlear nucleus, and the Purkinje cell layer of the vestibulocerebellum (Bouthenet et al., 1991; Mengod et al., 1992; Diaz et al., 1995).

Moderately dense levels of D_3 mRNA expression are observed in areas such as the cerebral cortex, the ventral pallidum, the amygdala, the nucleus of the horizontal limb of the diagonal band of Broca, thalamic nuclei including the anteroventral, laterodorsal and ventral posterolateral, the paraventricular and ventromedial hypothalamic nuclei, the superior colliculus, and the inferior olive (Bouthenet et al., 1991).

Moderate to dense expression of D_3 mRNA has also been detected in the dentate gyrus, olfactory bulb, and the anterior and intermediate lobes of the pituitary in in situ hybridization studies (Bouthenet et al., 1991). However, the observation of hybridization signal in these brain regions is controversial as D_3 mRNA was not detected in these brain regions in other studies by Northern analysis, in situ hybridization, or PCR (Sokoloff et al., 1990; Mengod et al., 1992), suggesting the possibility of nonspecific hybridization. Low densities of D_3 mRNA are reported in the cerebral cortex, caudate/putamen, ventral pallidum, substantia nigra pars reticulata, ventral tegmental area, and cerebellar cortex (Bouthenet et al., 1991; Mengod et al., 1992).

2. Distribution in human brain. Although not as extensively characterized, the distribution of D_3 mRNA in human brain appears to be generally similar to that observed in the rat. Enrichment of D_3 mRNA was observed in the nucleus accumbens and islands of Calleja with relatively low levels of expression in the anterior caudate and putamen (Landwehrmeyer et al., 1993b). D_3 mRNA has also been observed in the granular cell layer of the dentate gyrus (Meador-Woodruff et al., 1994)

B. Distribution of Putative D_3 Receptors

1. Distribution in rat brain. Although the distribution of D_3 receptors in rat brain has not been mapped in detail, the localization of D_3 receptors appears to parallel that of D_3 mRNA. D_3 receptors appear to be expressed in highest density in brain regions such as the islands of Calleja, olfactory bulb, and the pituitary intermediate lobe. Moderately dense D_3 binding is observed in the nucleus accumbens, the molecular layer of the vestibulocerebellum, and substantia nigra pars compacta. Relatively little D_3 binding is observed in the caudate/putamen (Levant et al., 1992; Gehlert et al., 1992; Lévesque et al., 1992; Landwehrmeyer et al., 1993a; Parsons et al., 1993; Booze and Wallace, 1995; Ricci et al., 1995). D_3-like immunoreactivity was associated with neuronal-type cells and was concentrated at the cell body perimeter (Ariano and Sibley, 1994; Larson and Ariano, 1995)

2. Distribution in human brain. The distribution of D_3 receptors in human brain is generally similar to that observed in the rat; however, the overall pattern of distribution appears to be somewhat less restricted (Herroelen et al., 1994). Highest densities of putative D_3 sites are reported in the nucleus accumbens and islands of Calleja (Landwehrmeyer et al., 1993b; Murray et al., 1994). Moderate amounts of D_3 binding were observed in the basal ganglia, parietal, temporal and occipital cortex, and cerebellar cortex, followed by substantia nigra, hippocampus, and the basolateral, lateral and basomedial amygdaloid nuclei (Herroelen et al., 1994; Murray et al., 1994; Lahti et al., 1995). D_3 receptors were also detected in moderate density in the pituitary, with somewhat greater labeling in the posterior lobe than the anterior (Herroelen et al., 1994)

C. Implications of Regional Distribution

One of the issues of interest regarding the D_3 receptor is whether, like the D_2 site, this receptor is localized pre- or postsynaptically. The detection of D_3 mRNA in the substantia nigra and ventral tegmental areas and putative binding sites in dopaminergic terminal fields suggests that a subset of D_3 receptors may be presynaptic. In keeping with this hypothesis, unilateral dopaminergic lesions produced a marked decrease in D_3 receptor density in the nucleus accumbens, suggesting the loss of presynaptic sites (Lévesque et al., 1995). Neurochemical studies also suggest a role for the D_3 site as a synthesis- and/or release-modulating autoreceptor (See Section VI.C.).

The D_3 receptor is also of interest because of its relatively restricted distribution in brain. Unlike the D_2 receptor, which is abundant in the caudate/putamen and pituitary as well as in limbic brain regions (Levant, 1996), very low levels of expression of the D_3 receptor are detected in either the caudate/putamen or pituitary, brain areas associated with the untoward neurological and endocrine effects produce by most conventional antipsychotics. These observations suggest that the D_3 receptor, alone or in conjunction with other receptors, may be a target for novel antipsychotic drugs that might be free of extrapyramidal and neuroendocrine effects (Sokoloff et al., 1990).

Finally, the detection of D_3 receptor mRNA and binding in vestibulocerebellum is of potential significance. D_3 receptor mRNA, but not D_2 receptor mRNA, is reported in the Purkinje cell layer of lobule X, whereas putative binding is observed in the molecular layer. Purkinje cell dendrites arborize in the molecular layer suggesting that the binding sites identified represent D_3 receptors localized on the Purkinje cell dendrites. Purkinje cells in cerebellar lobule X project to the vestibular system, which controls proximal muscle tone and thus, posture and gait. Clinically, disorders involving cerebellar lobule X produce symptoms such as ataxia, whereas lesions of this brain region cause rigidity (Ghez and Fahn, 1981). These symptoms are similar to the neurological side effects associated with antipsychotic drugs (Parkinsonian-like tremor, rigidity, and bradykinesia). Although the contribution of the blockade of striatal dopamine receptors in producing these symptoms is not disputed, cerebellar D_3 receptors could also contribute to

these side effects. Although this issue has not been directly addressed, recent evidence suggests that microinjection of D_3-selective antagonists into the vestibulocerebellum produces alterations in locomotor activity in rats (Barik and Debeaurepaire, 1996). The source of dopaminergic innervation and the function of the cerebellar D_3 receptors, however, is unclear. In addition, whereas cerebellar D_3 receptors are present in rats, mice and guinea pigs do not appear to express dopamine receptors in the vestibulocerebellum (Camps et al., 1990). Whether humans possess these sites has yet to be definitively determined.

VI. D_3 Receptors in Cellular and Organismal Function

One of the primary aims in the study of the novel dopamine receptors is the elucidation of their role in cellular and organismal function. To date, pharmacological and molecular methods have been used in attempt to selectively study these novel sites. In the case of the D_3 receptor, numerous pharmacological studies as well as several studies using targeted mutation and antisense technologies have been performed. To date, a large body of data has been generated. Because of the limitations of these experimental approaches, however, care must be taken in the interpretation of these findings.

Pharmacological studies have made considerable use of the agonists and antagonists identified as exhibiting selectivity for the D_3 receptor in vitro. Some of these compounds, particularly 7-OH-DPAT, have been widely employed in vivo to probe the functional role of the D_3 receptor in behavioral, electrophysiological, and neurochemical studies. Recent pharmacological characterization of the D_3 receptor suggests that the D_2/D_3-selectivity of many compounds varies depending on the in vitro assay conditions used (Burris et al., 1995; Levant et al., 1995) (See Section IV.A.). Accordingly, there has been concern over the selectivity of these drugs in vivo and the attribution of pharmacological effects to the D_3 receptor (Freedman et al., 1994a; Large and Stubbs, 1994). In addition, the vast majority of the studies of D_3-mediated effects have used a single drug, 7-OH-DPAT. As such, some observed effects may be idiosyncratic to this drug.

Another approach for the study of this novel receptor is the use of mice deficient in D_3 sites resulting from a targeted mutation of the D_3 receptor gene, or "knock-out" animals. Although this approach is of considerable merit, it also has significant limitations. Most notably, such "knock-out" animals are deficient in D_3 receptors, and perhaps other proteins, throughout development. Because of the considerable plasticity of the developing nervous system, compensatory adaptations may occur, such as the expression of other receptors in place of the D_3 receptor. As such, until proven, it cannot be assumed that "knock-out" animals represent otherwise normal animals that simply lack D_3 sites. Likewise, it cannot be assumed that such animals made in different laboratories or by different methods are the same.

An alternative technique for generating an animal's deficiency in a protein of interest is the use of antisense oligonucleotides. Although this approach avoids problems associated with developmental plasticity, caution must again be exercised as the product of the targeted mRNA is likely to only be reduced, not eliminated, and other compensatory changes may occur.

Clearly, all of the methodologies currently available for the study of the role of the D_3 receptor in cellular and organismal function possess certain limitations. Taken together, however, certain themes are gradually becoming apparent in the large body of data amassed to date that suggest a potential role for the D_3 receptor in several cellular and organismal functions.

A. Role in Behavior

Although the D_3 receptor has been implicated in numerous behaviors, the receptor is most widely cited in the modulation of locomotor activity (fig. 5). In contrast to the D_2 receptor, in which stimulation is believed to increase locomotion, stimulation of the D_3 site appears to inhibit locomotor activity. This effect was initially reported in several studies using the D_3-preferring drug 7-OH-DPAT. This drug produced a biphasic effect on locomotor activity in rats in which locomotion was inhibited at lower doses and stimulated at higher doses (Daly and Waddington, 1993; McElroy et al., 1993; Ahlenius and Salmi, 1994; Svensson et al., 1994a,b; Khroyan et al., 1995; Depoortere et al., 1996; Kagaya et al., 1996). The inhibitory effects of the drug were attributed to activity of the drug at the D_3 receptor; the stimulatory effects were attributed to the actions of higher doses of the drug at the D_2 receptor (Daly and Waddington, 1993; Ahlenius and Salmi, 1994; Svensson et al., 1994a). This interpretation was supported by demonstration that the inhibitory effects of 7-OH-DPAT were produced by doses of the drug that do not produce significant occupancy of D_2 receptors in vivo (Levant et al., 1996). The D_3-preferring agonist PD 128907 produced similar biphasic effects on locomotor activity (Pugsley et al., 1995), and inhibition of locomotor activity was observed after microinjection of 7-OH-DPAT into the nucleus accumbens (Gilbert and Cooper, 1995; Kling-Petersen et al., 1995). Inhibition of locomotor activity by 7-OH-DPAT has also been reported in mice (Starr and Starr, 1995).

Consistent with the effects of D_3 agonists on locomotor activity, the D_3-preferring antagonist nafadotride produced biphasic effects on locomotor activity in rats, stimulating locomotion at lower doses and inhibiting locomotion at higher doses (Sautel et al., 1995b). As with 7-OH-DPAT, doses of nafadotride that increased locomotor activity were shown to produce negligible occupancy of D_2 receptors, whereas those that inhibited locomotion produced significant D_2 occupancy (Levant and Vansell,

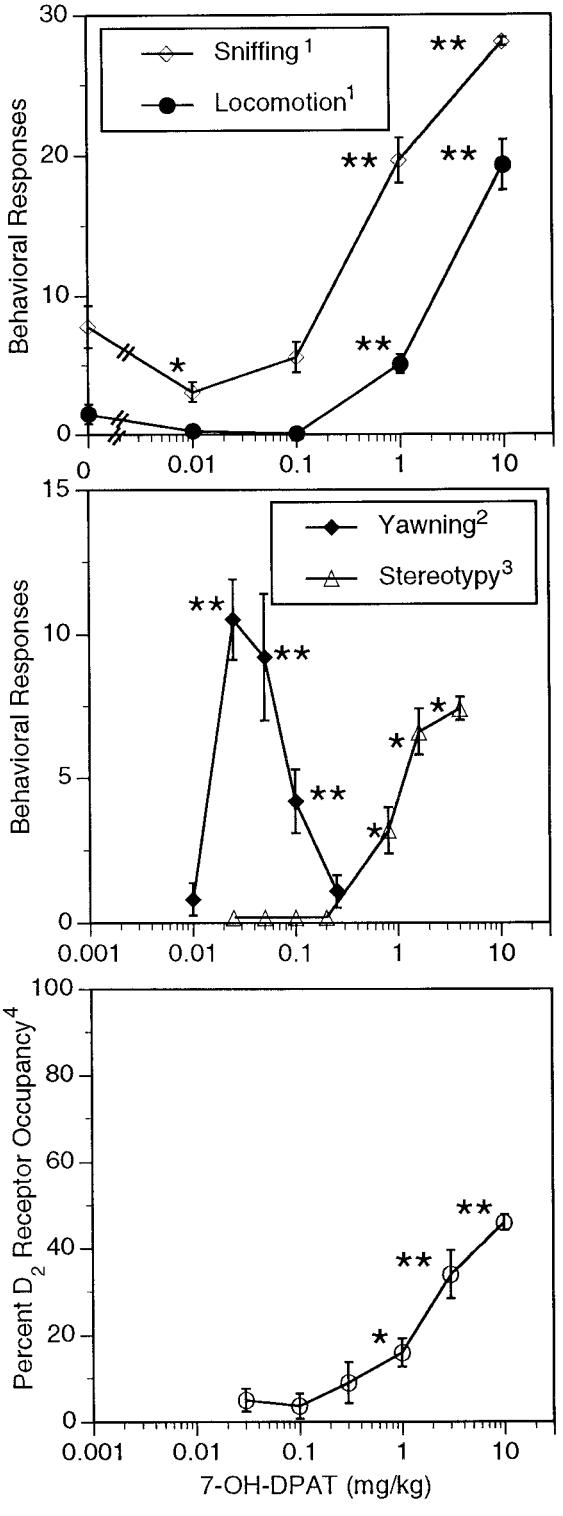

FIG. 5. Behavioral effects of 7-OH-DPAT in rat brain. Comparison with in vivo occupancy of D_2 dopamine receptors. Data are reported as number of exhibitions of a behavior during observation periods. In vivo occupancy of D_2 dopamine receptor by systemically administered (s.c.) 7-OH-DPAT was defined as percent protection of receptors from inactivation by 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) as determined by ex vivo [^{3}H]spiperone binding in striatal membranes. 1, Daly and Waddington (1993); 2, Kurashima et al. (1995); 3, Ferrari and Guiliani (1995); 4, Levant et al. (1995).

1997). Another D_3-preferring antagonist, U99194A, has also been reported to increase locomotor activity (Waters et al., 1993, 1994). Finally, increased locomotor activity and rearing behavior and hyperactivity in an exploratory test were observed in one strain of D_3 "knock-out" mice (Accili et al., 1996). Likewise, a preliminary report on another strain of D_3-deficient mice indicated a transient increase in activity in a novel environment compared with wild-type mice, although no alterations in agonist-stimulated locomotor behavior were observed (Xu et al., 1995; Koeltzow et al., 1995). Taken together, these findings indicate the probable involvement of the D_3 receptor in the modulation of locomotor activity in a manner opposite of that of the D_2 receptor.

Based on the somewhat limited in vivo and in vitro pharmacological data currently available, it is possible that the D_3 site may play a role in several additional behaviors. These include agonist-induced yawning and hypothermia (Damsma et al., 1993; Ahlenius and Salmi, 1994; Millan et al., 1994, 1995a,b; Ferrari and Guiliani, 1995; Khroyan et al., 1995; Kurashima et al., 1995), decreased sniffing (Daly and Waddington, 1993), decreased alcohol consumption (Meert and Clincke, 1994), and increased penile erection and ejaculatory behavior (Ahlenius and Larsson, 1995; Ferrari and Guiliani, 1995). Clearly, further study must confirm the role of the D_3 receptor in these behaviors, particularly in light of the significant variability in the in vitro pharmacological profile of the D_2 and D_3 sites on which much of the interpretation of these data is based. Likewise, in vivo occupancy studies may underestimate the interaction of an agonist with the D_2 site. Finally, in vivo interaction of the putative D_3 agonists with the D_3 receptor has yet to be demonstrated.

Stimulation of the D_3 receptor has also been implicated in intriguing behavioral effects involving reinforcement and reward. Of note, 7-OH-DPAT has been reported to decrease self-administration of cocaine (Caine and Koob, 1993) and self-stimulation of the ventral tegmental area (Depoortere et al., 1996). Likewise, stimulation of D_3 sites is implicated in blocking the reinforcing effects of cocaine and d-amphetamine (Kling-Petersen et al., 1994), decreasing the rate of food-reinforced responding in a fixed-ratio operant paradigm (Sanger et al., 1996), and producing an aversive effect in a conditioned place-preference paradigm (Chaperon and Thiebot, 1996). The subjective effects of 7-OH-DPAT and other D_3-preferring agonists generalize to cocaine in drug-discrimination paradigms in both rats and monkeys (Acri et al., 1995; Lamas et al., 1996). These observations have important implications for the understanding and treatment of drug addiction. However, as discussed above, further study must determine the role of specific dopamine receptor subtypes in these observations.

A variety of other behavioral and physiological effects of putatively D_3-preferring compounds have been re-

ported. These effects include conditioned taste aversion (Bevins et al., 1996), disruption of huddling behavior in rats (Kagaya et al., 1996), decreased grooming (Khroyan et al., 1995), alterations in performance in an elevated maze test (Rodgers et al., 1996), decreased prepulse inhibition (Caine et al., 1995), catalepsy (Millan et al., 1995b; Sautel et al., 1995b), enhancement of morphine-induced conditioned place preference (Rodriguez De Fonseca et al., 1995), inhibition of pilocarpine-induced limbic seizures (Alam and Starr, 1994), induction of depressant electroencephalogram patterns (Popoli et al., 1996), increased oxytocin secretion (Uvnas Moberg et al., 1995), and decreased gastric acid secretion (Glavin, 1994). The D_3 receptor has also been suggested to play a role in emesis in the dog (Yoshida et al., 1995) and decreased climbing in mice (Sautel et al., 1995b). The involvement of dopamine receptors in these effects is likely; however, evidence for the selective involvement of the D_3 site is currently lacking.

Although the body of literature of the pharmacological effects of D_3-preferring compounds has implicated the D_3 site in certain behaviors, such as the modulation of locomotor activity, these studies also indicate the probable lack of involvement of the D_3 receptor in other behaviors. For example, increases in sniffing and stereotyped behaviors produced by 7-OH-DPAT are observed only after treatment with doses that produce significant in vivo occupancy of D_2 receptors (Daly and Waddington, 1993; Damsma et al., 1993; Ferrari and Guiliani, 1995; Khroyan et al., 1995; Kurashima et al., 1995; Pugsley et al., 1995; Levant et al., 1996). Thus, these behaviors probably result from the stimulation of D_2 receptors.

B. Role in Neuronal Activity

As with behavioral studies, 7-OH-DPAT has been used to probe the effects of D_3 receptor stimulation on neuronal activity. The D_3-preferring agonist has been shown to inhibit firing of neurons in both the substantia nigra and ventral tegmental areas, as well as in brain slice preparations by activation of an 85 picosiemen K^+ channel (Bowery et al., 1994; Liu et al., 1994a; Devoto et al., 1995; Kreiss et al., 1995; Lejeune and Millan, 1995). 7-OH-DPAT has also been reported to decrease firing of spontaneously active or glutamate-driven neurons in the nucleus accumbens (Amano et al., 1994; Liu et al., 1994a). Although selective action of 7-OH-DPAT at D_3 receptors cannot be assumed in these studies, Kreiss et al. (1995) have shown that the potencies of ten dopamine agonists in inhibiting firing of neurons in the substantia nigra pars compacta correlated with their affinities at D_3, but not D_2 receptors. Caution, of course, must be exercised in the interpretation of such findings in view of the significant variability in the in vitro pharmacological profile of the D_2 and D_3 sites in various assay systems. In contrast, preliminary studies in D_3-receptor–deficient mice indicate increased sensitivity of nucleus accumbens neurons to the D_2/D_3 agonist quinpirole (Koeltzow et al., 1995). This observation may suggest a possible excitatory role for the D_3 receptor although up-regulation of D_2 receptor mechanisms must be ruled out by further study.

C. Role in Neurochemistry

In vivo and in vitro studies suggest a role for the D_3 site as an autoreceptor that modulates dopaminergic activity. Stimulation of D_3 receptors expressed in neuronal mesencephalic MN9D cells resulted in a dose-dependent inhibition of dopamine release (Tang et al., 1994b). Likewise, the D_3-preferring agonist 7-OH-DPAT produced decreases in dopamine release in vivo as assessed by microdialysis or voltametry, as well as in accumbal slice preparations (Damsma et al., 1993; Rivet et al., 1994; Yamada et al., 1994; Devoto et al., 1995; Gilbert et al., 1995; Patel et al., 1995; Gainetdinov et al., 1996). Similar effects were also reported for PD 128907 (Pugsley et al., 1995). Both 7-OH-DPAT and PD 128907 have also been shown to decrease extracellular dihydrophenylacetic acid concentrations as assessed by in vivo microdialysis consistent with a decrease in dopamine release (Pugsley et al., 1995; Gainetdinov et al., 1996). In addition, D_3 "knock-out" mice exhibited higher basal levels of extracellular dopamine (Cooper et al., 1996). It is difficult, however, to ascertain that the inhibition of dopamine release observed in heterogeneous tissues results from selective actions at the D_3 receptor as stimulation of D_2 receptors expressed in MN9D cells also inhibits dopamine release (Tang et al., 1994b). Likewise, similar inhibitory responses to PD 128907 were observed for both D_3 "knock-out" and wild-type mice (Cooper et al., 1996).

The D_3 receptor has also been implicated in the modulation of dopamine synthesis. In D_3-expressing MN9D cells, the application of agonist produced a decrease in K^+-stimulated tyrosine hydroxylase activity (O'Hara et al., 1996). In vivo, D_3-selective drugs 7-OH-DPAT and PD 128907 have been reported to decrease dopamine synthesis (Aretha et al., 1995; Gobert et al., 1995; Gainetdinov et al., 1996; Pugsley et al., 1995). This effect appears to be presynaptic, as it is observed in both normal rats and in rats treated with γ-butyrolactone, which blocks impulse flow in nigrostriatal and mesolimbic dopamine neurons (Aretha et al., 1995; Pugsley et al., 1995). The involvement of the D_3 receptor in this effect is supported by the observation that 7-OH-DPAT produced a greater decrease in dopamine synthesis in the nucleus accumbens, in which D_3 sites are relatively abundant, than in the caudate nucleus, in which D_3 sites are sparse (Aretha et al., 1995). A preliminary report by Nissbrandt et al. (1995) also suggests that reduction in the density of D_3 sites by intracerebroventricular infusion of antisense oligonucleotides for the D_3 receptor may result in increased dihydroxyphenylalanine accumulation, indicating a possible increase in dopamine synthesis. However, a preliminary report on D_3-recep-

tor–deficient mice indicated no alteration in dopamine synthesis compared with wild-type animals (Cooper et al., 1996). It must be borne in mind that these data are subject to same limitations as those discussed above for the behavioral studies. Even so, when taken together, these observations suggest a potential role for the D_3 receptor as an autoreceptor modulating dopamine release and/or synthesis. Further study, however, must confirm the role of specific dopamine receptor subtypes in these observations.

One additional observation suggests a possible role for the D_3 receptor in the modulation of the neuromodulatory peptide neurotensin. Although blockade of D_2 receptors increases expression of proneurotensin mRNA in the caudate and nucleus accumbens shell cone, blockade of D_2-like dopamine receptors with haloperidol decreased expression of proneurotensin mRNA in the ventromedial nucleus accumbens shell, an area enriched in D_3 receptor mRNA (Diaz et al., 1994). Although this observation suggests that blockade of D_3 sites may ultimately decrease neurotensinergic neurotransmission in some brain areas, it should be noted that the effects of D_3 receptor manipulations on neurotensin concentration or release have yet to be determined.

D. Role in Development

Expression of the D_3 receptor in brain occurs quite early in development. In rat brain, D_3 receptor mRNA is detectable by polymerase chain reaction as early as embryonic day 11 and is clearly detectable by embryonic day 14 (Cadoret et al., 1993). Similarly, in mouse brain, D_3 receptor mRNA is detectable on embryonic day 9.5, 4 days before the detection of D_2 receptor mRNA (Fishburn et al., 1996). D_3 receptor binding, as assessed with [^{3}H]7-OH-DPAT, is detectable in the islands of Calleja and olfactory tubercle at birth in mouse brain. D_3 binding in the nucleus accumbens is detectable on postnatal day 4, substantia nigra on postnatal day 8, and in the vestibulocerebellum on postnatal day 11. Binding in these brain areas was observed to increase in density through development until adult levels were reached. In addition, transient expression of D_3 binding was observed in the dorsolateral parietal cortex between postnatal days 6 and 15 (Demotes-Mainard et al., 1996).

Interestingly, during the 2nd trimester of gestation, D_2-like receptors are transiently expressed in the cortical-plate of developing human brain (Todd, 1992; Unis and Dorsa, 1993). Preliminary reports also indicate transient, dense expression of D_3 receptor mRNA in the cortical plate of human brain at midgestation (Unis and Dorsa, 1993; Unis et al., 1995), suggesting that these receptors are of the D_3 subtype. This transient expression of D_3 receptors suggests a role for dopamine in orchestrating neuronal migration and differentiation during this period of accelerated cortical development that is mediated by the D_3 receptor. This hypothesis is supported by the observation that stimulation of D_3 sites induces increased branching and extension of neurites in both mesencephalic MN9D cells and primary mesencephalic neuronal cultures (Swarzenski et al., 1994).

VII. Regulation of D_3 Receptor Density and Messenger Ribonucleic Acid Expression

A. Modulation by Tonic Dopaminergic Activity

Unilateral 6-hydroxydopamine lesion of the ascending dopaminergic projections results in up-regulation of striatal D_2 receptors (Seeman, 1981). In contrast, unilateral dopaminergic lesions have been reported to produce a marked decrease in both D_3 receptor mRNA and D_3 receptor in the nucleus accumbens (Lévesque et al., 1995). The decrease in the density of D_3 binding is consistent with a loss of presynaptic sites. On the other hand, the concurrent decrease in D_3 receptor mRNA expression tends to indicate a loss of D_3-receptor–expressing cell bodies and thus a probable decrease in postsynaptic sites. Although further study may be required to fully understand the regulation of the D_3 site after dopaminergic lesions, it is clear from this study that the regulation of D_3 sites is distinctly different from that of D_2 receptor sites.

In contrast to dopaminergic lesions, pharmacologically induced depletion of catecholamines produced different results. Treatment with reserpine for 5 days failed to alter expression of D_3 receptor mRNA (Lévesque et al., 1995). On the other hand, acute depletion of catecholamines, using reserpine and α-methyltyrosine, produced an apparent increase in affinity of a subset of putative D_3 sites, as assessed by using [^{3}H]7-OH-DPAT, without an increase in the total number of sites detected (Levant, 1995) (See Section III.B.). This observation suggests the rapid up-regulation of D_3 sites in the absence of tonic dopaminergic activity.

B. Modulation by Antidopaminergic Drugs

The fact that antidopaminergic drugs produce up-regulation of D_2 receptors is well-established (Seeman, 1981). Because the D_3 receptor has been proposed as a potential antipsychotic site, there has been a great deal of interest in whether antipsychotic drugs produce a similar up-regulation in D_3-sites. To date, several studies have been performed, examining the effects of antipsychotic drugs on the expression of D_3 receptor mRNA with differing results. Chronic treatment with haloperidol, sulpiride, and clozapine has been reported to produce increases in D_3-receptor mRNA in whole brain of three to five-fold as assessed by ribonuclease protection (Buckland et al., 1992, 1993). More modest increases in D_3 receptor mRNA (40–60%) were observed in olfactory tubercle after treatment with haloperidol and sulpiride, but not clozapine, for 14 days as assessed by polymerase chain reaction (Wang et al., 1996). Other studies, using different treatment paradigms, reported no change in D_3 receptor mRNA expression (Fishburn et al., 1994; Fox et

al., 1994; Lévesque et al., 1995) or D_3 binding (Lévesque et al., 1995). Clearly, the conflicting results observed in these studies may result from the different treatment paradigms used and must be resolved by further study. Moreover, these studies did not assess whether the observed antipsychotic-induced alterations in D_3 receptor mRNA expression resulted in changes in the density or affinity of D_3 receptors.

VIII. D_3 Receptors and Disease

A. Genetic Linkage to Disease

In addition to the truncated forms of the D_3 receptor believed to result from alternative splicing events (See Section II.C.), several polymorphisms have been identified in the human D_3 receptor gene. The *Bal*I, or *Msc*I, restriction fragment length polymorphism was first identified by Lannfelt and colleagues (1992). This polymorphism corresponds to a point mutation in the 1st exon of the D_3 receptor gene, which results in a serine-to-glycine substitution in the N-terminal extracellular domain of the receptor. This mutation appears to result in receptors with higher affinity for dopamine than wild-type receptors (Lundstrom and Turpin, 1996). An additional polymorphism, the *Msp*I, has been localized to the 4th intron of the gene (Sabaté et al., 1994).

Linkage studies have been performed in an attempt to establish the involvement of the D_3 receptor gene in the pathogenesis of schizophrenia and other neuropsychiatric disorders. These studies, which identify genes that exert a relatively large effect on a particular phenotype in families containing affected individuals, have failed to establish linkage of the D_3 receptor gene in schizophrenia (Coon et al., 1993; Wiese et al., 1993; Nanko et al., 1994b; Sabaté et al., 1994), bipolar disorder (Mitchell et al., 1993; Nanko et al., 1994a), or Tourette syndrome (Brett et al., 1993, 1995).

Association studies, however, have suggested a possible contribution of the D_3 receptor gene in schizophrenia. These studies compare the frequency of a given allele in unrelated persons of a given phenotype with a group of ethnically matched controls, with the aim of identifying candidate genes involved in polygenic inheritance. Initial studies identified an association between homozygosity for either allele of the *Bal*I polymorphism and schizophrenia in French and English populations (Crocq et al., 1992), suggesting that this gene may contribute to the susceptibility of developing the disease. This finding has been supported by several subsequent studies of subjects in the United Kingdom, France, and the United States, particularly in patients with good response to antipsychotic treatment (Mant et al., 1994; Kennedy et al., 1995; Griffon et al., 1996; Shaikh et al., 1996). One study, however, found a positive association between homozygosity and the *Bal*I polymorphism only in male subjects (Asherson et al., 1996), another only in patients with a familial history of the disease (Nimgaonkar et al., 1993). Even so, an association between *Bal*I polymorphism and schizophrenia has not been supported by several other studies of Chinese, Japanese, Swedish, German, British, Italian, and American populations (Jonsson et al., 1993; Nanko et al., 1993; Yang et al., 1993; Di Bella et al., 1994; Saha et al., 1994; Macciardi et al., 1994; Higuchi et al., 1995; Gaitonde et al., 1996; Nimgaonkar et al., 1996; Rietschel et al., 1996; Tanaka et al., 1996). No association has been detected between the *Msp*I polymorphism and schizophrenia (Dollfus et al., 1996; Griffon et al., 1996).

Association studies have also examined the potential contribution of the D_3 receptor gene to susceptibility to bipolar disorder. One study has indicated an increase in allele 1, containing genotypes of the *Bal*I polymorphism among bipolar families (Parsian et al., 1995). Several other studies of European and Japanese populations, however, have failed to detect an association between the D_3 receptor gene and this disorder (Rietschel et al., 1993; Shaikh et al., 1993; Manki et al., 1996; Souery et al., 1996). A lack of association with the D_3 receptor gene alleles has also been shown for alcoholism (Gorwood et al., 1995; Higuchi et al., 1996), cocaine dependence (Freimer et al., 1996), obsessive-compulsive disorder (Catalano et al., 1994), and Parkinson's disease (Nanko et al., 1994c; Higuchi et al., 1995).

Although there is no clear relationship between D_3 receptor alleles and the predisposition toward certain neuropsychiatric disorders, a recent study suggests a relationship between D_3 receptor genotypes and monoaminergic transmission in the central nervous system. Concentrations of 5-hydroxyindoleacetic acid in cerebrospinal fluid were shown to differ significantly between subjects with D_3-receptor homo- and heterozygote genotypes (Jonsson et al., 1996). Although further study must support and extend these observations, these studies, combined with studies of linkage and association of D_3 receptor alleles in neuropsychiatric disorders, may ultimately contribute to our understanding of the mechanism(s) by which certain genotypes may contribute to the predisposition to diseases.

B. Receptor Alterations in Neuropsychiatric Disorders

Investigation into alterations in the expression of the D_3 receptor in disease is still in the early stages. Accordingly, data available at present are relatively limited. Initial studies examining the densities of the D_2-like dopamine receptors in postmortem putamen tissues from schizophrenic patients using relatively nonselective radioligands suggested an elevation in D_4 sites but not in D_2 or D_3 sites (Seeman et al., 1993). Another postmortem study of schizophrenic brain reported that whereas normal subjects express mRNAs for both the D_3 receptor and the truncated splice variant D_{3nf}, the parietal and motor cortices of schizophrenic patients exhibited a selective loss of expression of D_3 receptor mRNA (Schmauss et al., 1993).

Investigation into alterations in the D_3 receptor in Parkinson's disease suggests that whereas decreases in expression of D_3 receptor mRNA are observed in certain brain regions, such as the olfactory tubercle during aging (Valerio et al., 1994), densities of both D_3 receptor mRNA and D_3 binding are not altered in postmortem brain of patients afflicted with Parkinson's disease (Hurley et al., 1996). Although no significant alterations in D_3 receptor expression in brain of Parkinson's patients have yet been reported, a decrease in D_3 receptor mRNA expression in lymphocytes of Parkinson's patients has been observed. In fact, the magnitude of the decrease in D_3 receptor mRNA expression correlated with the severity of the disease suggests that this might serve as a marker for monitoring disease progression (Nagai et al., 1996). The detection of D_3 receptor mRNA in human lymphocytes, however, has not been observed in some studies (Vile and Strange, 1996).

Finally, cocaine use has been reported to alter the density of the D_3 receptor. No changes in D_3 receptor mRNA expression were observed in the dorsal or ventral striata of postmortem brain of chronic cocaine abusers (Meador-Woodruff et al., 1995). However, the density of D_3 sites was observed to be increased from one to threefold in the caudate, nucleus accumbens, and substantia nigra of persons who had died from cocaine overdose (Staley and Mash, 1996).

Clearly, investigation of alterations in the D_3 receptor in disease is in the early stages. Further study must verify whether alterations in the density or the regulation of this receptor exist in various pathological conditions.

IX. Conclusion

In the short time since the identification of the 3rd dopamine receptor, considerable progress has been made toward understanding the function of this novel site. Although some avenues of investigation have yielded more definitive results than others, studies to date indicate the localization of the D_3 receptor in limbic and vestibulocerebellar brain areas that affect locomotion and perhaps play a role in reinforcement and reward. A subpopulation of the receptors appears to be autoreceptors, which modulate dopamine synthesis, release, and neuronal activity. These observations have lead to the hypotheses that the D_3 receptor may be an appropriate target in the treatment of neuropsychiatric disorders, such as schizophrenia and drug addiction. The role of D_3 sites in disease, however, remains to be established. Genetic association of D_3 receptor polymorphisms with neuropsychiatric disorders have been controversial. Nevertheless, alterations in expression of D_3 sites may occur in some diseases. Though the study of this receptor is clearly in the early stages, these findings lay the foundation for future investigation. Further study may ultimately aid in the elucidation of the role of the D_3 receptor in normo- and pathophysiology and its potential utility in the treatment of disease.

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