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REVIEW

Linking the Family of D_2 Receptors to Neuronal Circuits in Human Brain: Insights into Schizophrenia

Jeffrey N. Joyce, Ph.D., and James H. Meador-Woodruff, M.D.

The dopamine (DA) hypothesis of schizophrenia, which was based largely on evidence that pharmacological manipulations of DA systems influence the symptoms of schizophrenia, is undergoing a transformation due to our knowledge of the anatomy and pharmacology of additional subtypes of dopamine receptors. New research links the multiplicity of D_2-like receptors to divergent neuroanatomic sites of suspected pathology in schizophrenia. We hypothesize that this research suggests that D_2 receptors in the basal ganglia are the likely site of extrapyramidal symptoms and not antipsychotic effects. Rather, D_3 receptors of the mesolimbic system are a likely site of antipsychotic effects, and D_2 and D_4 receptors in the medial temporal lobe and limbic cortical areas are the sites of additional antipsychotic effects. This work also suggests that divergent DA receptor circuits are likely associated with the pathophysiology of this disorder.

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KEY WORDS: *D_2 dopamine receptors; D_3 dopamine receptors; D_4 dopamine receptors; Messenger RNA; Cortex; Hippocampus; Basal ganglia*

A productive approach to exploring the contribution of dopamine (DA) systems to schizophrenia was based on the identified D_2 receptor antagonist properties of antipsychotics. Among the brain structures thought to be involved in the site of antipsychotic action, the striatum emerged as an obvious target; it has the highest concentration of D_2 receptors in the brain, and chronic intake of neuroleptics often leads to motor disturbances associated with the nigrostriatal DA system. Moreover, it was found that striatal D_2-like receptors are elevated in schizophrenia (Owen et al. 1978). In spite of the clinical efficacy of D_2 antagonists, it has been difficult to reconcile the hypothesis that it is the actions of antipsychotics at D_2 receptors in the striatum that modulate psychosis with data indicating widespread disturbances in cortical function and structure in schizophrenia (Shapiro 1993; Pearlson et al. 1996). This discrepancy has been reinforced by the evidence that atypical antipsychotics such as clozapine have lower efficacy than typical antipsychotics (e.g., haloperidol) for D_2 receptor–mediated effects within the targets of the nigrostriatal DA system and possess a lower likelihood of inducing extrapyramidal side effects at doses that provide clinical improvement (Hogberg et al. 1987; Moghaddam and Bunney 1990; Merchant et al. 1992). Further, clozapine and haloperidol have differential effects on the striatal expression of the immediate-early gene c-fos: treatment with haloperidol, but not clozapine, increases striatal expression of fos protein (Deutch et al. 1992; Nguyen et al. 1992; Robertson and Fibiger 1992). Accordingly, blockade of D_2 receptors within the striatum seems

From the Thomas H. Christopher Center for Parkinson's Disease Research (JNJ), Sun Health Research Institute, Sun City, Arizona; and the Mental Health Research Institute and the Department of Psychiatry (JHM-W), University of Michigan, Ann Arbor, Michigan.

Address correspondence to: Dr. Jeffrey N. Joyce, Head and Senior Scientist, Christopher Center for Parkinson's Disease Research, Sun Health Research Institute, LJ Roberts Center, POB 1278, 10515 W Sante Fe Drive, Sun City, Arizona 85372.

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likely to be the major site of extrapyramidal side effects of antipsychotics, but may not be the primary site of antipsychotic effects.

If blockade of D_2 receptors within the striatum is not the site of action of antipsychotics, then it becomes imperative to discover whether actions at other members of the D_2 receptor family (e.g., D_3 and D_4) could be involved in either the antipsychotic activity and/or disturbances in function in schizophrenia (Meador-Woodruff, 1995). For example, typical antipsychotics can induce Parkinsonian-like symptoms through actions at D_2 receptors in the motor subdivision of the striatum; the atypical class of antipsychotics appears to act at other members of the D_2 receptor family. Consequently, the D_4 receptor had been studied because of the relatively higher affinity of clozapine for this receptor (Van Tol et al., 1991). In contrast, research on D_3 receptors has emphasized the relationship of this receptor to the mesolimbic DA system (Sokoloff et al., 1990), evidence that it responds differently from the D_2 receptor to chronic treatment with antipsychotics (Fishburn et al. 1994; Lévesque et al. 1995; Damask et al. 1996), and recent work showing that it may be regulated by antipsychotic medication in schizophrenics (Gurevich et al. in press). Finally, knowledge that D_2 and D_4 receptors are expressed in a number of cortical regions make these sites potentially important in regulating certain symptoms in schizophrenia. (Goldsmith and Joyce 1994, 1996; Meador-Woodruff et al. 1994a; Lahti et al. 1995).

NIGROSTRIATAL AND MESOLIMBIC DA RECEPTORS

Two major divisions of the DA systems exist within the basal ganglia, the nigrostriatal and mesolimbic systems (Figure 1). For the rat, the sources of the nigrostriatal and mesolimbic DA systems are based on a medial-lateral anatomy of dopamine systems. In the primate, however, the source of the nigrostriatal and mesolimbic dopamine projections reflect a more dorsal/ventral differentiation (Waters et al. 1988; Groenewegen and Haber 1989; Gibb 1992). Thus, based on the tracer studies, the mesolimbic DA system of the primate would include the A10 region (ventral tegmental area) and the dorsal tier of the pars compacta of the substantia nigra (SNpc) (Jimenez-Castellanos and Graybiel 1987; Lynd-Balta and Haber 1994a; 1994b), whereas the origination of the "nigrostriatal" DA system would be more restricted to the ventral tier of the SNpc (Szabo 1980; Tanaka et al. 1982; Lynd-Balta and Haber 1994a). The mesolimbic DA system projects to the ventral striatum (nucleus accumbens and ventral putamen) and has an important target the D_3 receptor (Lynd-Balta and Haber 1994b; Murray et al. 1994). The efferents of the ventral striatum remain segregated from dorsal striatal efferents, whose neurons reside in the putamen, receive afferents from the sensory/motor cortex, and integrate sensory-motor information while modulated by the nigrostriatal DA system. The D_2 receptor is an important target of the nigrostriatal DA system (Joyce et al. 1986; Murray et al. 1994). D_2 receptor binding is enriched within the matrix compartment of the dorsal striatum and in its efferents. In contrast, the D_3 receptor is enriched in the striosomal compartment of the ventral striatum and its efferents. Whereas the neurons expressing mRNA for D_2 and D_3 receptors are largely intermingled in the ventral striatum, mRNA encoding the D_3 receptor is much more abundant in the ventral than the dorsal striatum, and is expressed in clusters of neurons that may be correlated with dense patches of D_3 receptors observed autoradiographically (Figure 2). Furthermore, D_3 mRNA-bearing neurons are abundant in the primary and secondary targets of the ventral striatum. However, D_2/D_3 receptor interactions could continue to occur within the ventral striatum and its efferents as the majority of neurons coexpress D_2 and D_3 receptors (Gurevich and Joyce, in preparation). Moreover, it is now known that neurons in the globus pallidus as well as in the thalamus express D_4 receptor immunoreactivity (Mrzljak et al. 1996). Hence, the nigrostriatal and mesolimbic compartments of the striatum, their striatopallidal and striatonigral efferents, thalamic targets, and sources of input are not only segregated, but also likely influenced by DA through different members of the D_2 receptor family.

NIGROSTRIATAL AND MESOLIMBIC DA SYSTEMS IN SCHIZOPHRENIA

Elevations of D_2-like receptor binding in the striatum of schizophrenics have been consistently demonstrated in postmortem studies (Seeman et al. 1987). Efforts have also been made to study D_2-like receptor density in vivo using positron emission tomography (PET). Conflicting results have been reported. One set of studies indicated that the number of D_2 receptors is higher in the basal ganglia of a small group of drug-free schizophrenics (Wong et al. 1986). Several other groups have reported that this marker is not changed (Farde et al. 1990; Martinot et al. 1990). This discrepancy may be explainable by differences in the ligands used by the different groups for the DA receptors. In the first study reporting no change in D_2-like receptor density in schizophrenia, raclopride was the ligand used (Farde et al. 1990). This particular compound has a high selectivity for both the D_2 and D_3 receptors compared to the D_4 site, but low affinity for D_2-like receptors. In most studies reporting a positive finding, N-methylspiperone was used, which has a high affinity for all three of these receptors. Thus, one of the pharmacological differences between these

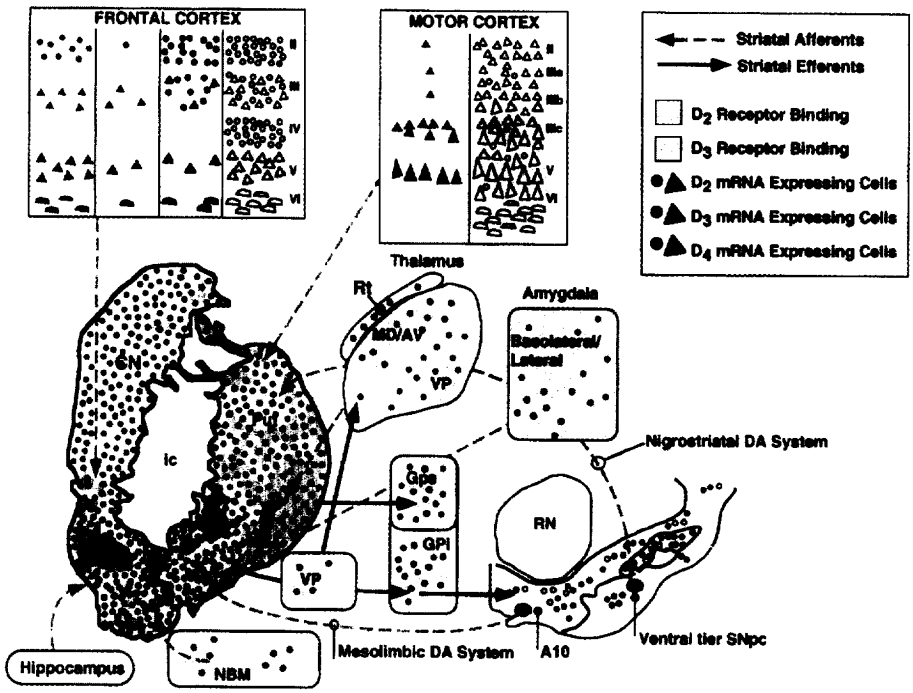

Figure 1. Dopamine receptor circuitry of basal ganglia. Two members of the D_2 receptor family, D_2 and D_3, are segregated to different circuits within the basal ganglia (Murray et al. 1994; Gurevich et al. in press; Meador-Woodruff et al. 1996). D_2 receptors are the primary target of the nigrostriatal DA system originating in the ventral tier of the SNpc (Szabo 1980; Lynd-Balta and Haber 1994a; 1994b), and are expressed in higher concentrations at several stations in the motor loop. This includes the sources of afferents (e.g., motor cortex) and the pallidal and thalamic targets of the motor loop (e.g., GPe, VP nucleus of the thalmus) (Alexander and Crutcher 1990; Graybiel 1995). In contrast, D_3 receptors are found in higher concentrations within the targets of the mesolimbic DA system originating in the medial and dorsal components of the SN (Jimenez-Castellanos and Graybiel 1987; Lund-Balta and Haber 1994a, 1994b) and are also highly concentrated at relay stations in the limbic loop (see Figure 2). This includes the sources of afferents (e.g., frontal cortex, nucleus basalis) and pallidal and thalamic targets of the limbic loop (e.g., VP, GPi, MD/AV nuclei of the thalamus). In addition, neurons of the GPe, GPi, RT, and interneurons of the cortex that express the D_4 receptor protein are indicated (Mrzljak et al. 1996). *Abbreviations*: CN, caudate nucleus; GPe, globus pallidus external; GPi, globus pallidus internal; MD/AV, medial dorsal and anteroventral nuclei of the amygdala; NBM, nucleus basalis of Meynert; ic, internal capsule; RN, red nucleus; RT, reticular nucleus of the thalmus; SNpc, substantia nigra pars compacta; VP, ventroposterior nucleus of the amygdala (near thalamus in figure); VP, ventral pallidum.

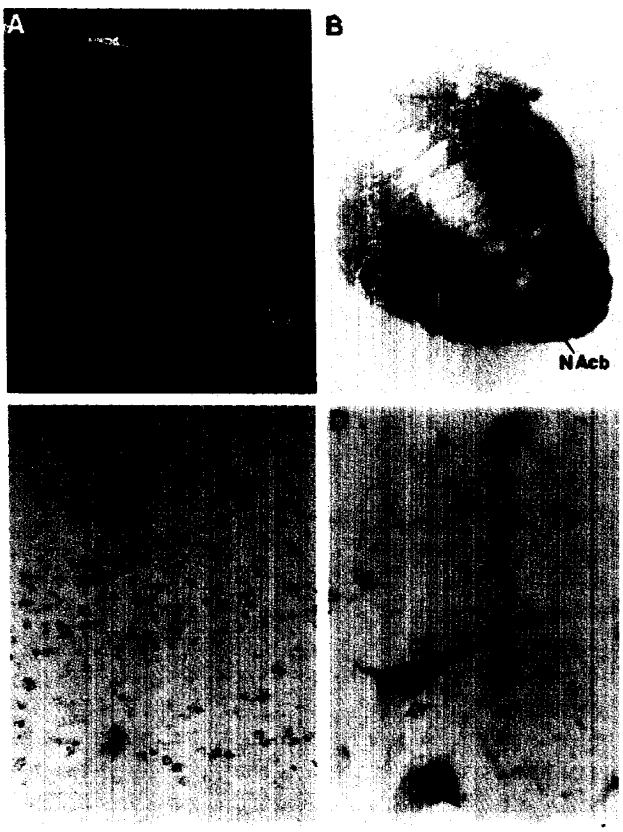

Figure 2. Segregation of D_3 receptors and mRNA in limbic striatum. (*A*) Autoradiographic demonstration of D_3 mRNA by in situ hybridization histochemistry using an [^{35}S]-labeled riboprobe shows higher concentrations in the ventral putamen and nucleus accumbens of the human, with clusters enriched with this mRNA. (*B*) This parallels the distribution of D_3 receptors demonstrated by receptor binding for [^{125}I]-trans-7-OH-PIPAT, which also are organized in patches in the ventral putamen and nucleus accumbens (*C*) Nonradioactive visualization of D_3 mRNA-bearing neurons in the human nucleus accumbens also shows distinct clusters. (*D*) Regions of human brain that are the targets of the ventral putamen and nucleus accumbens, such as the GPi, also exhibit D_3 mRNA-bearing neurons (visualized with fluorescein-UTP–labeled riboprobes). Different sources of material were used for the protocols demonstrated in the panels of this figure.

studies is the differing selectivity of the ligands for the D_4 site. Specifically, the "positive" study used a ligand with high affinity for the D_4 receptor, and the "negative" study used a low-affinity D_4 compound. A recent study by Nordstrom et al. (1995) call this interpretation into question, however, as they also used N-methylspiperone in a PET study and found no differences between schizophrenics and controls.

Seeman and associates (1993) have postulated that the elevation in [^{3}H]-spiroperidol binding in schizophrenics largely reflects changes in the density of D_4 receptors. Using nonselective radioligands in several different combinations to indirectly estimate the concentrations of D_2, D_2 plus D_3, or D_4 receptors, they argued that the elevation in [^{3}H]-YM0911-2 ($D_2 + D_3 + D_4$ receptors) binding in schizophrenics (after subtracting [^{3}H]-raclopride binding to D_2/D_3 sites) reflected binding to D_4 receptors. Although this finding has been supported (Murray et al. 1995; Sumiyoshi et al. 1995), one group has reported that in the presence of raclopride to displace binding to D_2/D_3 receptors, [^{3}H]-YM0911-2 does not show detectable binding in either control or schizophrenic striatum (Reynolds and Mason 1994). There is no evidence either that D_4 mRNA in the human striatum (Meador-Woodruff et al. 1996), or receptor protein detected with antibodies in the nonhuman primate striatum exist in any measurable levels (Mrzljak et al. 1996), making the interpretation of Seeman's results difficult. It would also appear that the pharmacology of this putative D_4 receptor is difficult to reconcile with our present knowledge of D_2-like receptors and may represent a non-D_4 site (Hubert H. Van Tol, personal communication) and/or may reflect antipsychotic induction of D_4 receptor expression (Schoots et al. 1995). Thus, although an increase of striatal D_4 sites in schizophrenia is one possible explanation for the discrepancies between the PET studies, this interpretation is difficult to support at this time.

Another important difference in comparing the postmortem and PET studies is the subject population studied. The increase of striatal D_2 receptors obtained from postmortem studies may not be due to the illness, but rather to long-term adaptations of DA receptors to chronic antipsychotic treatment. In animal studies, both short-term (1 to 3 weeks) and chronic treatment (6 or more months) with haloperidol elevates striatal D_2 receptors, which remain elevated even after drug withdrawal (Laruelle et al. 1992). Accordingly, elevations in D_2 receptors identified in schizophrenics may be related to the use of antipsychotics rather than to the illness itself. To substantiate a role for increases in D_2 receptor number in schizophrenia, it has been shown that drug-naive patients show an increase in the B_{max} for [^{3}H]-spiroperidol binding to D_2-like receptors (Owen et al. 1978), although this study was limited by small sample sizes. However, other data suggest that overexpression of D_2-like receptors in drug-naive patients occurs largely in the limbic region of the striatum and drug effects may account for the elevations in the motor region (Joyce et al. 1988; Mita et al. 1986). With the cloning of D_3 receptors, it has become clear that this elevation in [^{3}H]-spiroperidol binding in the ventral striatum may reflect this member of the D_2 receptor family.

In addition to its localization in the ventral striatum, the pharmacology of the D_3 receptor makes it an attractive candidate for involvement in schizophrenia and as a target for antipsychotics. For example, theoretical calculations imply that at clinically used doses antipsychotics occupy D_3 receptors at levels only slightly less than D_2 receptors (Schwartz et al. 1993). The examination of this receptor in schizophrenic brain, however, would provide a more direct test of the hypothesis that the D_3 receptor is involved in the illness. We have analyzed the binding of [^{125}I]-trans-7-OH-PIPAT to D_3 receptors by quantitative autoradiography in postmortem tissue from schizophrenics (Gurevich et al. in press). We found elevations (45% to 56%) in the number of D_3 receptors in the basal ganglia and ventral forebrain of schizophrenics compared with controls. In contrast to what has been observed for D_2 receptors, the schizophrenic cases free of antipsychotics at time of death showed twice as many D_3 receptors as controls, whereas those receiving antipsychotics had levels similar to or less than control values. In separate studies of the same cases, we identified that D_2 receptors were minimally elevated regardless of the history of antipsychotic treatment. Although the results need to be replicated, in contrast to the previously detected elevation of D_2 receptors in schizophrenia, a disease related elevation of D_3 receptors in the limbic striatum may be reduced by antipsychotics. These results may reflect differences in how D_3 and D_2 receptors are affected by antipsychotic treatment.

Animal models indicate that mesolimbic D_2-like receptors are regulated differently from those in motor regions. Following chronic treatment with typical antipsychotics, [^{3}H]-spiroperidol binding to D_2-like (D_2 and D_3) receptors is either not elevated in mesolimbic regions (Murugaiah et al. 1985) or elevations do not persist with continuous treatment (Clow et al. 1980; Prosser et al. 1989), in contrast to elevations in the motor subdivision. Furthermore, it has been reported that behavioral responses to DA agonists thought to be mediated by the mesolimbic DA system do not evidence a functional supersensitivity during continuous treatment with antipsychotics (Rupniak et al. 1985). Although one study (Buckland et al. 1992) has found that D_3 receptor mRNA is increased by both sulpiride and clozapine treatments, the convergence of published reports suggests that D_3 receptor and its mRNA are not elevated under conditions of antipsychotic treatment that lead to elevations in the D_2 receptor and its mRNA (Damask et al. 1996;

Fishburn et al. 1994; Lévesque et al. 1995). These differences in regulation of mesolimbic and nigrostriatal D_2-like receptors by chronic antipsychotic treatment may reflect the contribution of D_3 receptors to the D_2-like receptor population in the limbic striatum, although this remains to be directly tested.

The mesolimbic system is believed to be intimately involved in the regulation of emotions, long-term memory storage, and other related functions. This system is thought to act as a gate that is under the control of DA for modulating efferents from a number of other regions in the brain that are disturbed in schizophrenia (Mogenson et al. 1988; Amalric and Koog 1993; Joyce 1993). We hypothesize that alterations in D_3 receptor expression in ventral striatal neurons and their striatopallidal targets occurs in schizophrenics, perhaps because of the cortical regulation of these sites. It is these effects that are likely to be modified by antipsychotics, thus providing a mechanism of returning balance to limbic efferents that act through specific pallidal-thalamo-cortical circuits. Further, D_3 receptor mRNA has been reported in the human substantia nigra, a localization consistent with the D_3 receptor serving as a dopamine autoreceptor (Meador-Woodruff et al. 1994b). In addition to D_3 antagonists being candidates for antipsychotic agents, it is conceivable that D_3 agonists may also be useful antipsychotic agents, by presynaptically inhibiting ventral striatal dopamine release. Given the strong association between the ventral striatum and regulation of affect, as well as its role in reward and reinforcement, it might be speculated that manipulation of D_3 receptors in this region plays a role in modulating some psychotic symptoms (Mogenson et al. 1988). In contrast, the use of D_2 receptor "knockout" and antisense "knockdown" strategies in animals has confirmed the role of D_2 receptors in mediating extrapyramidal "motor" responses to dopaminergic agents (Baik et al. 1995; Zhang and Creese 1993).

The issue of which member of the D_2 receptor family is predominantly affected in the striatum in schizophrenia has not been resolved, but an interpretation of these recent data suggest that D_2 receptor blockade may be more closely related to the extrapyramidal effects of neuroleptic treatment, and antipsychotic efficacy with the regulation of the D_3 receptor.

CORTICOLIMBIC DOPAMINE SYSTEMS

Cortical DA systems also have been implicated in schizophrenia, particularly those associated with the prefrontal cortex. This structure has an integrating role, coordinating higher neural functions. Lesion studies have demonstrated that damage to the prefrontal cortex produces a syndrome of depression, apathy, lack of energy, anhedonia, and memory and concentration disturbances; this syndrome has been suggested to be similar to the schizophrenic deficit state or the negative symptom cluster associated with poor-prognosis schizophrenia (Davis et al. 1991). A number of functional imaging studies have demonstrated the impairment of functioning of the prefrontal cortex in schizophrenia, both at rest and during specific behavioral tasks associated with this region (Berman et al. 1988; Weinberger et al. 1988). It has been suggested that this hypoactivity may be associated with downregulation of the dorsolateral prefrontal cortical DA system, which in turn leads to an increase in DA activity in the ventral striatum via corticostriatal efferents (Davis et al. 1991; Weinberger et al. 1992; Rubin et al. 1991). Recent studies have suggested that, although D_2 and D_3 receptors and their mRNAs are expressed at low levels in the prefrontal cortex, the D_4 receptor may be much more abundant. D_4 receptor mRNA is robustly expressed in frontal cortical regions in human brain (Meador-Woodruff et al. 1996), and recent studies examining D_4 receptor binding and localization of the protein by detection of antibodies suggest high levels of cortical D_4 receptors as well (Lahti et al. 1995; Mrzljak et al. 1996).

There is now considerable evidence that other limbic cortical regions also are affected in schizophrenia symptoms (Shapiro 1993; Pearlson et al. 1996). For example, in vivo imaging of local cerebral glucose utilization in schizophrenic subjects show alterations in glucose utilization in several limbic regions, including the medial temporal lobe (Tamminga et al. 1988; Gur et al. 1994). There also is evidence that there is neuropathology in the temporal lobe, correlated with Schneiderian first-rank symptoms (Shapiro, 1993; Pearlson et al. 1996). For example, parahippocampal cytoarchitectonic abnormalities have been described (Jakob and Beckmann 1986; Falkai et al. 1988; Arnold et al. 1991), which may be related to disturbances in the normal progression of cell migration and differentiation during brain development (Akbarian et al. 1993), although this finding has more recently been called into question (Krimer et al. 1995). Several studies have revealed a distinctive pattern of DA innervation and receptor expression in humans in these same regions (Berger et al. 1991; Goldsmith and Joyce 1994; Meador-Woodruff et al. 1994a; Lahti et al. 1995). Until recently, however, no similar studies of disturbances in expression of D_2-like receptors in these regions have been attempted.

It is evident that the medial temporal lobe, including the hippocampus, has a complicated modular organization (Rosene and Van Hoesen 1987; Amaral 1993). This includes 'lamellar' and longitudinal forms of organization within the subfields of the hippocampus and in their sources of input from the entorhinal and perirhinal cortices. Recent work has suggested a similarly complex compartmental organization of D_2-like receptors and their mRNAs in the hippocampus and perirhi-

nal cortex of the human (Goldsmith and Joyce 1994, 1996; Meador-Woodruff et al. 1994a). While we believe that the expression of D_2 receptors predominates over that of D_3 receptors in the medial temporal lobe, several recent reports suggest abundant expression of both D_4 radioligand binding (Lahti et al. 1995), detection of D_4 receptors by immunolabeling (Mrzjiak et al. 1996) and D_4 mRNA (Meador-Woodruff et al. 1994a) in these regions as well (Figure 3).

Although the hippocampal subfields have higher expression of D_2 receptor binding sites, D_4 receptors may be expressed higher than the D_2 receptor in the parahippocampus based on examination of mRNA expression. Furthermore, D_2 and D_3 receptor expression is predominantly in pyramidal cells and D_4 receptor expression in nonpyramidal (interneurons) cells. This would suggest that DA acting through these receptors would affect information processing in different ways. D_2 receptor binding also shows a particularly complex pattern of expression in the multimodal association regions of the superior and inferior banks of the temporal lobe that may be of importance in understanding the functional parcellation of this region (Goldsmith and Joyce 1996). There is an organization of bands of elevated densities of D_2 receptors that form a modular organization along the rostrocaudal axis of the temporal lobe (Figure 4). They exhibit a highly laminar organization and are not found in primary sensory or association cortex outside the temporal lobe. This appears to be the first published observation of a modular organization of synaptic elements, identified by D_2 receptors, in non-primary sensory cortices of any species. The dopamine D_2 receptor–enriched bands were found in regions previously identified as having functional modules that underlie feature extraction and other complex multimodal information processing. Hence, D_2 receptor–enriched and –poor modules may provide a mechanism for functional regulation of compartments within these regions by DA.

CORTICOLIMBIC DA RECEPTORS IN SCHIZOPHRENIA

During development, the formation of synapses and of receptors in all cortical regions occurs as a coordinated onset of production, peak formation, and a phase of elimination. Lidow and associates (Lidow et al. 1991) have proposed that the adult laminar distribution of re-

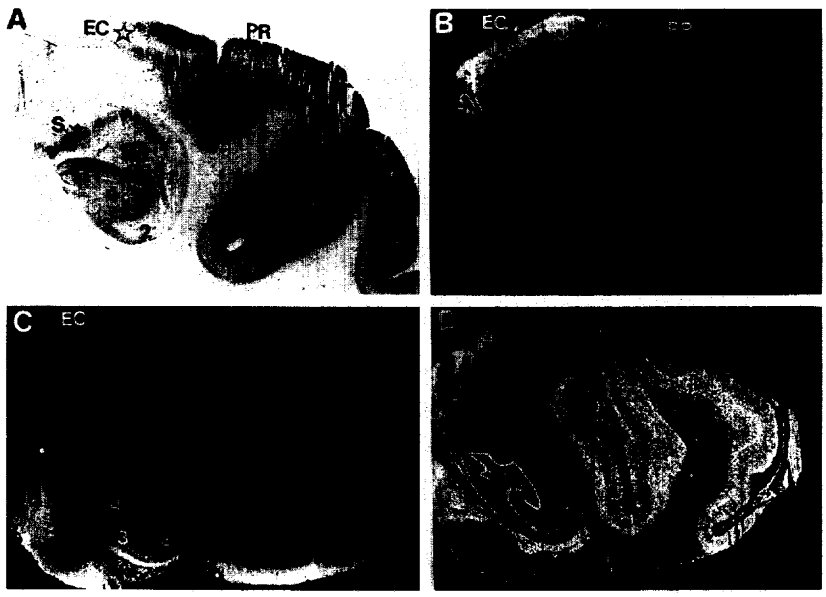

Figure 3. Distribution of D_2 receptors and the mRNAs encoding D_2, D_3, and D_4 receptors within the human medial temporal lobe. Autoradiographic demonstration of [^{125}I]-epidepride binding to D_2 receptors in medial temporal lobe (*A*) shows a high degree of overlap with that of D2 mRNA by in situ hybridization histochemistry using an [^{35}S]-labeled riboprobe (*B*). Both are expressed in high levels in the dg, CA4, and CA3 subfields, subiculum, perirhinal cortex, and the superior and inferior banks of the temporal lobe. There also are regions of mismatch such as the entorhinal cortex (low concentration of D_2 receptors) and in barrels of D_2 receptors within the superior and inferior banks of the temporal lobe. Expression of D_3 mRNA (*C*) is at lower concentrations than that for D_2 or D_4 (*D*), and binding to D_3 receptors also is at very low concentrations. Expression of D_4 mRNA largely overlaps that of the other members of the D_2 receptor family but is relatively enriched in the EC, PR, and temporal cortex (*D*). *Abbreviations*: b, barrels of high concentrations of D_2 receptors; dg, dentate gyrus; EC, entorhinal cortex; PR, perirhinal cortex; S, subiculum, CA 1-4, subfields of the hippocampus. Different sources of material were used for the protocols demonstrated in the panels of this figure.

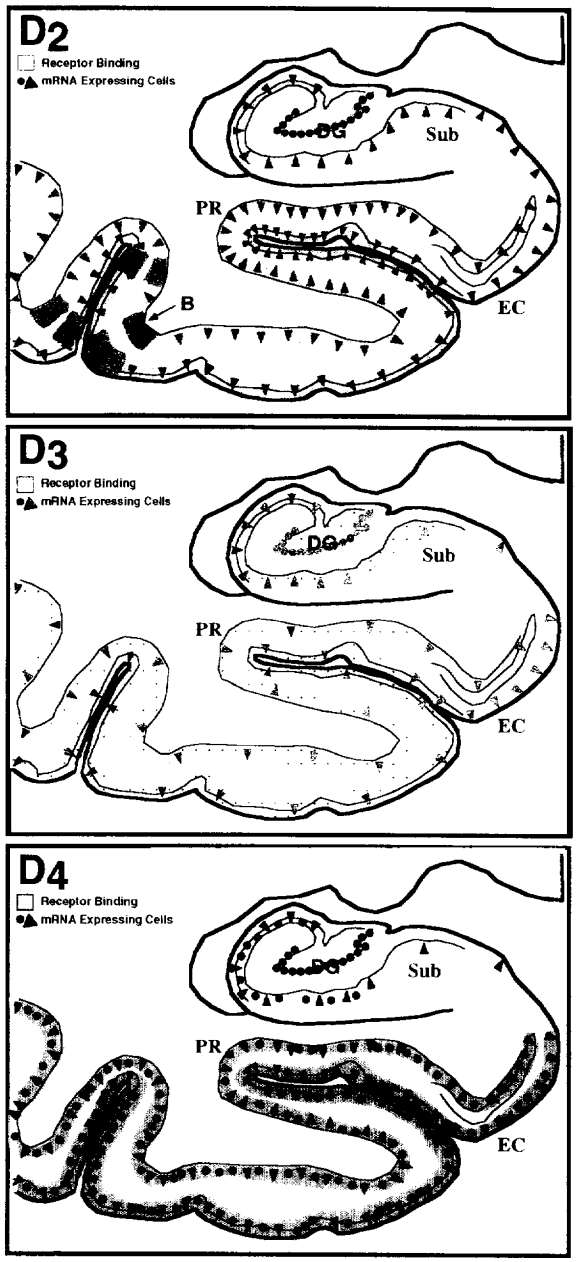

Figure 4. D_2 family of receptors within the medial temporal lobe. The relative expression of each member of the D_2 receptor family is depicted in the panels (Goldsmith and Joyce 1994, 1996; Meador-Woodruff et al. 1994a; Lahti et al. 1995; Mrzljak et al. 1996). The higher degree of stippling and number of circles and triangles represents higher concentrations of receptors and levels of mRNA, respectively. D_2 receptors and mRNA are relatively more enriched in the subfields of the hippocampus than in the temporal cortex, but bands of higher concentrations of D_2 receptors are organized in the temporal cortex (*top panel*). While there is overlap of D_3 mRNA with that of D_2 mRNA, the levels of expression are considerably lower (*middle panel*). D_4 receptor binding and levels of mRNA are enriched in the temporal lobe and may be a major target for DA in these regions (*bottom panel*), but appear to have higher expression in interneurons than pyramidal neurons (Mrzljak et al. 1996). For convenience, interneurons of the cortex that express the D_4 receptor protein are indicated with the symbol used for mRNA.

ceptors is the result of both the degree of production during early development and the extent of elimination of the receptor (and synapses) in later development. Furthermore, D_2-like receptors have been shown to play a direct role in cellular differentiation and morphology (Swarzenski et al. 1994; Reinoso et al. 1996). Thus, the laminar organization of DA receptors may be a sensitive descriptor of abnormal development of a cortical region. In contrast to examining the density of receptors in different regions of brain in schizophrenics, a better approach might be to examine the arrangement of DA receptors in these regions.

Although we have found no difference in overall concentration of D_2 receptors in the hippocampus or parahippocampal cortex of schizophrenics, we have observed an altered laminar pattern in the temporal neocortex (Goldsmith et al. in press). D_2 concentration was decreased in superficial laminae in all cases, and abnormally high concentrations of D_2 receptors were observed in the granular layer IV. We found that the modular organization of D_2 receptors in bands typical for the normal human temporal cortex also was modified. D_2-enriched bands were found less frequently in schizophrenics than in controls and with different laminar patterns in the bands and a modified width. The changes in receptor expression do not appear to reflect late-stage degenerative events that are evident in Alzheimer's disease (Ryoo et al. 1994; Joyce JN, Myer AJ (submitted): Modular organization of D_2 receptors is lost in Alzheimer's disesase. Neurobiol Aging). Although these results need to be replicated, the altered laminar arrangement of D_2 receptors may imply an active role of this D_2 receptor disturbance in abnormal brain development of this region (Swarzenski et al. 1994; Reinoso et al. 1996) Given the relationship between neuropathology in this brain region and positive symptoms in schizophrenia, D_2 receptor blockade here may diminish those particular symptoms (Tamminga et al. 1988; Joyce 1993).

CONCLUSION

The DA hypothesis of schizophrenia suggests that a dopaminergic defect exists in the limbic system of schizophrenic patients that involves D_2-like receptors. We now know, however, that the D_2 receptor identified in the past is in fact a combination of the members of the D_2-like family of receptors, the D_2, D_3, and D_4 receptors. These three receptor subtypes are enriched in different anatomical regions of the human brain: D_2 receptors in the medial temporal lobe structures and dorsal striatum; D_3 receptors in the ventral striatum and its efferents; and D_4 in much of the neocortex. This implies contributions to different normal and abnormal behavioral functions. Furthermore, there now is evidence to suggest that these receptor subtypes may be differen-

tially regulated. These considerations allow for a more complex formulation of the hypothesis of a dopaminergic dysregulation in schizophrenia: regionally-specific receptor expression may be an important determinant of efficacy and/or side effects of treatment, as well as critical underlying substrates of circuit-specific dysfunction in this illness. An understanding of this regional heterogeneity of DA receptor expression may prove fruitful in future drug development strategies to target more profitably treatment of specific symptoms associated with schizophrenia.

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REFERENCES

Akbarian S, Vinuela A, Kim JJ, Potkin SG, Bunney WE Jr, Jones EG (1993): Distorted distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase neurons in temporal lobe of schizophrenics implies anomalous cortical development. Arch Gen Psychiat 50:178–187

Alexander GE, Crutcher MD (1990): Functional architecture of basal ganglia circuits: Neural substrates of parallel processing. TINS 13:266–271

Amalric M, Koob GF (1993): Functionally selective neurochemical afferents and efferents of the mesocorticolimbic and nigrostriatal dopamine system. Prog Brain Res 99:209–226

Amaral DG (1993): Emerging principles of intrinsic hippocampal organization. Curr Opin Neurobiol 3:225–229

Arnold SE, Hyman BT, Van Hoesen GW, Damasio AR (1991): Some cytoarchitectural abnormalities of the entorhinal cortex in schizophrenia. Arch Gen Psychiatr 48:625–632

Baik JH, Picetti T, Saiardi A, Thiriet G, Dierich A, Depaulis A, Le Meur M, Borerelli E (1995): Parkinsonian-like locomotor impairment in mice lacking dopamine D_2 receptors. Nature 377:424–428

Berger B, Gaspar P, Verney C (1991): Dopaminergic innervation of the cerebral cortex: Unexpected differences between rodents and primates. TINS 14:21–27

Berman KF, Illowsky BP, Weinberger DR (1988): Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. IV. Further evidence for regional and behavioral specificity. Arch Gen Psychiatr 45:616–622

Buckland PR, O'Donovan MC, McGuffin P (1992): Changes in dopamine D_1, D_2 and D_3 receptor mRNA levels in rat brain following antipsychotic treatment. Psychopharmacology (Berl) 106(4):479–483

Clow A, Theodorou AE, Jenner P, Marsden CD (1980): A comparison of striatal and mesolimbic dopamine function in the rat during 6-month trifluoperazine administration. Psychopharmacology 69:227–233

Damask SP, Bovenkerk KA, de la Pena G, Hoversten KM, Peters DB, Valentine AM, Meador-Woodruff JH (1996): Differential effects of clozapine and haloperidol on dopamine receptor mRNA expression in rat striatum and cortex. Mol Brain Res 41:241–249

Davis KL, Kahn RS, Ko G, Davidson M (1991): Dopamine in schizophrenia: A review and reconceptualization. Am J Psychiatr 148:1474–1486

Deutch AY, Lee MC, Iadorola MJ (1992): Regionally specific effects of atypical antipsychotic drugs on striatal Fos expression: the nucleus accumbens shell as a locus of antipsychotic action. Mol Cell Neurosci 3:332–341

Falkai P, Bogerts B, Rozumak M (1988): Limbic pathology in schizophrenia: the entorhinal region—a morphometric study. Biol Psychiatr 24:515–521

Farde L, Wiesel FA, Stone-Elander S, Halldin C, Nordstrom AL, Hall H, Sedvall G (1990): D_2 dopamine receptors in neuroleptic-naive schizophrenic patients. A positron emission tomography study with [^{11}C]raclopride. Arch Gen Psychiatr 47:213–219

Fishburn CS, David C, Carmon S, Fuchs S (1994): The effect of haloperidol on D_2 dopamine receptor subtype mRNA levels in the brain. FEBS Lett 339:63–66

Gibb WRG (1992): Melanin, tyrosine hydroxylase, calbindin and substance P in the human midbrain and substantia nigra in relation to nigrostriatal projections and differential neuronal susceptibility in Parkinson's disease. Brain Res 581:283–291

Goldsmith S, Joyce JN (1994): D_2 receptor expression in hippocampus and parahippocampal cortices of human, rat and cat in comparison with tyrosine hydroxylase immunoreactive fibers. Hippocampus 4:1–20

Goldsmith S, Joyce JN (1996): Dopamine D_2 receptors are organized in bands in normal human temporal cortex. Neuroscience 74:435–451

Goldsmith S, Shapiro R, Joyce JN (in press): Disrupted pattern of dopamine D_2 receptor in the temporal in schizophrenics: A postmortem study. Arch Gen Psychiatr

Graybiel AM (1995): The basal ganglia. TINS 18:60–62

Gur RE, Jaggi JL, Shtasel DL, Ragland JD, Gur RC (1994): Cerebral blood flow in schizophrenia: Effects of memory processing on regional activation. Biol Psychiatr 35:3–15

Gurevich EV, Bordelon Y, Shapiro R, Arnold S, Gur R, Joyce JN (in press): Mesolimbic dopamine D_3 receptors and use of antipsychotics in schizophrenic patients: A postmortem study. Arch Gen Psychiatr

Haber SN, Groenewegen HJ (1989): Interrelationship of the distribution of neuropeptides and tyrosine hydroxylase immunoreactivity in the human substantia nigra. J Comp Neurol 290:53–68

Hogberg T, Ramsby S, Ogren SO, Norinder U (1987): New selective dopamine D_2 antagonists as antipsychotic agents: Pharmacological, chemical, structural, and theoretical considerations. Acta Pharmacol 24:289–328

Jakob H, Beckmann H (1986): Prenatal developmental dis-

turbances in the limbic allocortex in schizophrenics. J Neural Transm 65:303–326

Jimenez-Castellanos J, Graybiel AM (1987): Subdivisions of the dopamine-containing A_8-A_9-A_{10} complex identified by their differential mesostriatal innervation of striosomes and extrastriosomal matrix. Neuroscience 23: 223–242

Joyce JN (1993): The dopamine hypothesis of schizophrenia: Limbic interactions with serotonin and norepinephrine. Psychopharmacology 112:S16–S34

Joyce JN, Sapp DW, Marshall JF (1986): Human striatal dopamine receptors are organized in compartments. Proc Natl Acad Sci U S A 83:8002–8006

Joyce JN, Lexow N, Bird E, Winokur A (1988): Organization of dopamine D_1 and D_2 receptors in human striatum: receptor autoradiographic studies in Huntington's disease and schizophrenia. Synapse 2:546–557

Krimer LS, Herman MM, Saunders RC, Boyd JC, Kleinman JE, Hyde TM, Weinberger DR (1995): Qualitative and quantitative analysis of the entorhinal cortex cytoarchitectural organization in schizophrenia. Soc Neurosci Abstr 21:239

Lahti RA, Roberts RC, Tamminga CA (1995): D_2-family receptor distribution in human postmortem tissue: An autoradiographic study. Neuroreport 6:2505–2512

Laruelle M, Jaskiw GE, Kipska BK, Kolachana B, Casanova MF, Kleinman JE, Weinberger DR (1992): D_1 and D_2 receptor modulation in rat striatum and nucleus accumbens after chronic haloperidol treatment. Brain Res 575:47–56

Lévesque D, Martres M-P, Diaz J, Griffon N, Lammers CH, Sokoloff P, Schwartz J-C (1995): A paradoxical regulation of the dopamine D_3 receptor expression suggests the involvement of an anterograde factor from dopamine neurons. Proc Natl Acad Sci U S A 92:1719–1723

Lidow MS, Goldman-Rakic PS, Rakic P (1991): Synchronized overproduction of neurotransmitter receptors in diverse regions of the primate cerebral cortex. Proc Natl Acad Sci U S A 88:10218–10221

Lynd-Balta E, Haber SN (1994a): The organization of midbrain projections to the ventral striatum in the primate. Neuroscience 59:609–623

Lynd-Balta E, Haber SN (1994b): The organization of midbrain projections to the striatum in the primate: sensorimotor-related striatum versus ventral striatum. Neuroscience 59:625–640

Martinot J-L, Peron-Magnan P, Huret JD, Mazoyer B, Baron JC, Boulenger JP, Loch C, Maziere B, Caillard V, Loo H, Syrota A (1990): Striatl D_2 dopaminergic receptors assessed with positron emission tomography and [^{76}Br]-bromospiperone in untreated schizophrenic patients. Am J Psychiatr 147:44–50

Meador-Woodruff JH (1995): Neuroanatomy of dopamine receptor gene expression: Potential substrates for neuropsychiatric illness. Clin Neuropharmacol 18(suppl 1): S14–S24

Meador-Woodruff JH, Grandy DK, Van Tol HHM, Damask SP, Little O, Civelli KY, Watson SJ (1994a): Dopamine receptor gene expression in the human medial temporal lobe. Neuropsychopharmacology 10:239–248

Meador-Woodruff JH, Damask SP, Watson SJ (1994b): Differential expression of autoreceptors in the ascending dopamine systems of the human brain. Proc Natl Acad Sci U S A 91:8297–8301

Meador-Woodruff JH, Damask SP, Wang J, Haroutunian V, Davis KL, Watson SJ (1996): Dopamine receptor mRNA expression in human striatum and neocortex. Neuropsychopharmacology 15:17–30

Merchant KM, Dobie DJ, Dorsa DM (1992): Expression of the proneurotensin gene in the rat brain and its regulation by antipsychotic drugs. Ann NY Acad Sci 668:54–69

Mita T, Handa S, Nishino N, Kuno T, Nakai H, Yamadori T, Mizoi Y, Tanaka C (1986): Decreased serotonin S^2 and increased dopamine D_2 receptors in chronic schizophrenics. Biol Psychiatr 21:1407–1414

Mogenson GJ, Yang CR, Yim CY (1988): Influence of dopamine on limbic inputs to the nucleus accumbens. Ann NY Acad Sci 537:86–100

Moghaddam B, Bunney BS (1990): Acute effect of typical and atypical antipsychotic drugs on the release of dopamine from prefrontal cortex, nucleus accumbens, and striatum of the rat: An in vivo microdialysis study. J Neurochem 54:1755–1760

Mrzljak L, Bergson C, Pappy M, Huff R, Levenson R, Goldman-Rakic PS (1996): Localization of dopamine D_4 receptors in GABAergic neurons of the primate brain. Nature 381:245–248

Murray AM, Ryoo H, Gurevich E, Joyce JN (1994): Localization of dopamine D_3 receptors to mesolimbic and D_2 receptors to mesostriatal regions of human forebrain. Proc Natl Acad Sci U S A 91:11271–11275

Murray AM, Hyde TM, Knable MB, Herman MM, Bigelow LB, Carter JM, Weinberger DR, Kleinman JE (1995): Distribution of putative D_4 dopamine receptors in postmortem striatum from patients with schizophrenia. J Neurosci 15:2186–2191

Murugaiah K, Theodorou A, Mann S, Clow A, Jenner P, Marsden CD (1985): Chronic continuous administration of neuroleptic drugs alters cerebral dopamine receptors and increases spontaneous dopaminergic action in striatum. Nature 296:570–573

Nguyen TV, Kasofsky B, Birnbaum R, Cohen B, Hyman SE (1992): Differential expression of c-fos and Zif 268 in rat striatum following haloperidol, clozapine, and amphetamine. Proc Natl Acad Sci U S A 89:4270–4274

Nordstrom AL, Farde L, Eriksson L, Halldin C (1995): No elevated D_2 dopamine receptors in neuroleptic-naive schizophrenic patients revealed by positron emission tomography and [^{11}C]N-methylspiperone. Psychiatr Res 61:67–83

Owen F, Cross AJ, Crow TJ, Londgen A, Poulter M, Riley GJ (1978): Increased dopamine-receptor sensitivity in schizophrenia. Lancet 2:223–225

Pearlson GD, Petty RG, Ross CA, Tien AY (1996): Schizophrenia: A disease of heteromodal association cortex. Neuropsychopharmacology 14:1–18

Prosser ES, Pruthi R, Csernansky JG (1989): Differences in the time course of dopaminergic supersensitivity following chronic administration of haloperidol, molindone, or sulpiride. Psychopharmacology 99:109–116

Reinoso BS, Undie AS, Levit P (1996): Dopamine receptors

mediate differential morphological effects on cerebral cortical neurons in vitro. J Neurosci Res 43:439–453

Reynolds GP, Mason SL (1994): Are striatal dopamine D_4 receptors increased in schizophrenia? J Neurochem 63:1576–1577

Robertson GS, Fibiger HC (1992): Neuroleptics increase c-fos expression in the forebrain: Contrasting effects of haloperidol and clozapine. Neuroscience 46:315–328

Rosene DL, Van Hoesen GW (1987): The hippocampal formation of the primate brain. In Jones EG, Peters A (eds), Cerebral Cortex, vol 6, New York, Plenum Publishing, pp 361–370

Rubin P, Holm S, Friberg L, Videbech P, Andersen HS, Bendsen B, Stromso N, Larsen JK, Lassen NA, and Hemmingsen R (1991): Altered modulation of prefrontal and subcortical brain activity in new diagnosed schizophrenia and schizophreniform disorder. Arch Gen Psychiatry 48:987–995

Rupniak NMJ, Hall MD, Kelly E, Fleminger S, Kilpatric G, Jenner P, Marsden CD (1985): Mesolimbic dopamine function is not altered during continuous chronic treatment of rats with typical or atypical neuroleptic drugs. J Neural Transm 62:249–266

Ryoo H, Joyce JN (1994): The loss of dopamine D_2 receptors varies along the rostrocaudal axis of the hippocampal complex in Alzheimer's disease. J Comp Neurol 348:94–110

Schoots O, Seeman P, Guan H-C, Paterson AD, Van Tol HHM (1995): Long-term haloperidol elevates dopamine D_4 receptors by 2-fold in rats. Eur J Pharmacol 289:67–72

Schwartz J-C, Lévesque D, Martres M-P, Sokoloff P (1993): Dopamine D_3 receptor: Basic and clinical aspects. Clin Neuropharmacol 16:295–314

Seeman P, Bzowej NH, Guan HC, Bergeron C, Reynolds GP, Bird ED, Riederer P, Jellinger K, Tourtellote WW (1987): Human brain D_1 and D_2 dopamine receptors in schizophrenia, Alzheimer's, Parkinson's and Huntington's disease. Neuropsychopharmacology 1:5–15

Seeman P, Guan H-C, Van Tol HHM (1993): Dopamine D_4 receptors elevated in schizophrenia. Nature 1993:365: 441–445

Shapiro RM (1993): Regional neuropathology in schizophrenia: Where are we? Where are we going? Schizophrenia Res 10:187–239

Sokoloff P, Giros B, Martres M-P, Bouthenet M-L, Schwartz J-C (1990): Molecular cloning and characterization of a novel dopamine receptor (D_3) as a target for neuroleptics. Nature 347:146–151

Sumiyoshi T, Stockmeier CA, Overholser JC, Thompson PA, Metzler HY (1995): Dopamine D_4 receptors and effects of guanine nucleotides on [^{3}H]-raclopride binding in postmortem caudate nucleus of subjects with schizophrenia or major depression. Brain Res 681:109–116

Swarzenski BC, Tang L, Oh YJ, O'Malley KL, Todd RD (1994): Morphogenic potentials of D2, D3, and D4 dopamine receptors revealed in transfected neuronal cell lines. Proc Nat Acad Sci U S A 91:649–653

Szabo J (1980): Organization of the ascending striatal afferents in monkeys. J Comp Neurol 189:307–321

Tamminga CA, Burrows GH, Chase TN, Alphs LD, Thaker GK (1988): Dopamine neuronal tracts in schizophrenia: Their pharmacology and in vivo glucose metabolism. Ann NY Acad Sci U S A 537:443–450

Tanaka C, Ishikawa M, Shinoda S (1982): Histochemical mapping of catecholaminergic neurons and their ascending fiber pathways in the rhesus monkey brain. Brain Res Bull 9:255–270

Van Tol HHM, Bunzow JR, Guan H-C, Sunahara RK, Seeman P, Niznik HB, Civelli O (1991): Cloning of the gene for a human dopamine D_4 receptor with high affinity for the antipsychotic clozapine. Nature 350:610–614

Waters CM Peck R, Rossor M, Reynolds GP, Hunt SP (1988): Immunocytochemical studies on the basal ganglia and substantia nigra in Parkinson's disease and Huntington's Chorea. Neurosci 25:419–438

Weinberger DR, Berman KF, Illowsky BP (1988): Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. III. A new cohort and evidence for a monoaminergic mechanism. Arch Gen Psychiatr 45: 609–615

Weinberger DR, Berman KF, Suddath R, Torrey EF (1992): Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: A magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. Am J Psychiatr 149:890–897

Wong DF, Wagner HN, Tune LE, Dannals RF, Pearlson GD, Links JM, Tamminga CA, Broussole EP, Ravert HT, Wilson AA, et al. (1986): Positron emission tomography reveals elevated D_2 dopamine receptors in drug-naive schizophrenics. Science 234:1558–1563

Zhang M, Creese I (1993): Antisense oligodeoxynucleotide reduces brain dopamine D_2 receptors: behavioral correlates. Neurosci Lett 161:223–236