

Linking the Family of D₂ Receptors to Neuronal Circuits in Human Brain: Insights into Schizophrenia

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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 D₂-like receptors to divergent neuroanatomic sites of suspected pathology in schizophrenia. We hypothesize that this research suggests that D₂ receptors in the basal ganglia are the likely site of extrapyramidal

symptoms and not antipsychotic effects. Rather, D₃ receptors of the mesolimbic system are a likely site of antipsychotic effects, and D₂ and D₄ 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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A productive approach to exploring the contribution of dopamine (DA) systems to schizophrenia was based on the identified D₂ 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 D₂ 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 D₂-like receptors are elevated in schizophrenia (Owen et al. 1978). In spite of the clinical efficacy of D₂ antagonists, it has been difficult to reconcile the hypothesis that it is the actions of antipsychotics at D₂ 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 D₂ 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 D₂ receptors within the striatum seems

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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 D₂ 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 D₂ receptor family (e.g., D₃ and D₄) 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 D₂ receptors in the motor subdivision of the striatum; the atypical class of antipsychotics appears to act at other members of the D₂ receptor family. Consequently, the D₄ receptor had been studied because of the relatively higher affinity of clozapine for this receptor (Van Tol et al., 1991). In contrast, research on D₃ receptors has emphasized the relationship of this receptor to the mesolimbic DA system (Sokoloff et al., 1990), evidence that it responds differently from the D₂ 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 D₂ and D₄ 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 D₃ receptor (Lynd-Balta and Haber 1994b; Murray et al. 1994). The efferents of the ventral striatum remain segregated from dorsal striatal effer-

ents, 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 D₂ receptor is an important target of the nigrostriatal DA system (Joyce et al. 1986; Murray et al. 1994). D₂ receptor binding is enriched within the matrix compartment of the dorsal striatum and in its efferents. In contrast, the D₃ receptor is enriched in the striosomal compartment of the ventral striatum and its efferents. Whereas the neurons expressing mRNA for D₂ and D₃ receptors are largely intermingled in the ventral striatum, mRNA encoding the D₃ 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 D₃ receptors observed autoradiographically (Figure 2). Furthermore, D₃ mRNA-bearing neurons are abundant in the primary and secondary targets of the ventral striatum. However, D₂/D₃ receptor interactions could continue to occur within the ventral striatum and its efferents as the majority of neurons coexpress D₂ and D₃ receptors (Gurevich and Joyce, in preparation). Moreover, it is now known that neurons in the globus pallidus as well as in the thalamus express D₄ 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 D₂ receptor family.

NIGROSTRIATAL AND MESOLIMBIC DA SYSTEMS IN SCHIZOPHRENIA

Elevations of D₂-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 D₂-like receptor density in vivo using positron emission tomography (PET). Conflicting results have been reported. One set of studies indicated that the number of D₂ 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 D₂-like receptor density in schizophrenia, raclopride was the ligand used (Farde et al. 1990). This particular compound has a high selectivity for both the D₂ and D₃ receptors compared to the D₄ site, but low affinity for D₂-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

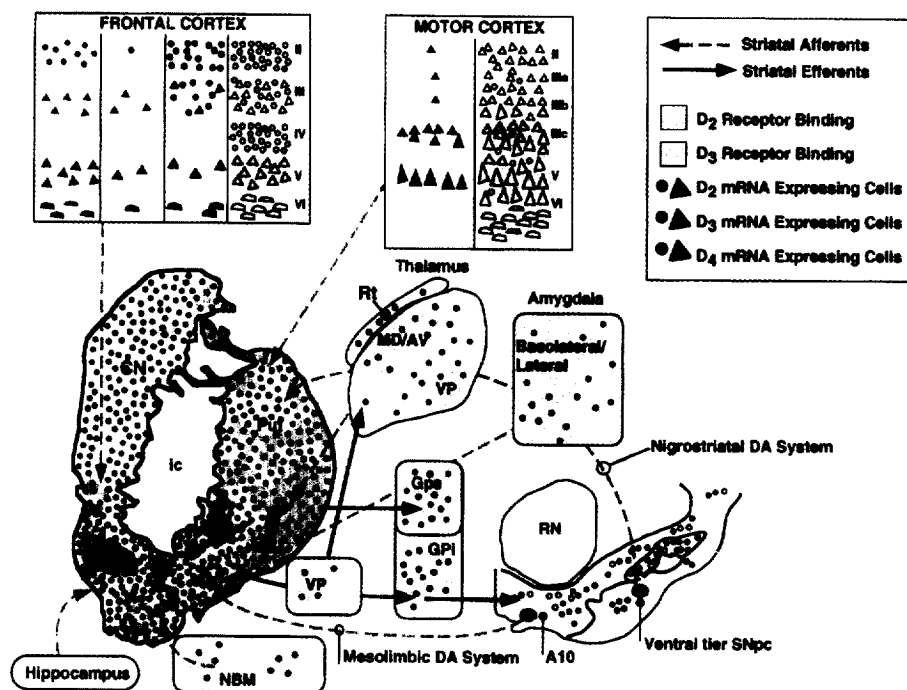


Figure 1. Dopamine receptor circuitry of basal ganglia. Two members of the D₂ receptor family, D₂ and D₃, are segregated to different circuits within the basal ganglia (Murray et al. 1994; Gurevich et al. in press; Meador-Woodruff et al. 1996). D₂ receptors are the primary target of the nigrostriatal 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 thalamus) (Alexander and Crutcher 1990; Graybiel 1995). In contrast, D₃ 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 cortex that express the D₄ 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 thalamus; SNpc, substantia nigra pars compacta; VP, ventroposterior nucleus of the amygdala (near thalamus in figure); VP, ventral pallidum.

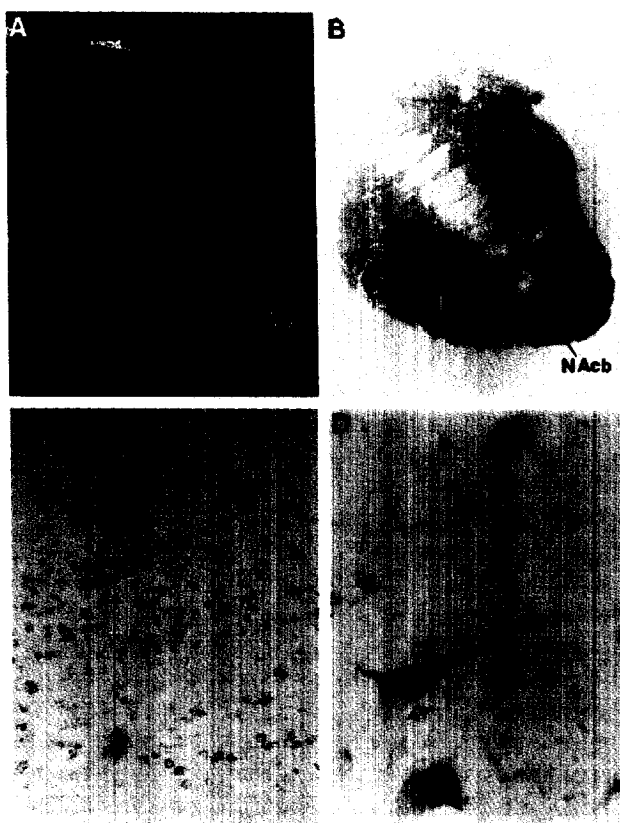


Figure 2. Segregation of D₃ receptors and mRNA in limbic striatum. (A) Autoradiographic demonstration of D₃ mRNA by in situ hybridization histochemistry using an [³⁵S]-labeled riboprobe shows higher concentrations in the ventral putamen and nucleus accumbens of the human, with clusters enriched with this mRNA. (B) This parallels the distribution of D₃ receptors demonstrated by receptor binding for [¹²⁵I]-trans-7-OH-PIPAT, which also are organized in patches in the ventral putamen and nucleus accumbens. (C) Nonradioactive visualization of D₃ 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 D₃ 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 D₄ site. Specifically, the "positive" study used a ligand with high affinity for the D₄ receptor, and the "negative" study used a low-affinity D₄ 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 [³H]-spiroperidol binding in schizophrenics largely reflects changes in the density of D₄ receptors. Using nonselective radioligands in several different combinations to indirectly estimate the concentrations of D₂, D₂ plus D₃, or D₄ receptors, they argued that the elevation in [³H]-YM0911-2 (D₂ + D₃ + D₄ receptors) binding in schizophrenics (after subtracting [³H]-raclopride binding to D₂/D₃ sites) reflected binding to D₄ 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 D₂/D₃ receptors, [³H]-YM0911-2 does not show detectable binding in either control or schizophrenic striatum (Reynolds and Mason 1994). There is no evidence either that D₄ 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 D₄ receptor is difficult to reconcile with our present knowledge of D₂-like receptors and may represent a non-D₄ site (Hubert H. Van Tol, personal communication) and/or may reflect antipsychotic induction of D₄ receptor expression (Schoots et al. 1995). Thus, although an increase of striatal D₄ 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 D₂ 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 D₂ receptors, which remain elevated even after drug withdrawal (Laruelle et al. 1992). Accordingly, elevations in D₂ 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 D₂ receptor number in schizophrenia, it has been shown that drug-naïve patients show an increase in the B_{max} for [³H]-spiroperidol binding to D₂-like receptors (Owen et al. 1978), although this study was limited by small sample sizes. However, other data suggest that overexpression of

D₂-like receptors in drug-naïve 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 D₃ receptors, it has become clear that this elevation in [³H]-spiroperidol binding in the ventral striatum may reflect this member of the D₂ receptor family.

In addition to its localization in the ventral striatum, the pharmacology of the D₃ 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 D₃ receptors at levels only slightly less than D₂ 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 D₃ receptor is involved in the illness. We have analyzed the binding of [¹²⁵I]-trans-7-OH-PIPAT to D₃ receptors by quantitative autoradiography in postmortem tissue from schizophrenics (Gurevich et al. in press). We found elevations (45% to 56%) in the number of D₃ receptors in the basal ganglia and ventral forebrain of schizophrenics compared with controls. In contrast to what has been observed for D₂ receptors, the schizophrenic cases free of antipsychotics at time of death showed twice as many D₃ 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 D₂ 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 D₂ receptors in schizophrenia, a disease related elevation of D₃ receptors in the limbic striatum may be reduced by antipsychotics. These results may reflect differences in how D₃ and D₂ receptors are affected by antipsychotic treatment.

Animal models indicate that mesolimbic D₂-like receptors are regulated differently from those in motor regions. Following chronic treatment with typical antipsychotics, [³H]-spiroperidol binding to D₂-like (D₂ and D₃) 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 D₃ receptor mRNA is increased by both sulpiride and clozapine treatments, the convergence of published reports suggests that D₃ receptor and its mRNA are not elevated under conditions of antipsychotic treatment that lead to elevations in the D₂ receptor and its mRNA (Damask et al. 1996;

Fishburn et al. 1994; Lévesque et al. 1995). These differences in regulation of mesolimbic and nigrostriatal D₂-like receptors by chronic antipsychotic treatment may reflect the contribution of D₃ receptors to the D₂-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 D₃ 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, D₃ receptor mRNA has been reported in the human substantia nigra, a localization consistent with the D₃ receptor serving as a dopamine autoreceptor (Meador-Woodruff et al. 1994b). In addition to D₃ antagonists being candidates for antipsychotic agents, it is conceivable that D₃ 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 D₃ receptors in this region plays a role in modulating some psychotic symptoms (Mogenson et al. 1988). In contrast, the use of D₂ receptor "knockout" and antisense "knock-down" strategies in animals has confirmed the role of D₂ receptors in mediating extrapyramidal "motor" responses to dopaminergic agents (Baik et al. 1995; Zhang and Creese 1993).

The issue of which member of the D₂ receptor family is predominantly affected in the striatum in schizophrenia has not been resolved, but an interpretation of these recent data suggest that D₂ receptor blockade may be more closely related to the extrapyramidal effects of neuroleptic treatment, and antipsychotic efficacy with the regulation of the D₃ 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 dis-

turbances; 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 D₂ and D₃ receptors and their mRNAs are expressed at low levels in the prefrontal cortex, the D₄ receptor may be much more abundant. D₄ receptor mRNA is robustly expressed in frontal cortical regions in human brain (Meador-Woodruff et al. 1996), and recent studies examining D₄ receptor binding and localization of the protein by detection of antibodies suggest high levels of cortical D₄ 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 (Krimmer 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 D₂-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 D₂-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 D₂ receptors predominates over that of D₃ receptors in the medial temporal lobe, several recent reports suggest abundant expression of both D₄ radioligand binding (Lahti et al. 1995), detection of D₄ receptors by immunolabeling (Mrzjak et al. 1996) and D₄ mRNA (Meador-Woodruff et al. 1994a) in these regions as well (Figure 3).

Although the hippocampal subfields have higher expression of D₂ receptor binding sites, D₄ receptors may be expressed higher than the D₂ receptor in the parahippocampus based on examination of mRNA expression. Furthermore, D₂ and D₃ receptor expression is predominantly in pyramidal cells and D₄ receptor expression in nonpyramidal (interneurons) cells. This would suggest that DA acting through these receptors would affect information processing in different ways. D₂ 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 D₂ 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 D₂ receptors, in non-primary sensory cortices of any species. The dopamine D₂ receptor-enriched bands were found in regions previously identified as having functional modules that underlie feature extraction and other complex multimodal information processing. Hence, D₂ 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-

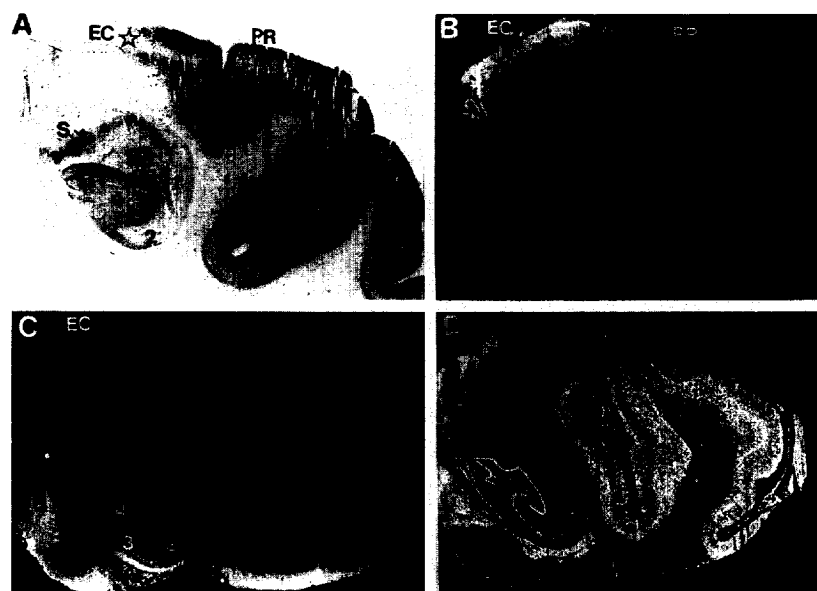


Figure 3. Distribution of D₂ receptors and the mRNAs encoding D₂, D₃, and D₄ receptors within the human medial temporal lobe. Autoradiographic demonstration of [¹²⁵I]-epidepride binding to D₂ receptors in medial temporal lobe (A) shows a high degree of overlap with that of D₂ mRNA by in situ hybridization histochemistry using an [³⁵S]-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 D₂ receptors) and in barrels of D₂ receptors within the superior and inferior banks of the temporal lobe. Expression of D₃ mRNA (C) is at lower concentrations than that for D₂ or D₄ (D), and binding to D₃ receptors also is at very low concentrations. Expression of D₄ mRNA largely overlaps that of the other members of the D₂ receptor family but is relatively enriched in the EC, PR, and temporal cortex (D). *Abbreviations:* b, barrels of high concentrations of D₂ 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.

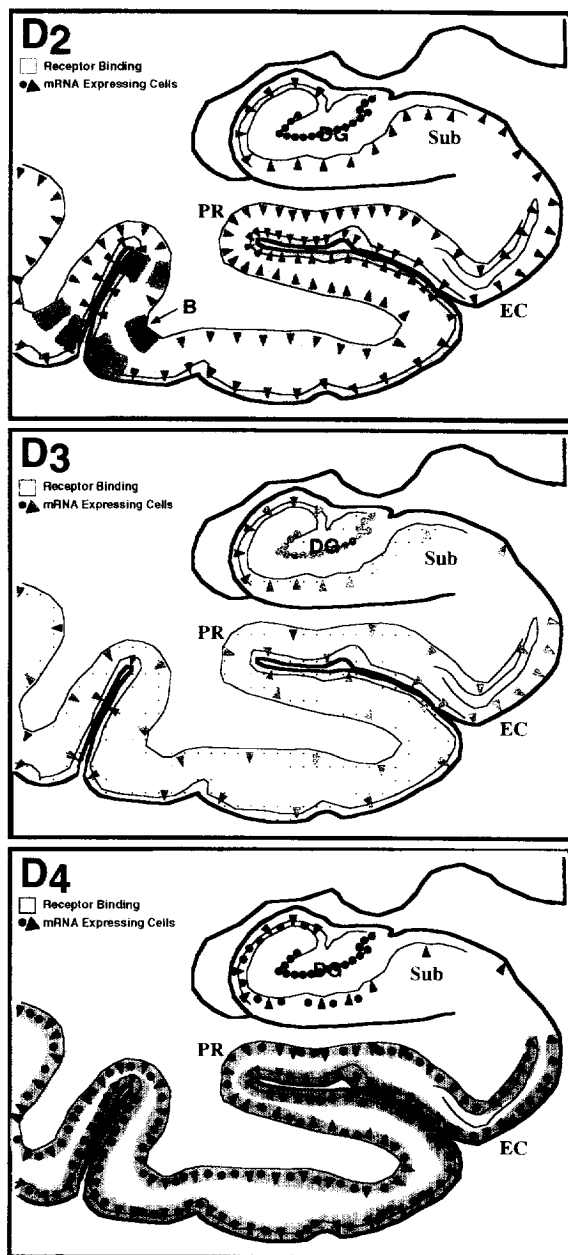


Figure 4. D₂ family of receptors within the medial temporal lobe. The relative expression of each member of the D₂ receptor family is depicted in the panels (Goldsmith and Joyce 1994, 1996; Meador-Woodruff et al. 1994a; Lahti et al. 1995; Mrzljak et al. 1996). The higher degree of stippling and number of circles and triangles represents higher concentrations of receptors and levels of mRNA, respectively. D₂ receptors and mRNA are relatively more enriched in the subfields of the hippocampus than in the temporal cortex, but bands of higher concentrations of D₂ receptors are organized in the temporal cortex (*top panel*). While there is overlap of D₃ mRNA with that of D₂ mRNA, the levels of expression are considerably lower (*middle panel*). D₄ 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 D₄ 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, D₂-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 D₂ 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*). D₂ concentration was decreased in superficial laminae in all cases, and abnormally high concentrations of D₂ receptors were observed in the granular layer IV. We found that the modular organization of D₂ receptors in bands typical for the normal human temporal cortex also was modified. D₂-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 D₂ receptors is lost in Alzheimer's disease. *Neurobiol Aging*). Although these results need to be replicated, the altered laminar arrangement of D₂ receptors may imply an active role of this D₂ 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, D₂ 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 D₂-like receptors. We now know, however, that the D₂ receptor identified in the past is in fact a combination of the members of the D₂-like family of receptors, the D₂, D₃, and D₄ receptors. These three receptor subtypes are enriched in different anatomical regions of the human brain: D₂ receptors in the medial temporal lobe structures and dorsal striatum; D₃ receptors in the ventral striatum and its efferents; and D₄ 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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