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The Relevance of the Dopamine-D_1 Receptor in the Cognitive Symptoms of Schizophrenia

Patricia S. Goldman-Rakic, Ph.D.

An understanding of the role of the prefrontal cortex in normal cognitive processes has advanced our comprehension of the pathophysiology underlying the cognitive deficits in schizophrenia. Studies of single-neuron activity in monkeys during performance of delayed-response tasks have confirmed the involvement of the prefrontal cortex in working memory. The "memory fields" of prefrontal neurons are analogous to the receptive fields of visual neurons and the cellular expression of a working memory process that allows mnemonic information to guide behavior. D_1-dopamine antagonists produce a dose-dependent effect (U-shaped) on the firing rate of cells with memory fields during delayed-response tasks. Disordered cognitive processes in schizophrenia can be attributed to impairment of function in the prefrontal cortex, as evidenced by hypometabolic activity in the prefrontal cortex and selective impairment in working memory tasks. Advances in our understanding of the role of D_1 receptors in the cognitive deficits observed in schizophrenia should provide us with a rational basis for developing alternative antipsychotic treatments and may provide insight into the cellular basis of the disorder. ***[Neuropsychopharmacology 21:S170–S180, 1999]*** *© 1999 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

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THE ROLE OF THE PREFRONTAL CORTEX IN SCHIZOPHRENIA

A number of the characteristic symptoms of schizophrenia, including the disorganization in thought and behavior, may be explained by a deficiency in working memory (Goldman-Rakic 1991; Goldman-Rakic and Selemon 1997). The role of the cortex in establishing internal representations of the outside world is well known, and the use of a computational workspace to recall and manipulate information is integral to storage and processing functions of the brain. The working memory dysfunction, or disruption in "on line" thought processing, that is evident in cognitive disturbances of schizophrenia has been ascribed to cellular mechanisms intrinsic to the prefrontal cortex (Goldman-Rakic 1995).

The importance of the prefrontal cortex in cognition and the cognitive deficits observed in schizophrenia is supported by neuropsychological and neurophysiological studies (Goldberg et al. 1993; Levin 1984; Merriam et al. 1990; Morihisa et al. 1983; Weinberger et al. 1986, 1988; Wolkin et al. 1988). Schizophrenic patients perform poorly on prefrontal cortex-mediated tasks that involve working memory (Park and Holzman 1992; Wexler et al. 1999). These tasks require that the subject retains knowledge of the information provided by an environmental cue in order to perform the appropriate

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behavioral response some time after the cue has been removed (Goldman-Rakic 1987). In monkeys, the spatial delayed-response task is used to study working memory. In this task, the monkey is required to hold in working memory the spatial location of an environmental cue during a delay period following removal of the cue. Performance of spatial delayed-response tasks involves the dorsolateral prefrontal cortex in humans (Freedman and Oscar-Berman 1986; Verin et al. 1993) and nonhuman primates (Friedman and Goldman-Rakic 1994; Goldman et al. 1971; Funahashi et al. 1989; Fuster and Alexander 1971; Verin et al. 1993).

Studies of single-neuron activity in monkeys during performance of delayed-response tasks have confirmed the involvement of the prefrontal cortex in working memory (Batuev et al. 1981, 1985; Funahashi et al. 1986; Fuster 1973; Fuster and Alexander 1971; Fuster et al. 1982; Joseph and Barone 1987; Kojima and Goldman-Rakic 1982, 1984; Niki and Watanabe 1976). Neurons that serve an important function in working memory typically display an increase in discharge rate after cue presentation and sustained activity during the delay period until the response is executed (Batuev et al. 1985; Funahashi et al. 1986; Fuster and Alexander 1971; Niki and Watanabe 1976). When errors occur in a task that is dependent on working memory function, they are associated with a failure of the corresponding neurons to maintain delay period activity. Delay period activity of prefrontal neurons codes the spatial coordinates of visual cues during a delayed-response task and provides a mnemonic code for direction over the full perimeter of visual space. These neuronal "memory fields" are analogous to the receptive fields of visual neurons and the cellular expression of a working memory process that allows mnemonic information to guide behavior (Funahashi et al. 1989).

The involvement of the prefrontal cortex in schizophrenia is supported by studies designed to probe morphologic differences between schizophrenic and normal brains. The activities of the prefrontal cortex necessarily involve interactions within a complex array of related areas (Goldman-Rakic 1988a, 1988b; Goldman-Rakic et al. 1993; Selemon and Goldman-Rakic 1988). Early attempts to identify neuropathologic features of the brains of schizophrenic patients did not lead to the identification of one specific neural abnormality (Andreasen 1988). However, quantitative neuroanatomical studies during the past two decades, using computerized positron emission tomography (PET), magnetic resonance imaging (MRI), and other modern techniques, have begun to converge on subtle abnormalities in a variety of key areas in the schizophrenic brain. Brain regions reported to be abnormal in schizophrenics include the hippocampus (Suddath et al. 1990), amygdala (Rossi et al. 1994; Shenton et al. 1992), entorhinal cortex (Arnold et al. 1991; Honer et al. 1996), cingulate cortex (Benes et al. 1992), planum temporale (Petty et al. 1995), mediodorsal thalamic nucleus (Andreasen et al. 1994; Pakkenberg 1990), and nucleus accumbens (Pakkenberg 1990). Enlarged ventricular spaces and smaller cortical volumes also have been observed (Cannon and Marco 1994; Weinberger et al. 1983). Many of the brain regions identified as structurally abnormal in schizophrenics have connections with either the prefrontal cortex or the nucleus accumbens, or both (O'Donnell and Grace 1998).

The importance of the prefrontal cortex in schizophrenia is supported by PET and dynamic single-photon emission computed tomography (D-SPECT) studies that have assessed the metabolic characteristics and/or blood perfusion of the prefrontal cortex in schizophrenic patients during performance of behavioral tasks (Ariel et al. 1983; Berman et al. 1986; Buchsbaum et al. 1984; Farkas et al. 1984; Kurachi et al. 1985; Liddle et al. 1992; Paulman et al. 1990; Volkow et al. 1987; Weinberger et al. 1986, 1988; Wolkin et al. 1988). In 1986, Weinberger et al. observed that schizophrenic patients failed to show an increase in regional cerebral blood flow (rCBF) in the dorsolateral prefrontal cortex while performing the Wisconsin Card Sorting Test (WCST), a measure of frontal lobe neuropsychological function (Weinberger et al. 1986). In a more recent study by Paulman et al. (1990), D-SPECT was conducted to assess regional and hemispheric rCBF in 40 chronic male schizophrenics (20 medicated and 20 unmedicated) and 31 gender- and age-matched healthy controls during performance of the WCST and the Luria–Nebraska Battery. Consistent with Weinberger et al. (1986), the results confirmed a deficit in bilateral frontal rCBF in male schizophrenic patients at rest and during the WCST; frontal flow deficits were most prominent in paranoid patients, and right temporal deficits were most prominent in nonparanoid patients. This study also extended previous findings by showing that reduced left frontal rCBF was associated with neuropsychological impairment on the WCST and the Luria–Nebraska Battery. In addition, increased hemispheric CBF was correlated with the presence of positive schizophrenic symptoms (Paulman et al. 1990). In summary, the evidence for compromised metabolism and blood flow in schizophrenia now seems incontrovertible.

Cell counting and planimetric analyses have now also identified regions of cell loss and cortical volume changes in schizophrenic patients (Benes 1993; Bogerts 1993; Heckers 1997; Shapiro 1993), although definitive evidence for cell loss has been presented only in a limited number of studies (Selemon and Goldman-Rakic 1999). The schizophrenic cortex is normal in appearance, and lesions such as those found in classic neurodegenerative disorders (e.g., Huntington's disease) are not present. Recent morphometric studies of the dorsolateral prefrontal cortex, however, reveal a pathologic

condition in the schizophrenic brain that is characterized by an impoverished neuronal connectivity (Rajkowska et al. 1998; Selemon et al. 1995, 1998). With the application of a direct three-dimensional (3-D) counting technique (Williams and Rakic 1988), neuronal densities in prefrontal area 9 and visual cortical area 17 were calculated to be 17% and 10% higher in brains from schizophrenic patients as compared with healthy controls (Selemon et al. 1995). When measurements were made in prefrontal area 46, a 21% increase in density was measured in schizophrenic brains (Selemon et al. 1998). Based on a model in which the distance between neurons is diminished without a change in the number of neurons, we proposed the "reduced neuropil hypothesis" to relate prefrontal cognitive disturbances to atrophy of neuronal processes, without actual neuronal loss (Selemon and Goldman-Rakic 1999). Collectively, the results of these studies suggest that a reduced neuropil form of pathology may occur over widespread regions in the schizophrenic cortex (Selemon et al. 1995, 1998).

THE DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA AND DOPAMINE SYSTEMS

Dopamine (DA)-responsive systems have been implicated in schizophrenia, tardive dyskinesia, Parkinson's disease, Tourette's syndrome, hyperprolactinemia, and possibly Huntington's disease (Gingrich and Caron 1993). There are two major dopaminergic systems in the brain, the mesolimbic and the nigrostriatal. The mesolimbic dopamine system is involved in cognition and modulation of reward and consists of projections from the ventral tegmental area (VTA) to the nucleus accumbens (mesolimbic) and to the cortex (mesocortical). The nigrostriatal dopamine system is primarily involved in modulation of motor behaviors and consists of ascending projections from the substantia nigra (SN) to the striatum (caudate nucleus and putamen) (Role and Kelly 1991). As originally formulated, the DA hypothesis of schizophrenia postulated that increased DA activity (possibly in the mesolimbic system) was the cause of symptoms (Matthysse 1973; Meltzer and Stahl 1976). However, the negative symptoms of schizophrenia, including flattening of affect, anhedonia, anergia or psychomotor retardation, and cognitive deficits, are associated with hypoactivity in the prefrontal cortex DA system. In fact, improvements in negative symptoms have been noted in some patients treated with DA agonists (Angrist et al. 1980, 1982; Sanfilipo et al. 1996), and modifications of the hypothesis have been necessary to address the pathophysiology of negative symptoms (MacKay 1980; Meltzer 1979).

Knowledge of the structure and function of dopamine receptors has increased substantially in recent years with the application of techniques from molecular biology (Gingrich and Caron 1993). Cloning of the 5 mammalian DA-receptor subtypes and development of subtype-specific ligands has facilitated the investigation of the role of DA in cognitive processes and schizophrenia. These five receptor subtypes can be broadly classified into the D_1 and D_2 families; the D_1 family includes the D_1 and D_5 subtypes, and the D_2 family includes the D_2, D_3, and D_4 subtypes (Seeman and Van Tol 1994).

In general, D_1, D_2, and D_3 receptors are prominent in subcortical regions, D_4 receptors are distributed in both limbic and cortical regions, and D_1 and D_5 receptors are relatively more prominent in striatum and cortex than in brain stem nuclei (Meador-Woodruff et al. 1996). The distribution of D_2 receptors is clinically significant, because the antipsychotic efficacy of classic neuroleptics has been correlated with their degree of activity at D_2 receptors (Creese et al. 1976; Seeman et al. 1976). D_2-receptor subtype distribution has been examined in an autoradiographic study of postmortem human brain tissue using the specific D_2 agonist [^{3}H]CV 205-502 and the antagonist [^{3}H]spiroperidol (Camps et al. 1989). High densities of both ligands were observed in the caudate nucleus and putamen (striatum), nucleus accumbens, olfactory tubercle, and the substantia nigra pars compacta. Lower densities were observed in the globus pallidus and hippocampus. Negligible amounts of binding were observed in the olfactory bulb, diencephalon, brainstem, cerebellum, and neocortex. A strong correlation was observed between the anatomical distribution of D_2 receptors and reported regional endogenous dopamine concentrations (Camps et al. 1989). Receptor-binding assays with the selective D_2 antagonist [^{3}H]-raclopride (Lidow et al. 1989) have shown similar results, with lower concentrations of D_2-receptor binding sites observed in the cortex as compared to the striatum.

D_1 receptors recently have been proposed to play an important role in the pathophysiology of schizophrenia (Lynch 1992). Recent studies using antagonists and agonists selective for the D_1 receptor have shown differences in the distribution of D_1 receptors in schizophrenic patients as compared with healthy controls (the reader is referred to Sedvall et al. in this issue for a review of PET and audioradiography localization studies in schizophrenic patients). For example, decreased D_1-receptor binding has been observed in the prefrontal cortex of drug-naive schizophrenic patients, with the reduction in prefrontal D_1 receptors correlated with the severity of negative symptoms and cognitive disturbances (Okubo et al. 1997).

D_1 RECEPTORS IN PREFRONTAL CORTEX

Dopaminergic innervation of the cerebral cortex is well-documented (Berger et al. 1986; Brown et al. 1979; Kehr

et al. 1976). Radiolabeled ligands have been used to determine the distributions of the D_1- and D_2-receptor subtypes within the prefrontal cortex in studies of in vitro receptor binding (Camps et al. 1989; Cortés et al. 1989; Goldman-Rakic et al. 1990; Hall et al. 1988; Lidow et al. 1989; Richfield et al. 1989) and in vivo PET (Farde et al. 1987, 1988). In studies using the D_1-receptor antagonist [^{3}H]SCH 23390 and the D_2-receptor antagonist [^{3}H]raclopride, or [^{3}H]SCH 23390 and [^{3}H]spiperone in the presence of mianserin (to block labeling of 5-HT_{2A} and 5-HT_{2C} sites), a low density of [^{3}H]raclopride (D_2 receptors) binding was observed in all layers of the cortical areas studied. The highest densities of [^{3}H]-raclopride binding were observed in layer V of frontal, parietal, and occipital lobes. The density of binding for D_1 receptors with [^{3}H]SCH 23390 was 10 to 20 times higher than D_2-receptor density in all cortical areas, including the prefrontal cortex (Figure 1). Both [^{3}H]SCH 23390 and [^{3}H]raclopride binding sites display a rostral-caudal gradient, with the highest concentrations observed in the prefrontal cortex and the lowest concentrations in the occipital cortex (Lidow et al. 1989, 1991).

Ligands specific for various subtypes of dopaminergic, adrenergic, and serotonergic receptors have allowed us to observe distinctive laminar-specific distributions for monoamine receptors in the cerebral cortex. Although there is overlap among the dopaminergic, adrenergic, and serotonergic receptors, subtypes within the same receptor class tend to have complementary laminar profiles and even different localizations where cellular compartments (Goldman-Rakic et al. 1996; (Goldman-Rakic et al. 1990). Similar studies using [^{3}H]SCH 23390 in post-mortem human brain tissue have confirmed a laminar cortical distribution of D_1 receptors (Cortés et al. 1989). Interestingly, multivariate analysis demonstrated that advancing age is correlated with a marked decrease in the density of D_1 receptors in human brains (Cortés et al. 1989).

D_1 receptor-specific antibodies have been used in immunohistochemical studies to characterize the distribution of the D_1 receptors in the primate prefrontal cortex at the resolution of light and electron microscopy (Smiley et al. 1994). D_1-immunoreactive neurons are observed in all cortical layers, but are particularly visible in layers II, III, and V (Bergson et al. 1995). In addition, D_1 receptors are associated with pyramidal neurons, often in cell dendrites and spines (Figure 2) (Smiley et al. 1994). Similar to the distribution of D_1-binding sites observed in autoradiographic studies, a bilaminar distribution (layers 1b-II and V-VI) of neurophil labeling is

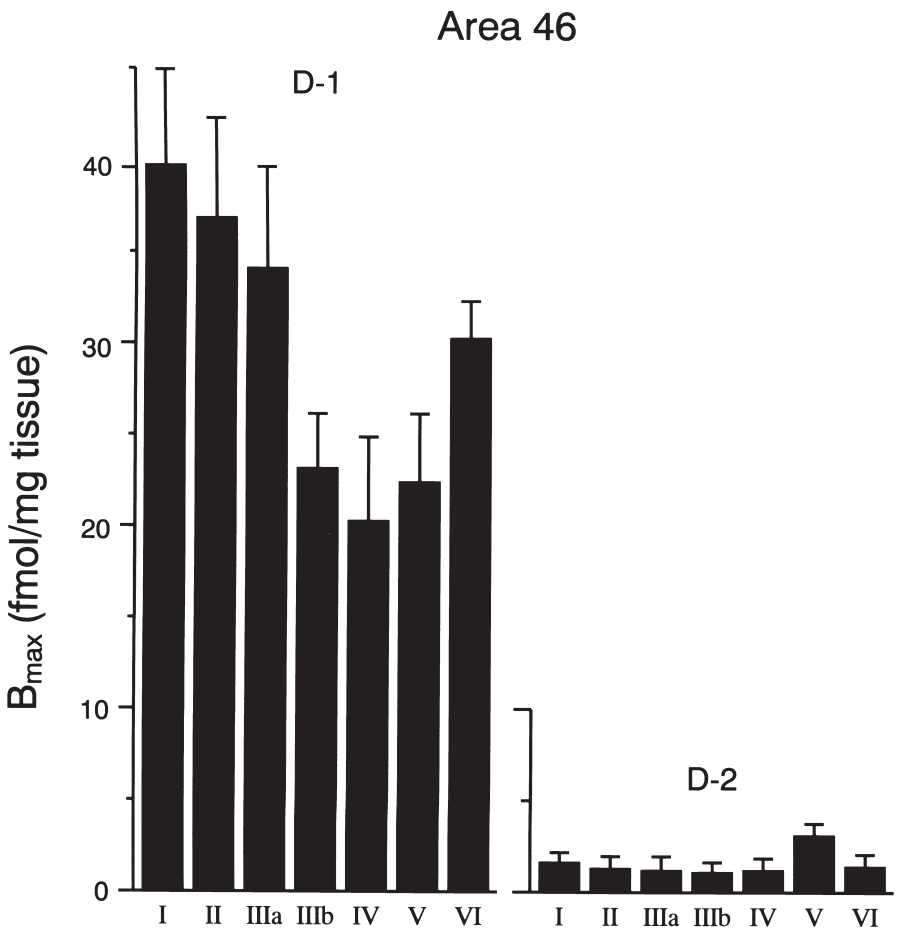

Figure 1. Histogram comparing layer-by-layer distribution of D_1-specific [^{3}H]SCH 22390 binding sites to D_2-specific [^{3}H]raclopride binding sites in area 46 of prefrontal cortex in the rhesus monkey (From data shown in Goldman-Rakic et al. 1990).

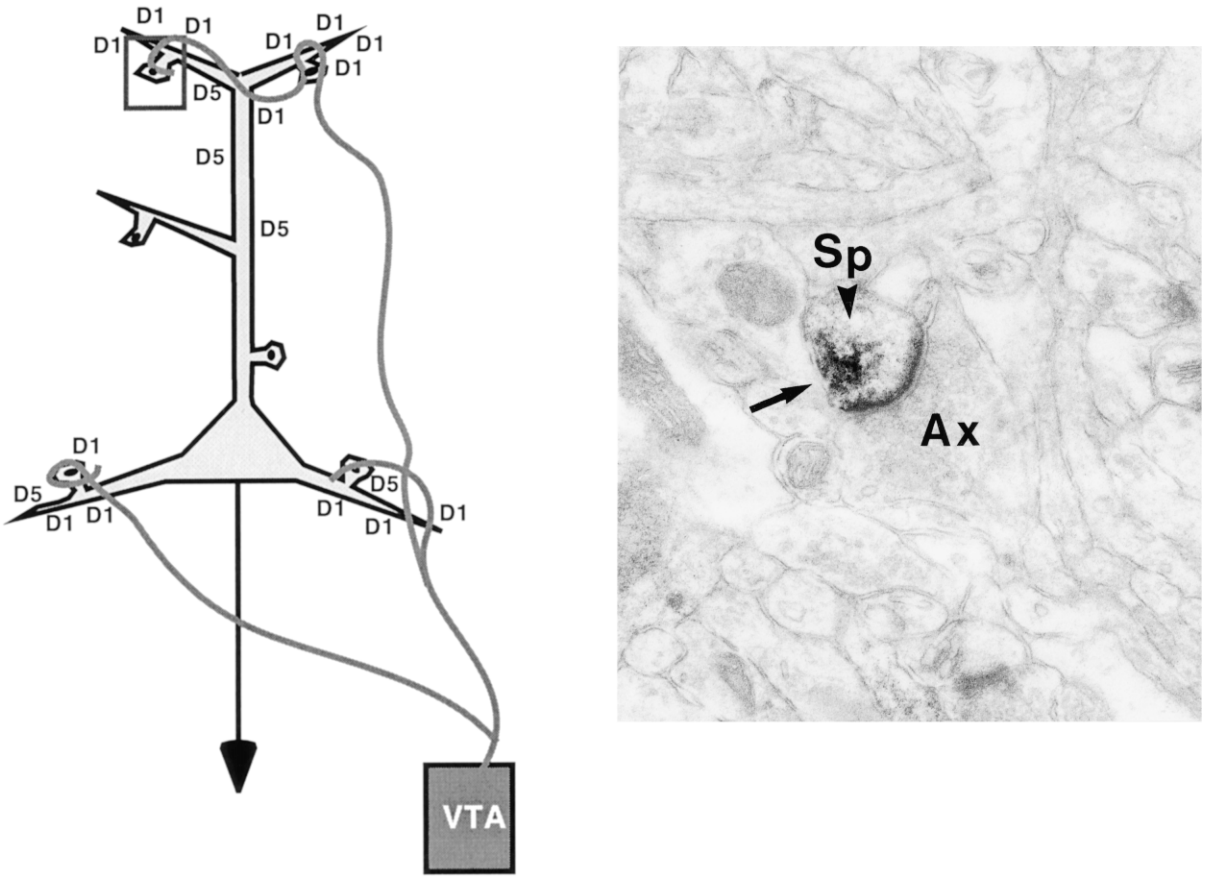

Figure 2. Diagrammatic representation of a cortical pyramidal cell indicating the relative location of D_1 receptors on the shafts and spines at distal portions of the basilar and apical dendritic tree. The photomicrograph shows an unidentified axon (Ax) of the asymmetric (excitatory) type terminating on a D_1-containing spine (Sp) as revealed by the dark label in the spine produced by immunocytochemical response to a D_1-specific antibody (photomicrograph courtesy of E. Christopher Muly and P.S. Goldman-Rakic).

also observed. Electron microscopic analysis reveals that D_1 receptors are frequently located postsynaptically in the prefrontal cortex, although presynaptic sites are also observed. When localized presynaptically, D_1 receptors are often observed in axon terminals that form asymmetric synaptic specializations. Double-label localization experiments demonstrate coexpression of D_1 and D_5 receptors within neurons of both the neocortex and the hippocampus. Ultrastructurally, D_1-antibody staining is prominent in spines; whereas, D_5-antibody staining is dominant in dendritic shafts (Bergson et al. 1995).

Three possible cellular mechanisms of DA modulation of working memory function seem to operate in the prefrontal cortex (Goldman-Rakic 1998). One mechanism is direct nonsynaptic modulation of pyramidal neurons. The second mechanism is indirect synaptic modulation of pyramidal neurons via feedforward inhibition from GABAergic interneurons. The third possible mechanism is direct synaptic modulation of receptors on the distal dendrites and spines of pyramidal neurons. Synaptic triad complexes have been observed in the prefrontal cortex in which the spines of a pyramidal neuron receive input from both a dopamine terminal and a glutamate terminal. This triad suggests dopamine modulation of excitatory input on pyramidal neurons that project to the thalamus, the striatum, and to other areas of the cortex (Goldman-Rakic 1998). Although the receptors involved in these triads have not been identified, electrophysiological studies from our laboratory (discussed in detail below) indicate that the D_1 receptor may be involved in regulating excitatory neurotransmission in the prefrontal cortex (Williams and Goldman-Rakic 1995).

THE INVOLVEMENT OF D_1 RECEPTORS IN MEMORY AND COGNITION

Although the normally low concentrations of D_2 receptors and high concentrations of D_1 receptors present in the prefrontal cortex suggest the involvement of the D_1

receptor in mnemonic processes, additional evidence to support this hypothesis comes from experiments with the potent D_1 antagonists SCH 23390 and SCH 39166 (Chipkin et al. 1988). In these experiments, SCH 23390 and SCH39166 were injected into several areas of the prefrontal cortex of rhesus monkeys and an oculomotor delayed-response (ODR) task was used to monitor their effects on working memory (Sawaguchi and Goldman-Rakic 1991). The D_1 antagonists induced errors and increased the latency of response during the performance of the ODR task, which required memory-guided saccades; these deficits were dose-dependent and delay period sensitive. Performance on a control task requiring visually guided saccades showed that the D_1 antagonists had no effects on sensory or motor functions. These results suggest that activation of D_1 receptors is critical for memory processes mediated by the prefrontal cortex, although the specific types of neurons affected by the D_1 antagonists were not determined.

Iontophoresis of drugs onto neurons in conjunction with single-cell recording of neural activity during behavior is now possible (Funahashi et al. 1989, 1990; Williams and Goldman-Rakic 1995). Using this technology, the involvement of D_1 receptors in mnemonic processes of the prefrontal cortex has been tested. Williams and Goldman-Rakic (1995) examined the effects of SCH 39166 on cell firing in the dorsolateral prefrontal cortex of monkeys while they performed an ODR task (Williams and Goldman-Rakic 1995). Consistent with previous findings, spatially tuned memory fields were observed in prefrontal neurons; that is, neurons responded maximally during the delay period for targets in one or a few adjacent target locations. However, in contrast to our previous finding that D_1 antagonists were detrimental to working memory (Sawaguchi and Goldman-Rakic 1991), iontophoresis of SCH 39166 enhanced the neuronal memory fields in 11 of 12 neurons. Similar results were obtained with the less selective D_1 antagonists, SCH 23390, NNC 010756, and A 60924 (Williams and Goldman-Rakic 1995). The neuronal memory field activation caused by D_1-receptor blockade could be reversed by iontophoresis of the partial D_1 agonist, SKF 38393. The D_2-receptor antagonist, raclopride, caused a generalized inhibition of firing without the selective effects on neuronal memory fields observed with D_1-specific agents. In this study, an increased activation of memory fields of prefrontal neurons was achieved only through D_1-receptor activation, suggesting a memory-enhancing action at the doses used (Williams and Goldman-Rakic 1995).

Another important observation in this study was the dose dependence of D_1-antagonist effects. At high doses, D_1 antagonists caused a nonspecific inhibition of cell firing, affecting not only the memory field of the cells but neuronal activity during all phases of the ODR task and at all target locations. The dose-related effects observed at the cellular level are consistent with the results of other physiological and behavioral studies (Arnsten et al. 1994; Cai and Arnsten 1997; Hu and Wang 1988; Murphy et al. 1996). The dependence of working memory on D_1-receptor activation is a "U-shaped" function, where the optimal range of dopamine concentrations and cortical receptor activation characterizes the state of normal cognitive performance. Currently available antipsychotic agents consistently are not effective in treating the negative symptoms and cognitive deficits of schizophrenia (Angrist et al. 1980; Meltzer et al. 1994). The results of the Williams and Goldman-Rakic (1995) study raise the possibility that antipsychotic medications may have unforeseen effects on D_1- and D_2-receptor levels, causing the D_1-receptor levels to fall outside of the optimal range. Additional studies of the effects of D_1-specific agonists and antagonists on working memory function are in progress.

D_1 Receptors and Antipsychotics

Long-term exposure (≥6 months) to typical antipsychotic drugs (D_2 antagonists) increases the level of D_2 receptors and produces a downregulation of D_1 receptors in primate cerebral cortex (Figure 3) (Lidow and Goldman-Rakic 1994, 1997; Lidow et al. 1997; Nordström et al. 1992; Wolkin et al. 1989). The level of D_2 receptors rises relatively quickly after the beginning of exposure (Nordström et al. 1992; Wolkin et al. 1989); whereas, effects on cortical D_1 receptors are slower to appear. D_1 and D_5 receptors are both subject to this downregulation (Lidow et al. 1997), which occurs at a detectable level only after months of exposure to antipsychotic drugs. The mechanism by which D_2 antagonists reduce cortical D_1- and D_5-receptor levels is not known (Lidow et al. 1998).

We are currently studying the effects of a D_1-receptor agonist (ABT-431, Abbott) on working memory (ODR task) in primates that have had long-term neuroleptic treatment. To date, the results are encouraging. Whether or not D_1 or D_2 receptors are involved in the primary pathophysiology of schizophrenia is still unknown (Goldman-Rakic and Selemon 1997). To the extent that maintaining receptor occupancy at a certain level is important to normal cognitive function, the use of appropriate doses of D_1-receptor antagonists or agonists in a clinical trial setting is an important area of future study.

CONCLUSIONS

Schizophrenic patients manifest negative symptoms and cognitive deficits throughout the course of their illness, and these symptoms tend to be more constant than positive symptoms such as hallucinations and de-

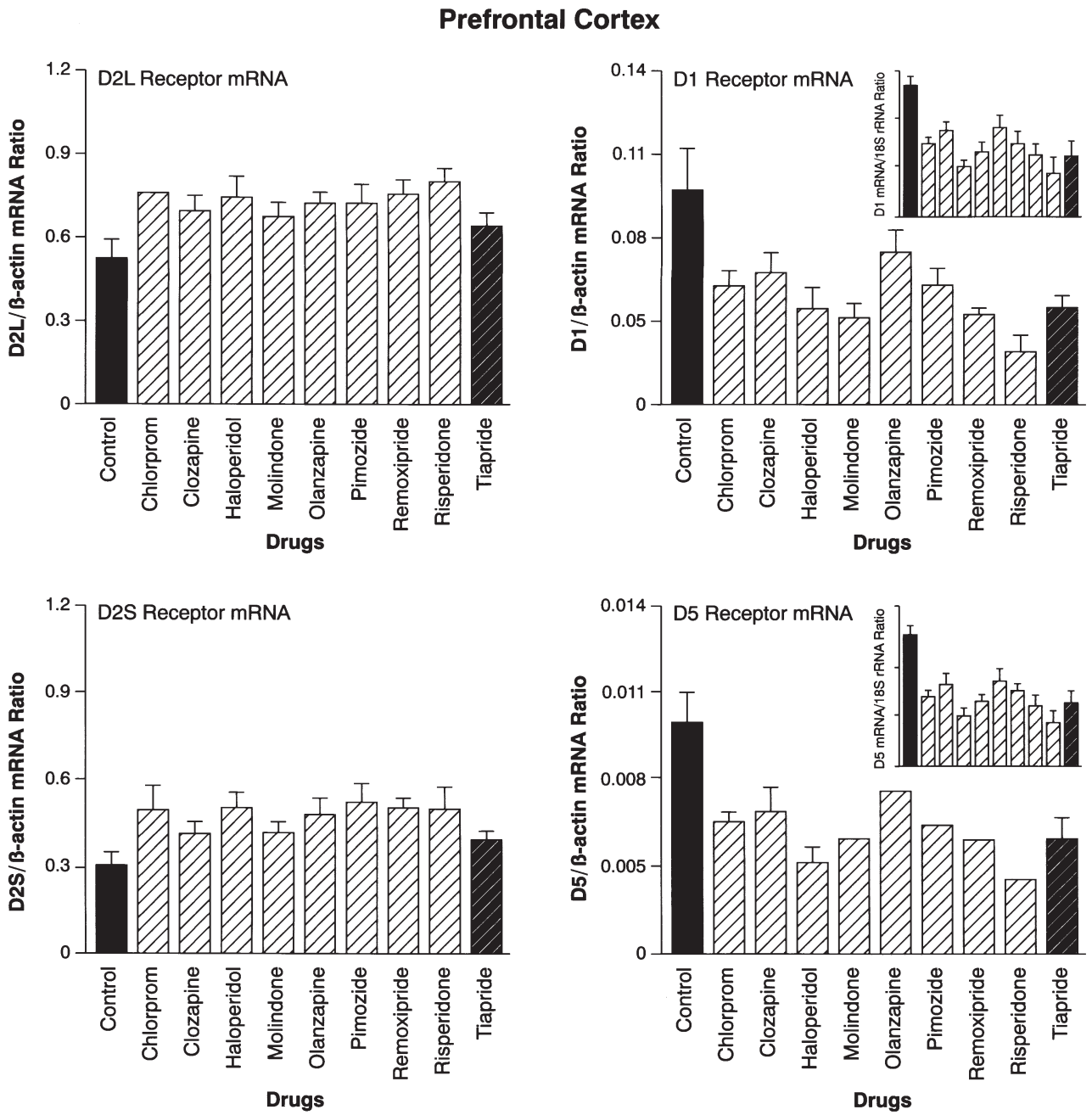

Figure 3. Bar graphs representing changes in the levels of D_2-long (L), D_2-short $(S)_2$, D_1 and D_5 mRNAs in response to 6 months of daily treatment with nine pharmacologically distinct drugs but common D2 antagonist properties. The bar graphs represent mean dopamine receptor mRNA expressed per β-actin mRNA ± (standard error of the mean) with the mean ratio for the drug-free control group designated as one and the remainder of the data normalized accordingly (adapted from Lidow and Goldman-Rakic 1997; Lidow et al. 1998).

lusions, which are more episodic in nature (Weinberger 1988). These deficit symptoms include emotional dullness; impaired judgement; poor initiative, motivation, or drive; lack of insight; difficulty in planning; impaired problem solving and abstract reasoning; decreased concern for personal hygiene; and social withdrawal. Neuropsychological and neurophysiological studies confirm the importance of the prefrontal cortex in cognition and in cognitive deficits observed in schizophrenia.

Studies of single-neuron activity in monkeys during performance of delayed-response tasks have confirmed the involvement of the prefrontal cortex in working memory. Separate populations of neurons have been identified whose activity is temporally linked to spe-

cific components of the delayed-response task (Fuster et al. 1982). One type of neuronal population, called a "memory field," seems to be associated with maintaining the representation of the environmental cue during the delay between cue presentation and behavior. There is evidence that D_1 receptors in the prefrontal cortex are involved in working memory. D_1 antagonists, administered to neurons via iontophoresis, produce a dose-dependent effect (U-shaped) on the firing rate of cells within memory fields during delayed-response tasks. At high doses, D_1 antagonists cause a nonspecific inhibition of cell firing, affecting not only the memory field of the cells but also the neuronal activity during all phases of the delayed-response task and all target locations. However, at lower doses, D_1 antagonists produce a delay-specific enhancement of cell firing within memory fields.

Disordered cognitive processes in schizophrenia can be attributed to impairment of function in the prefrontal cortex. The schizophrenic brain is normal in gross appearance, and the types of lesions observed in neurodegenerative disorders such as Huntington's disease are not present (Selemon and Goldman-Rakic 1999). However, recent studies have shown increased neuronal density in the prefrontal and to a lesser extent in the occipital cortices of schizophrenics as compared to healthy controls (Selemon et al. 1998). This increased neuronal density characterizes the more subtle pathology of schizophrenia, presumably indicating a compromised cell structure, impoverished neural connectivity, and loss of functional interneuron communication.

Direct evidence of prefrontal dysfunction in schizophrenia comes from studies using physiological brain imaging techniques. Schizophrenic patients show an inability to learn how to perform the WCST (Goldberg et al. 1987) and reduced activation of dorsolateral prefrontal cortex while engaged in the WCST (Weinberger et al. 1986). Schizophrenic subjects also show significant impairments on oculomotor delayed-response tasks (Park and Holzman 1992), a behavioral paradigm that has been demonstrated to be a selective and reliable measure of dorsolateral prefrontal cortex function. Furthermore, the degree of prefrontal hypometabolism has been correlated with clinical ratings of negative symptoms.

Although the involvement of dopamine D_2 receptors in schizophrenia has been studied extensively because typical antipsychotics are D_2 antagonists, recently, more attention has been focused on the role of D_1 receptors in schizophrenia. Autoradiographic and PET studies have determined that there is a high density of D_1 receptors compared with D_2 receptors in the prefrontal cortex; this density is altered in schizophrenic patients. Increasingly, more detailed information is becoming available concerning the localization of D_1 receptors and their involvement in cognition and schizophrenia. Further characterization of D_1 receptors in the prefrontal cortex should lead to additional insights on the neuropharmacology of cognition as well as on effective treatments for schizophrenia.

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