Pharmacological Manipulation of D_1-Dopamine Receptor Function in Schizophrenia

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The most widely accepted hypothesis concerning the pathophysiology of schizophrenia, the dopamine hypothesis, suggests that the symptoms of schizophrenia are mediated in part by a functional hyperactivity in the dopamine system in the brain, primarily at D_2-dopamine receptors. Recent data suggest that D_1-dopamine receptors may also play a major role in the pathophysiology of schizophrenia. Using positron emission tomography (PET), increased variability and reduced D_1-receptor binding have been observed in the basal ganglia and frontal cortex of drug-naive schizophrenia patients. Such alterations have also been found in some in vitro studies. These results suggest that the ratio of D_1- over D_2-regulated dopamine signaling in some brain regions is reduced in schizophrenia. A clinical trial of SCH 39166, a selective D_1-dopamine receptor antagonist, showed no evidence of antipsychotic activity in schizophrenic patients. Instead, it appeared that selective D_1-receptor antagonism may have aggravated symptoms. Although these findings do not support the prediction that selective D_1-dopamine receptor antagonism produces antipsychotic effects, they do not preclude the possibility that combined D_1- and D_2-receptor antagonism may act synergistically to ameliorate symptoms in schizophrenia. In addition, clinical evaluation of D_1 agonists in schizophrenia should be undertaken. [***Neuropsychopharmacology 22:S181–S188, 1999***] *© 1999 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

Dopamine receptors have been divided into two major families, D_1 and D_2, based primarily on pharmacological and biochemical criteria (Sunahara et al. 1993). However, recent advances in the molecular biology of the dopamine receptor system have led to the identification and characterization of at least five distinct central dopamine receptor subtypes (D_1, D_2, D_3, D_4, and D_5) (Sunahara et al. 1993). The D_1-dopamine receptor subfamily consists of two subtypes, D_1 and D_5, and the D_2-receptor subfamily is composed of D_2-, D_3-, and D_4-receptor subtypes (Lachowicz and Sibley 1997). These receptors are distinguished based on their primary structure, chromosomal location, mRNA size and tissue distribution, and biochemical and pharmacological differences (Sunahara et al. 1993). For example, D_1-like receptors activate adenylate cyclase; whereas, D_2-like receptors have no effect on or inhibit adenylate cyclase (Lachowicz and Sibley 1997).

Historically, development of pharmacologic treatments for schizophrenia has been dominated by the dopamine hypothesis, which states that the symptoms of schizophrenia are produced by excess activity in central dopaminergic systems, primarily at D_2 receptors. Evidence for dopaminergic dysfunction was based on

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observations that the effective antipsychotics are potent antagonists at D_2-dopamine receptors (Creese et al. 1976; Seeman et al. 1976), and drugs that increase dopamine release produce psychotomimetic effects (Lieberman et al. 1987). The results of more recent studies suggest that D_1-dopamine receptors also may play a major role in the pathophysiology of schizophrenia.

Understanding of the etiology of schizophrenia has increased in the past two decades, in part because of the development of more sophisticated brain-imaging and histological techniques and selective radioligands that allow visualization of abnormalities in brain chemistry (Sedvall et al. 1986). Questions related to laterality and regional specificity of alterations of dopamine signaling necessitate the simultaneous recording of dopamine-regulated mechanisms in a vast number of brain regions. This can be achieved at low resolution using positron emission tomography (PET) with suitable radioligands, which bind to specific components of dopamine signaling pathways, such as receptors and transporters. Using autoradiography in postmortem brain tissue from humans and in situ hybridization histochemistry, visualization of receptor binding sites and areas of gene expression can be achieved with a much higher resolution. These new chemical methods, in combination with computer graphics for image presentation, allow the construction of three-dimensional (3-D) computed information banks of human brain anatomy. Information banks will help define the neuronal circuitry of the human brain and identify relevant neurochemical aberrations in the pathophysiology of schizophrenia (Sedvall and Farde 1995).

This review summarizes the current state of understanding regarding dopamine receptor distribution in the brain based on autoradiographic studies of receptor binding in postmortem tissue and in vivo PET studies, as well as in studies of dopamine-receptor mRNA expression identified by in situ hybridization. Evidence is presented implicating the D_1-dopamine receptor in the pathophysiology of schizophrenia. In addition, this review focuses on emerging evidence concerning the efficacy of pharmacological manipulation of D_1-receptor function in the treatment of schizophrenia.

DOPAMINE RECEPTOR DISTRIBUTION

PET Studies

In PET, high-affinity ^{11}C-labeled ligands are administered intravenously to the subject, and the accumulation of radioactive ligand is measured in various sections of the brain. The positron camera records the gamma radiation produced upon disintegration of ^{11}C-labeled atoms. PET provides data on the relative distribution of receptors and specific binding characteristics

of receptor ligands in the living human brain (Sedvall et al. 1986). Furthermore, it is possible to examine not only the distribution of receptors but also some quantitative aspects of receptor function and drug–receptor interactions in vivo (Sedvall et al. 1990; Wiesel et al. 1990).

Following the classification of dopamine receptors into the D_1- and D_2-receptor subfamilies, the pharmacology of the D_2 receptor was well characterized because of the existence of a number of selective D_2-receptor antagonists and agonists (Seeman 1980). More recently, the development of selective antagonists and agonists has enabled the evaluation of the D_1 receptor.

Farde et al. (1987) conducted a PET study in three healthy male subjects and two male drug-treated schizophrenic patients injected with tracer doses of the D_1-receptor antagonist, [^{11}C]SCH 23390 and the selective D_2-receptor antagonist [^{11}C]raclopride. In healthy subjects, a high accumulation of radioactivity in the striatum (caudate nucleus and putamen) was observed with both [^{11}C]SCH 23390 and [^{11}C]raclopride; the radioactive accumulation in the striatum was several-fold higher than the accumulation observed in any other brain region. This finding is similar to the accumulation of [^{11}C]SCH 23390 observed in the striatum of monkey brain (Halldin et al. 1986). In contrast to the accumulation of both D_1- and D_2-receptor antagonists in the striatum, [^{11}C]SCH 23390, but not [^{11}C]raclopride, showed a noticeable localization of radioactivity in the neocortex, indicating the relative predominance of D_1 receptors over D_2 receptors in this region (Farde et al. 1987). This result is consistent with studies in monkeys showing D_1-receptor prominence in major cortical areas (Goldman-Rakic et al. 1990; Lidow et al. 1991). The localization of a very low density of D_2 receptors in the human neocortex has also been observed with [^{11}C]raclopride. In humans, [^{11}C]SCH 23390 does not appear to accumulate in the cerebellum, indicating a negligible density of D_1 receptors (Farde et al. 1987); the ratio of receptor binding in the putamen (a dopamine-rich structure) to receptor binding in the cerebellum (a region with a negligible density of D_1-dopamine receptors) was 3.0 (Table 1).

Although SCH 23390 is a D_1-receptor antagonist, it also has affinity for other binding sites, such as 5-HT receptors (McQuade et al. 1988; Yamamoto and Kebabian 1989). SCH 39166, a benzonaphthazepine, has been characterized both in vitro and in vivo as a potent and selective D_1-dopamine antagonist (Chipkin et al. 1988). SCH 39166 has a lower affinity for 5-HT receptors, and is thus a more selective D_1 antagonist than SCH 23390 (Taylor et al. 1991). PET studies with [^{11}C]SCH 39166 in cynomolgus monkeys demonstrated accumulation of radioactivity in the striatum (Halldin et al. 1991; Sedvall et al. 1991) and neocortex (Sedvall et al. 1991). In healthy human subjects, [^{11}C]SCH 39166 rapidly passed the blood–brain barrier and accumulated in the stria-

Table 1. Radioactivity Ratios of Receptor Binding in the Putamen to Receptor Binding in the Cerebellum Using Various Radioligands in PET Studies of Healthy Male Volunteers

Radioligand	Number of Subjects	Radioactivity Ratio Putamen/Cerebellum	Reference
[^{11}C]SCH 23390	3	3.0	Farde et al. 1987
[^{11}C]SCH 39166	9	1.54	Karlsson et al. 1995a
(+)-[^{11}C]NNC 112	4	4.0	Halldin et al. 1998

tum, a region with a high density of D$_1$ receptors (Karlsson et al. 1995a). However, the low ratio (1.54 ± 0.18 SD) of receptor binding in the putamen to the cerebellum indicates that [11C]SCH 39116 is less suitable as a radioligand for applied PET studies (Karlsson et al. 1995a) (Table 1).

Recently, a new highly selective radioligand, (+)-[^{11}C]NNC 112, was developed for PET. The active (+) enantiomer of [^{11}C]NNC 112 has a high affinity for D$_1$ receptors, 100-fold lower affinity for 5-HT$_{2A}$ receptors, and virtually no affinity for all other central receptors (Halldin et al. 1998). Halldin et al. (1998) used (+)-[^{11}C]NNC 112 with PET to examine striatal and neocortical D$_1$ receptors in cynomolgus monkeys and in healthy male volunteers. Following injection of (+)-[^{11}C]NNC 112 in healthy male subjects, high radioactivity ratios were observed in the striatum, nucleus accumbens, and the frontal cortex relative to the cerebellum; the radioactivity ratio of the putamen to the cerebellum was 4.0 (Table 1) and the corresponding ratios of the frontal cortex to cerebellum and the nucleus accumbens to cerebellum were 2.0 and 2.8, respectively. These ratios were higher than the ratios obtained with [^{11}C] SCH 23390 (Farde et al. 1987). The regional distribution of radioactivity was similar to the distribution of D$_1$ receptors observed in previous studies using [^{11}C]SCH 23390, with the highest density in the basal ganglia, lower density in the neocortex, and with negligible presence of D$_1$ receptors in the cerebellum (Halldin et al. 1998).

Together, in vivo PET studies using a variety of radioligands indicate high dopamine-receptor densities in the caudate nucleus and putamen and lower densities in the nucleus accumbens. However, whereas D$_1$ receptors are also found in the cerebral cortex, there are only minute amounts of D$_2$ receptors in most cortical regions. Although PET studies have estimated receptor densities in the major dopaminergic projection areas, the density of dopamine receptors in small or low-density brain regions has been difficult to quantify, partly because of the limited resolution (3 mm) of the PET technique (Sedvall and Farde 1995).

Postmortem Studies

Autoradiography in postmortem brain tissue provides a higher resolution for visualization of radioligand binding sites and can serve as an anatomical correlate to PET studies (Hall et al. 1994). At necropsy, a frozen human hemisphere can supply about 1,500 100-μm thin sections, offering 50-μm resolution (Sedvall and Farde 1995). The density and distribution of D$_1$ and D$_2$ receptors have been investigated in vitro using receptor autoradiography postmortem in human brain tissue (Hall et al. 1988, 1993, 1994). Using brain homogenates and whole hemisphere autoradiograms with [^{3}H]SCH 23390 and [^{3}H]raclopride as radioligands, D$_2$ receptors were found to be equally distributed between the caudate nucleus and the putamen (Hall et al. 1994). This was in contrast to the distribution of D$_1$ receptors, which showed a higher density in the medial caudate nucleus but an even distribution throughout the putamen. The localization of a very high density of D$_1$ receptors in the medial caudate nucleus has also been observed in human postmortem autoradiographic studies with [^{3}H]SCH 39166 (Hall et al. 1993). This specific distribution pattern of the D$_1$ receptors in the medial basal ganglia has not been observed in more recent PET studies (Hall et al. 1994). Autoradiographic examination of [^{11}C]NNC 687 and [^{11}C]NNC 756, two selective D$_1$ radioligands with favorable signal-to-noise ratios, in postmortem human brain sections confirmed the high density of D$_1$ receptors in the striatum (Halldin et al. 1993).

As in PET studies, marked labeling of the D$_1$-dopamine receptor in human cortical regions by [^{3}H]SCH 23390 has been observed using autoradiography (Hall et al. 1988, 1993). This result is supported by findings using the more selective D$_1$-receptor ligand [^{3}H]SCH 39166 (Hall et al. 1993). In vitro autoradiography using a new ^{125}I-labeled, high-affinity dopamine transporter ligand (PE2I) has provided detailed qualitative and quantitative evidence that the dopamine transporter is almost exclusively localized in the basal ganglia (Hall et al. 1999). In addition, the anatomical distribution of dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 3-methoxytyramine (3-MT), using high-performance liquid chromatography (HPLC) has been investigated by Hall et al. (1994). High levels of dopamine, DOPAC, HVA, and 3-MT were predominantly found in the basal ganglia, with the highest levels in the lateral putamen (Hall et al. 1994).

Overall, the distribution of the dopamine-receptor subtypes observed in autoradiographic studies of post-mortem human brain tissue is in agreement with data obtained from human PET studies. Studies using human brain tissue confirm the presence of high densities of D_1 receptors and low densities of D_2 in the cerebral cortex (Hall et al. 1994) and that the levels of D_1 receptors in the cortex are lower than in the striatum (Hall et al. 1988). Thus, the human postmortem studies show that the densities of D_1 and D_2 receptors roughly parallel each other, although the D_1 receptor is the dominating receptor subtype in most cortical regions.

mRNA Expression Studies

Neurotransmitter pathways can be visualized in the brain through mapping of gene expression using in situ hybridization (Sedvall and Farde 1995). This technique shows where mRNA for a specific gene is expressed in the brain. Advances in the molecular biology of the dopamine-receptor system have allowed the identification and characterization of the genes that encode for the D_1- and D_2-receptor subtypes (Sunahara et al. 1993).

A heterogeneous distribution of D_1-receptor mRNA in the cynomolgus monkey striatum has been observed with high levels of mRNA in what are called "patch" compartments of the striatum (Rappaport et al. 1993). More recently, [^{3}H]SCH 23390 autoradiography was combined with in situ hybridization to compare the regional distribution of D_1-receptor binding sites to the distribution of cells expressing mRNAs encoding D_1 receptors in the cynomolgus monkey brain (Brené et al. 1995). Using these techniques, it was possible to show that D_1-receptor mRNA-positive cells were unevenly distributed in the striatum (Brené et al. 1995). Specifically, D_1-receptor mRNA was higher in the caudate nucleus than in the putamen, possibly indicating stronger D_1-receptor influence in the caudate. Clusters of cells with a threefold higher intensity of D_1-receptor mRNA expression were found in the caudate nucleus and putamen, as compared to surrounding regions. In general, the distribution of D_1 receptors as shown by [3H]SCH 23390 binding was more homogeneous than the D_1 mRNA distribution, although some of the D_1 mRNA-intensive cell clusters in the caudate nucleus seemed to be matched to regions of higher intensity [3H]SCH 23390 binding (Brené et al. 1995).

The distribution of D_1-receptor mRNA in neocortex was more distinct and heterogeneous than the binding of [^{3}H]SCH 23390 (Brené et al. 1995). This could be explained by the fact that the mRNA coding for the receptor is localized almost exclusively in the cell bodies; whereas, the receptors are localized to dendrites and axons. In situ hybridization also showed cells of different sizes expressing D_1-receptor mRNA in layers II–VI of neocortex, with D_1-receptor mRNA-positive cells

most abundant in layer V. The differential distribution of D_1-receptor, mRNA-positive cells to different layers of neocortex and in cells with different sizes implies that dopamine acting through D_1 receptors can modulate function within different cortical circuits. Overall, these findings highlight the importance of mapping the distribution of dopamine receptors and the cellular association of mRNAs in order to understand D_1-receptor function better (Brené et al. 1995).

DOPAMINE RECEPTORS IN THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

It has been proposed that the symptoms of schizophrenia are related to dopaminergic hyperactivity and an abnormally high density of D_2-dopamine receptors in the brain (Mackay et al. 1980; Owen et al. 1978; Seeman et al. 1984). However, most data supporting a role for D_2 receptors in schizophrenia come from postmortem studies in patients who were previously treated with typical antipsychotics (D_2 antagonists), and increased D_2 densities have been observed after long-term treatment with typical antipsychotics in animals (Burt et al. 1977; Clow et al. 1980; Owen et al. 1980). Furthermore, recent PET studies have failed to show a consistent increase in D_2-receptor density in the striatum of drug-free schizophrenics despite the use of a number of selective radioligands (Farde et al. 1990; Hietala et al. 1994; Nordström et al. 1995; Okubo et al. 1997; Wong et al. 1986). For example, the use of PET with [^{11}C]raclopride in healthy subjects and neuroleptic-naive schizophrenic patients found no significant difference in D_2-receptor density (Bmax) or affinity (Kd) in caudate nucleus or putamen (Farde et al. 1990). In addition, a normal density of D_2 receptors in the striatum of neuroleptic-naive schizophrenic patients was observed in a PET study using the radioligand [^{11}C]N-methylspiperone ([^{11}C]NMSP) (Nordström et al. 1995).

The lack of an apparent difference in striatal D_2-receptor density fails to support the hypothesis that schizophrenia is related to an increased density of D_2 receptors (Okubo et al. 1997; Sedvall and Farde 1995). The results from PET studies raise the possibility that individual dopamine receptor subtypes may not be exclusively involved in the maintenance or expression of schizophrenia, which implies that other receptors may be involved (Okubo et al. 1997). Specifically, D_1-dopamine receptors have been proposed to play an important role in the pathophysiology of schizophrenia (Goldman-Rakic 1994; Lynch 1992).

Alterations in D_1-receptor binding have been observed in some (but not all) studies. One postmortem study investigating the radioligand binding properties of D_1 and D_2 receptors found a significant difference in the ratio of D_1 to D_2 receptors between schizophrenic

patients and healthy controls and a decrease in striatal D_1-receptor density in schizophrenics (Hess et al. 1987). More recently, PET studies examined D_1 and D_2 receptor characteristics in young drug-naive schizophrenic patients and age-matched, healthy controls (Sedvall et al. 1995). Using a combination of selective radiolabeled ligands, it was found that the characteristics of total D_1 and D_2 receptors in the caudate and putamen were not significantly different between schizophrenic patients and healthy controls. However, there was a significant reduction in D_1 signal in high-intensity regions of the basal ganglia when [^{11}C]SCH 23390 was used. These results suggest the possibility of reduced D_1-receptor density in the patch compartment of the basal ganglia in schizophrenic patients (Sedvall et al. 1995). It should be noted that low D_1-receptor density in this compartment may result in the reduced activity of the D_1/D_2 regulatory feedback system to limbic brain regions in schizophrenia (Sedvall and Farde 1995).

Okubo et al. (1997) conducted a PET study using [^{11}C]SCH 23390 and [^{11}C]NMSP as tracers to examine the distribution of D_1 and D_2 receptors, respectively, in brains of drug-naive or drug-free schizophrenic patients. The study failed to detect any difference in either the striatal D_1 receptors or the ratio of D_1 to D_2 receptors in the striatum. However, the mean values of D_1-receptor binding affinity in the prefrontal cortex for both drug-naive and drug-free schizophrenic patients were significantly lower than for the control group. The decreased D_1-receptor binding in drug-naive schizophrenic patients implies that the D_1-receptor system in the prefrontal cortex may be involved in schizophrenia. This study also showed that the reduction in prefrontal D_1 receptors was correlated with the severity of negative symptoms (e.g., emotional withdrawal) and to poor performance on the Wisconsin Card Sorting Test (WCST) (Okubo et al. 1997). Together, these findings suggest that dysfunction in D_1-receptor modulation in the prefrontal cortex may contribute to the negative symptoms and cognitive deficits observed in schizophrenia (Okubo et al. 1997).

D_1-RECEPTOR ANTAGONISTS FOR THE TREATMENT OF SCHIZOPHRENIA

There is general agreement that most antipsychotic agents produce their therapeutic effects through activity at dopaminergic, noradrenergic, and/or serotonergic systems (Sedvall 1996), with a central role for D_2-dopamine receptors (Creese et al. 1976; Seeman et al. 1976). Clinical support for a role of D_1 receptors in schizophrenia is based on the observation that the "atypical" antipsychotic drug clozapine produces a relatively high D_1-receptor occupancy (33% to 59%) in the putamen (Farde et al. 1992, 1994). Although clozapine

occupies D_2 receptors to a smaller extent than typical antipsychotics, its occupation of D_1 receptors is greater than that of typical antipsychotics ($\sim$40% versus 0%–36%). Thus, the unique clinical profile of clozapine may be related to its activity at both D_1 and D_2 receptors (Wiesel et al. 1990).

SCH 39166

As reviewed in the present paper, the selective D_1 receptor antagonist SCH 39166 has been used to investigate the distribution and density of D_1 receptors in both human postmortem studies (Hall et al. 1993) and PET studies (Karlsson et al. 1995a). SCH 39166 is the first selective D_1-receptor antagonist developed for clinical trials. SCH 39166 was developed for clinical trials in schizophrenia, in part, because animal models predicted that selective D_1-receptor antagonists may have antipsychotic effects (Chipkin et al. 1988; Nielsen and Andersen 1992). In humans, single 100-mg oral doses of SCH 39166 have been shown to induce approximately 70% D_1-receptor occupancy in the basal ganglia, which is sufficient to investigate the antipsychotic potential of D_1-receptor antagonism in clinical studies (Karlsson et al. 1995a).

An open-label study was conducted to determine the efficacy and safety of SCH 39166 as an antipsychotic in schizophrenic patients. Seventeen acutely ill, drug-free schizophrenic patients received SCH 39166 for 4 weeks (Karlsson et al. 1995b). Doses were escalated from 10 mg to 100 mg twice daily according to a fixed schedule over 17 days, and remained at 100 mg twice daily for another 11 days. Plasma levels of SCH 39166 were predicted to produce a range from 49% to 78% D_1-receptor occupancy in the striatum. This is similar to the occupancy obtained by selective D_2-receptor antagonists in doses that produce antipsychotic effects, but higher than the D_1-receptor occupancy in patients treated with clozapine (Farde et al. 1992). Antipsychotic efficacy was measured using the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impression (CGI) scale.

SCH 39166 was withdrawn prematurely in 10 patients because of patient refusal to take the study drug (eight patients) or deterioration of psychotic symptoms (two patients) (Karlsson et al. 1995b). No significant improvements in total BPRS were observed during treatment with SCH 39166, as compared to baseline in the seven patients who completed the study. Similarly, no changes in CGI scores compared to baseline values were observed in any of the patients during treatment with SCH 39166. There was not only a lack of an antipsychotic effect with SCH 39166, as compared to the effects produced by other antipsychotics, but there was also little evidence of placebo effect, which might be expected from previous placebo-controlled clinical trials in schizophrenia (Table 2). Five patients who discontin-

Table 2.   Comparison of the Antipsychotic Efficacy of SCH 39166 with other Antipsychotics and Placebo in Schizophrenic Patients

Study	Drug	% Decrease in BPRS	Dropouts (% of Patients)
Härnryd et al. 1984	Sulpiride	50	24
	Chlorpromazine	47	28
Farde et al. 1988	Raclopride	64	18
Härnryd et al. 1989	Melperone	76	20
	Placebo	24	40
Wiesel et al. 1994	Ritanserin	30	10
Karlsson et al. 1995b	SCH 39166	10	59

BPRS = Brief Psychiatric Rating Scale.

ued treatment early became more agitated and/or hostile, and three patients were not assessable with BPRS because of lack of cooperation. After discontinuation of SCH 39166 treatment, all of the patients improved when treated with typical antipsychotics or clozapine (Karlsson et al. 1995b).

The lack of improvement in BPRS and CGI scores together with the high withdrawal rate in this study indicate that selective D_1-receptor antagonism with SCH 39166 does not produce antipsychotic effects in schizophrenic patients (Karlsson et al. 1995b). Instead, the lack of placebo effect, the deterioration in some patients, and the symptom improvement after withdrawal of SCH 39166 suggest that selective D_1-receptor antagonism with SCH 39166 may actually aggravate psychoses in some patients with schizophrenia. Although these findings are unexpected based on the effects of selective D_1-receptor antagonists in animal models, they could have been predicted from PET experiments (Sedvall et al. 1995) if the reduced D_1-receptor binding and psychosis are related to endogenously reduced D_1 function in schizophrenia. If confirmed, these observations could have theoretical and possibly practical clinical significance, and should, therefore, motivate controlled clinical evaluation of selective D_1-receptor agonists in schizophrenic patients.

Notably, most of the patients in the SCH 39166 study responded to typical antipsychotics, which further emphasizes the role of D_2-receptor antagonism in antipsychotic action (Karlsson et al. 1995b). The potential of combined D_1- and D_2-receptor antagonism to produce synergistically ameliorative effects in schizophrenia cannot be discounted based on this study alone, because only the effects of selective D_1 blockade were studied. Typical antipsychotics stimulate dopamine synthesis and release in the brain by feedback from D_2 receptors (Nybäck and Sedvall 1968), and such drugs have little effect on D_1 receptors. Consequently, the stimulation of dopamine release by conventional neuroleptics may counteract or normalize the reduced D_1- to D_2-receptor balance observed in PET studies of schizophrenic patients (Sedvall et al. 1995).

Treatment of rhesus monkeys with typical and atypical antipsychotics has shown reduced D_1-receptor densities in the prefrontal cortex, an effect that may have been induced by dopamine release (Lidow and Goldman-Rakic 1994). Of particular interest, typical and atypical antipsychotics seem to down-regulate D_1 receptors in prefrontal and temporal association regions, two areas commonly associated with schizophrenia (Lidow and Goldman-Rakic 1994). Such effects may indicate that atypical as well as typical antipsychotics induce stimulation of D_1-receptor–regulated pathways and increase the D_1-receptor to D_2-receptor balance in the brain (Sedvall and Farde 1995). This common effect may be important for antipsychotic action.

CONCLUSIONS

Progress has been made in the past two decades in understanding the neurophysiology of schizophrenia attributable to advances in the development of selective radioligands and neuroimaging techniques. The role of dopamine in the pathophysiology of schizophrenia continues to be characterized through PET in living human brain, and at higher resolution using postmortem human brain tissue and autoradiographic methods. At present, these techniques have uncovered evidence regarding the increased variability and reduced D_1-receptor binding in the brains of drug-naive schizophrenic patients. This may indicate that the ratio of D_1- over D_2-regulated dopamine signaling in some brain regions is reduced in schizophrenia.

Although selective D_1-receptor antagonism alone has no apparent antipsychotic effect and may actually aggravate the symptoms of schizophrenia, the results of clinical experiments do not rule out synergistically ameliorative effects with combined D_1- and D_2-receptor antagonism. Moreover, the evidence suggests that D_1-receptor agonism may represent an effective pharmacotherapeutic approach in the treatment of schizophrenia.

Confirmation of the efficacy of these pharmacotherapeutic options will require controlled clinical evaluation in schizophrenic patients.

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