Pharmacological Manipulation of D₁-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 D₂-dopamine receptors. Recent data suggest that D₁-dopamine receptors may also play a major role in the pathophysiology of schizophrenia. Using positron emission tomography (PET), increased variability and reduced D₁-receptor binding have been observed in the basal ganglia and frontal cortex of drug-naïve schizophrenia patients. Such alterations have also been found in some in vitro studies. These results suggest that the ratio of D₁- over D₂-regulated dopamine signaling in some brain regions is reduced in schizophrenia. A clinical

trial of SCH 39166, a selective D₁-dopamine receptor antagonist, showed no evidence of antipsychotic activity in schizophrenic patients. Instead, it appeared that selective D₁-receptor antagonism may have aggravated symptoms. Although these findings do not support the prediction that selective D₁-dopamine receptor antagonism produces antipsychotic effects, they do not preclude the possibility that combined D₁- and D₂-receptor antagonism may act synergistically to ameliorate symptoms in schizophrenia. In addition, clinical evaluation of D₁ agonists in schizophrenia should be undertaken. [Neuropsychopharmacology 22:S181-S188, 1999] © 1999 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.

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Dopamine receptors have been divided into two major families, D₁ and D₂, 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 cen-

tral dopamine receptor subtypes (D₁, D₂, D₃, D₄, and D₅) (Sunahara et al. 1993). The D₁-dopamine receptor subfamily consists of two subtypes, D₁ and D₅, and the D₂-receptor subfamily is composed of D₂, D₃, and D₄-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, D₁-like receptors activate adenylyl cyclase; whereas, D₂-like receptors have no effect on or inhibit adenylyl 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 D₂ receptors. Evidence for dopaminergic dysfunction was based on

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observations that the effective antipsychotics are potent antagonists at D₂-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 D₁-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 D₁-dopamine receptor in the pathophysiology of schizophrenia. In addition, this review focuses on emerging evidence concerning the efficacy of pharmacological manipulation of D₁-receptor function in the treatment of schizophrenia.

DOPAMINE RECEPTOR DISTRIBUTION

PET Studies

In PET, high-affinity ¹¹C-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 ¹¹C-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 D₁- and D₂-receptor subfamilies, the pharmacology of the D₂ receptor was well characterized because of the existence of a number of selective D₂-receptor antagonists and agonists (Seeman 1980). More recently, the development of selective antagonists and agonists has enabled the evaluation of the D₁ 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 D₁-receptor antagonist, [¹¹C]SCH 23390 and the selective D₂-receptor antagonist [¹¹C]raclopride. In healthy subjects, a high accumulation of radioactivity in the striatum (caudate nucleus and putamen) was observed with both [¹¹C]SCH 23390 and [¹¹C]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 [¹¹C]SCH 23390 observed in the striatum of monkey brain (Halldin et al. 1986). In contrast to the accumulation of both D₁- and D₂-receptor antagonists in the striatum, [¹¹C]SCH 23390, but not [¹¹C]raclopride, showed a noticeable localization of radioactivity in the neocortex, indicating the relative predominance of D₁ receptors over D₂ receptors in this region (Farde et al. 1987). This result is consistent with studies in monkeys showing D₁-receptor prominence in major cortical areas (Goldman-Rakic et al. 1990; Lidow et al. 1991). The localization of a very low density of D₂ receptors in the human neocortex has also been observed with [¹¹C]raclopride. In humans, [¹¹C]SCH 23390 does not appear to accumulate in the cerebellum, indicating a negligible density of D₁ 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 D₁-dopamine receptors) was 3.0 (Table 1).

Although SCH 23390 is a D₁-receptor antagonist, it also has affinity for other binding sites, such as 5-HT receptors (McQuade et al. 1988; Yamamoto and Keabian 1989). SCH 39166, a benzonaphthazepine, has been characterized both *in vitro* and *in vivo* as a potent and selective D₁-dopamine antagonist (Chipkin et al. 1988). SCH 39166 has a lower affinity for 5-HT receptors, and is thus a more selective D₁ antagonist than SCH 23390 (Taylor et al. 1991). PET studies with [¹¹C]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, [¹¹C]SCH 39166 rapidly passed the blood-brain barrier and accumulated in the stri-

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 D₁ 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 39166 is less suitable as a radioligand for applied PET studies (Karlsson et al. 1995a) (Table 1).

Recently, a new highly selective radioligand, (+)-[¹¹C]NNC 112, was developed for PET. The active (+) enantiomer of [¹¹C]NNC 112 has a high affinity for D₁ 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 (+)-[¹¹C]NNC 112 with PET to examine striatal and neocortical D₁ receptors in cynomolgus monkeys and in healthy male volunteers. Following injection of (+)-[¹¹C]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 [¹¹C]SCH 23390 (Farde et al. 1987). The regional distribution of radioactivity was similar to the distribution of D₁ receptors observed in previous studies using [¹¹C]SCH 23390, with the highest density in the basal ganglia, lower density in the neocortex, and with negligible presence of D₁ 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 D₁ receptors are also found in the cerebral cortex, there are only minute amounts of D₂ 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- μ m thin sections, offering 50- μ m resolution (Sedvall and Farde 1995). The density and distribution of D₁ and D₂ 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 [³H]SCH 23390 and [³H]raclopride as radioligands, D₂ 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 D₁ 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 D₁ receptors in the medial caudate nucleus has also been observed in human postmortem autoradiographic studies with [³H]SCH 39166 (Hall et al. 1993). This specific distribution pattern of the D₁ receptors in the medial basal ganglia has not been observed in more recent PET studies (Hall et al. 1994). Autoradiographic examination of [¹¹C]NNC 687 and [¹¹C]NNC 756, two selective D₁ radioligands with favorable signal-to-noise ratios, in postmortem human brain sections confirmed the high density of D₁ receptors in the striatum (Halldin et al. 1993).

As in PET studies, marked labeling of the D₁-dopamine receptor in human cortical regions by [³H]SCH 23390 has been observed using autoradiography (Hall et al. 1988, 1993). This result is supported by findings using the more selective D₁-receptor ligand [³H]SCH 39166 (Hall et al. 1993). In vitro autoradiography using a new ¹²⁵I-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 D₁ receptors and low densities of D₂ in the cerebral cortex (Hall et al. 1994) and that the levels of D₁ receptors in the cortex are lower than in the striatum (Hall et al. 1988). Thus, the human postmortem studies show that the densities of D₁ and D₂ receptors roughly parallel each other, although the D₁ 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 D₁- and D₂-receptor subtypes (Sunahara et al. 1993).

A heterogeneous distribution of D₁-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, [³H]SCH 23390 autoradiography was combined with *in situ* hybridization to compare the regional distribution of D₁-receptor binding sites to the distribution of cells expressing mRNAs encoding D₁ receptors in the cynomolgus monkey brain (Brené et al. 1995). Using these techniques, it was possible to show that D₁-receptor mRNA-positive cells were unevenly distributed in the striatum (Brené et al. 1995). Specifically, D₁-receptor mRNA was higher in the caudate nucleus than in the putamen, possibly indicating stronger D₁-receptor influence in the caudate. Clusters of cells with a threefold higher intensity of D₁-receptor mRNA expression were found in the caudate nucleus and putamen, as compared to surrounding regions. In general, the distribution of D₁ receptors as shown by [3H]SCH 23390 binding was more homogeneous than the D₁ mRNA distribution, although some of the D₁ 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 D₁-receptor mRNA in neocortex was more distinct and heterogeneous than the binding of [3H]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 D₁-receptor mRNA in layers II–VI of neocortex, with D₁-receptor mRNA-positive cells

most abundant in layer V. The differential distribution of D₁-receptor, mRNA-positive cells to different layers of neocortex and in cells with different sizes implies that dopamine acting through D₁ 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 D₁-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 D₂-dopamine receptors in the brain (Mackay et al. 1980; Owen et al. 1978; Seeman et al. 1984). However, most data supporting a role for D₂ receptors in schizophrenia come from postmortem studies in patients who were previously treated with typical antipsychotics (D₂ antagonists), and increased D₂ 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 D₂-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 [¹¹C]raclopride in healthy subjects and neuroleptic-naïve schizophrenic patients found no significant difference in D₂-receptor density (B_{max}) or affinity (K_d) in caudate nucleus or putamen (Farde et al. 1990). In addition, a normal density of D₂ receptors in the striatum of neuroleptic-naïve schizophrenic patients was observed in a PET study using the radioligand [¹¹C]N-methylspiperone ([¹¹C]NMSP) (Nordström et al. 1995).

The lack of an apparent difference in striatal D₂-receptor density fails to support the hypothesis that schizophrenia is related to an increased density of D₂ 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, D₁-dopamine receptors have been proposed to play an important role in the pathophysiology of schizophrenia (Goldman-Rakic 1994; Lynch 1992).

Alterations in D₁-receptor binding have been observed in some (but not all) studies. One postmortem study investigating the radioligand binding properties of D₁ and D₂ receptors found a significant difference in the ratio of D₁ to D₂ receptors between schizophrenic

patients and healthy controls and a decrease in striatal D₁-receptor density in schizophrenics (Hess et al. 1987). More recently, PET studies examined D₁ and D₂ receptor characteristics in young drug-naïve 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 D₁ and D₂ receptors in the caudate and putamen were not significantly different between schizophrenic patients and healthy controls. However, there was a significant reduction in D₁ signal in high-intensity regions of the basal ganglia when [¹¹C]SCH 23390 was used. These results suggest the possibility of reduced D₁-receptor density in the patch compartment of the basal ganglia in schizophrenic patients (Sedvall et al. 1995). It should be noted that low D₁-receptor density in this compartment may result in the reduced activity of the D₁/D₂ regulatory feedback system to limbic brain regions in schizophrenia (Sedvall and Farde 1995).

Okubo et al. (1997) conducted a PET study using [¹¹C]SCH 23390 and [¹¹C]NMSP as tracers to examine the distribution of D₁ and D₂ receptors, respectively, in brains of drug-naïve or drug-free schizophrenic patients. The study failed to detect any difference in either the striatal D₁ receptors or the ratio of D₁ to D₂ receptors in the striatum. However, the mean values of D₁-receptor binding affinity in the prefrontal cortex for both drug-naïve and drug-free schizophrenic patients were significantly lower than for the control group. The decreased D₁-receptor binding in drug-naïve schizophrenic patients implies that the D₁-receptor system in the prefrontal cortex may be involved in schizophrenia. This study also showed that the reduction in prefrontal D₁ 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 D₁-receptor modulation in the prefrontal cortex may contribute to the negative symptoms and cognitive deficits observed in schizophrenia (Okubo et al. 1997).

D₁-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 D₂-dopamine receptors (Creese et al. 1976; Seeman et al. 1976). Clinical support for a role of D₁ receptors in schizophrenia is based on the observation that the "atypical" antipsychotic drug clozapine produces a relatively high D₁-receptor occupancy (33% to 59%) in the putamen (Farde et al. 1992, 1994). Although clozapine

occupies D₂ receptors to a smaller extent than typical antipsychotics, its occupation of D₁ receptors is greater than that of typical antipsychotics (~40% versus 0%–36%). Thus, the unique clinical profile of clozapine may be related to its activity at both D₁ and D₂ receptors (Wiesel et al. 1990).

SCH 39166

As reviewed in the present paper, the selective D₁ receptor antagonist SCH 39166 has been used to investigate the distribution and density of D₁ receptors in both human postmortem studies (Hall et al. 1993) and PET studies (Karlsson et al. 1995a). SCH 39166 is the first selective D₁-receptor antagonist developed for clinical trials. SCH 39166 was developed for clinical trials in schizophrenia, in part, because animal models predicted that selective D₁-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% D₁-receptor occupancy in the basal ganglia, which is sufficient to investigate the antipsychotic potential of D₁-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% D₁-receptor occupancy in the striatum. This is similar to the occupancy obtained by selective D₂-receptor antagonists in doses that produce antipsychotic effects, but higher than the D₁-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	Ritanserlin	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 D₁-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 D₁-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 D₁-receptor antagonists in animal models, they could have been predicted from PET experiments (Sedvall et al. 1995) if the reduced D₁-receptor binding and psychosis are related to endogenously reduced D₁ function in schizophrenia. If confirmed, these observations could have theoretical and possibly practical clinical significance, and should, therefore, motivate controlled clinical evaluation of selective D₁-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 D₂-receptor antagonism in antipsychotic action (Karlsson et al. 1995b). The potential of combined D₁- and D₂-receptor antagonism to produce synergistically ameliorative effects in schizophrenia cannot be discounted based on this study alone, because only the effects of selective D₁ blockade were studied. Typical antipsychotics stimulate dopamine synthesis and release in the brain by feedback from D₂ receptors (Nyback and Sedvall 1968), and such drugs have little effect on D₁ receptors. Consequently, the stimulation of dopamine release by conventional neuroleptics may counteract or normalize the reduced D₁- to D₂-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 D₁-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 D₁ 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 D₁-receptor-regulated pathways and increase the D₁-receptor to D₂-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 D₁-receptor binding in the brains of drug-naïve schizophrenic patients. This may indicate that the ratio of D₁- over D₂-regulated dopamine signaling in some brain regions is reduced in schizophrenia.

Although selective D₁-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 D₁- and D₂-receptor antagonism. Moreover, the evidence suggests that D₁-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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REFERENCES

- Brené S, Hall H, Lindefors N, Karlsson P, Halldin C, Sedvall G (1995): Distribution of messenger RNAs for D₁-dopamine receptors and DARP-32 in striatum and cerebral cortex of the cynomolgus monkey: Relationship to D₁ dopamine receptors. *Neuroscience* 67:37–48
- Burt DR, Creese I, Snyder SH (1977): Antischizophrenic drugs: Chronic treatment elevated dopamine receptor binding in brain. *Science* 196:326–328
- Chipkin RE, Iorio LC, Coffin VL, McQuade RD, Berger JG, Barnett AJ (1988): Pharmacological profile of SCH 39166: A dopamine D₁ selective benzonaphthazepine with potential antipsychotic activity. *J Pharmacol Exp Ther* 247:1093–1102
- Clow A, Theodorou A, Jenner P (1980): Changes in rat striatal dopamine turnover and receptor activity during one year's neuroleptic administration. *Eur J Pharmacol* 63:135–144
- Creese I, Burt DR, Snyder SH (1976): Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science* 192:481–483
- Farde L, Halldin C, Stone-Elander S, Sedvall G (1987): PET analysis of human dopamine receptor subtypes using ¹¹C-SCH 23390 and ¹¹C-raclopride. *Psychopharmacology* 92:278–284
- Farde L, Nordström A-L, Nyberg S, Halldin C, Sedvall G (1994): D₁-, D₂- and 5-HT₂-receptor occupancy in clozapine-treated patients. *J Clin Psychiat* 55:67–69
- Farde L, Nordström A-L, Wiesel F-A, Pauli S, Halldin C, Sedvall G (1992): Positron emission tomographic analysis of central D₁ and D₂ dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. *Arch Gen Psychiat* 49:538–544
- Farde L, Wiesel F-A, Jansson P, Uppfeldt G, Wahlen A, Sedvall G (1988): An open label trial of raclopride in acute schizophrenia. Confirmation of D₂-dopamine receptor occupancy by PET. *Psychopharmacology* 94:1–7
- Farde L, Wiesel F-A, Stone-Elander S, Halldin C, Nordström A-L, Hall H, Sedvall G (1990): D₂ dopamine receptors in neuroleptic-naïve schizophrenic patients. A positron emission tomography study with [¹¹C]raclopride. *Arch Gen Psychiat* 47:213–219
- Goldman-Rakic P (1994): Cerebral cortical mechanisms in schizophrenia. *Neuropsychopharmacology* 10:225–275
- Goldman-Rakic PS, Lidow MS, Gallager DW (1990): Overlap of dopaminergic, adrenergic, and serotonergic receptors and complementarity of their subtypes in primate prefrontal cortex. *J Neurosci* 10:2125–2138
- Hall H, Farde L, Sedvall G (1988): Human dopamine receptor subtypes—In vitro binding analysis using ³H-SCH 23390 and ³H-raclopride. *J Neural Transm* 73:7–21
- Hall H, Halldin C, Guilloteau D, Chalon S, Emond P, Besnard J, Farde L, Sedvall G (1999): Visualization of the dopamine transporter in the human brain postmortem with the new selective ligand [125I]PE2I. *Neuroimage* 9:108–116
- Hall H, Halldin C, Sedvall G (1993): Binding of [³H]SCH 39166 to human post mortem brain tissue. *Pharmacol Toxicol* 72:152–158
- Hall H, Sedvall G, Magnusson O, Kopp J, Halldin C, Farde L (1994): Distribution of D₁- and D₂-dopamine receptors, and dopamine and its metabolites in the human brain. *Neuropsychopharmacology* 11:245–256
- Halldin C, Farde L, Barnett A, Sedvall G (1991): Synthesis of carbon-11 labeled SCH 39166, a new selective dopamine D-1 receptor ligand, and preliminary PET investigations. *Int J Radiat Appl Instrum* 42:451–455
- Halldin C, Foged C, Chou YH, Karlsson P, Swahn CG, Sandell J, Sedvall G, Farde L (1998): Carbon-11-NNC 112: A radioligand for PET examination of striatal and neocortical D₁-dopamine receptors. *J Nucl Med* 39:2061–2068
- Halldin C, Foged C, Farde L, Karlsson P, Hansen K, Grønvald F, Swahn CG, Hall H, Sedvall G (1993): [¹¹C]NNC 687 and [¹¹C]NNC 756, dopamine D-1 receptor ligands. Preparation, autoradiography, and PET investigation in monkey. *Nucl Med Biol* 20:945–953
- Halldin C, Stone-Elander S, Farde L, Ehrin E, Fasth KJ, Långström B, Sedvall G (1986): Preparation of ¹¹C-labeled SCH 23390 for the in vivo study of dopamine D-1 receptors using positron emission tomography. *Int J Radiat Appl Instrum* 37:1039–1043
- Härnryd C, Bjerkenstedt L, Björk K, Gullberg B, Oxenstierna G, Sedvall G, Wiesel F-A, Wik G, Åberg-Wistedt A (1984): Clinical evaluation of sulpiride in schizophrenic patients—A double-blind comparison with chlorpromazine. *Acta Psychiat Scand* 311:7–30
- Härnryd C, Bjerkenstedt L, Gullberg B (1989): A clinical comparison of melperone and placebo in schizophrenic women on a milieu therapeutic ward. *Acta Psychiat Scand* 352:40–47
- Hess EJ, Bracha HS, Kleinman JE, Creese I (1987): Dopamine receptor subtype imbalance in schizophrenia. *Life Sci* 40:1487–1497
- Hietala J, Syvälahti E, Vuorio K, Någren K, Lehtinen V, Ruotsalainen U, Rakkolainen V, Lehtinen V, Wegelius U (1994): Striatal D₂ dopamine receptor characteristics in neuroleptic-naïve schizophrenic patients studied with positron emission tomography. *Arch Gen Psychiat* 51:116–123
- Karlsson P, Sedvall G, Halldin C, Swahn CG, Farde L (1995a): Evaluation of SCH 39166 as PET ligand for central D₁ dopamine receptor binding and occupancy in man. *Psychopharmacology* 121:300–308
- Karlsson P, Smith L, Farde L, Härnryd C, Sedvall G, Wiesel F-A (1995b): Lack of apparent antipsychotic effect of the

- D₁-dopamine receptor antagonist SCH39166 in acutely ill schizophrenic patients. *Psychopharmacology* 121:309–316
- Lachowicz JE, Sibley DR (1997): Molecular characteristics of mammalian dopamine receptors. *Pharmacol Toxicol* 81:105–113
- Lidow MS, Goldman-Rakic PS (1994): A common action of clozapine, haloperidol, and remoxipride on D₁- and D₂-dopaminergic receptors in the primate cerebral cortex. *Proc Nat Acad Sci USA* 91:4353–4356
- Lidow MS, Goldman-Rakic PS, Gallager DW, Rakic P (1991): Distribution of dopaminergic receptors in the primate cerebral cortex: Quantitative, autoradiographic analysis using [³H]raclopride, [³H]spiperone, and [³H]SCH23390. *Neuroscience* 40:657–671
- Lieberman JA, Kane JM, Alvir J (1987): Provocative tests with psychostimulant drugs in schizophrenia. *Psychopharmacology* 91:415–433
- Lynch MR (1992): Schizophrenia and the D₁ receptor: focus on negative symptoms. *Prog Neuropsychopharmacol Biol Psychiat* 16:797–832
- Mackay AVP, Bird E, Spokes EG (1980): Dopamine receptors and schizophrenia: Drug effect or illness? *Lancet* 2:915–916
- McQuade RD, Ford D, Duffy RA, Chipkin RE, Iorio L, Barnett A (1988): Serotonergic component of SCH23390: In vitro and in vivo binding analyses. *Life Sci* 43:1861–1869
- Nielsen EB, Andersen PH (1992): Dopamine receptor occupancy in vivo: Behavioral correlates using NNC-112, NNC-687 and NNC-756, new selective dopamine D₁ receptor antagonists. *Eur J Pharmacol* 219:35–44
- Nordström A-L, Farde L, Eriksson L, Halldin C (1995): No elevated D₂ dopamine receptors in neuroleptic-naïve schizophrenic patients revealed by positron emission tomography and [¹¹C]N-methylspiperone. *Psychiat Res* 61:67–83
- Nyback H, Sedvall G (1968): Effect of chlorpromazine on accumulation and disappearance of catecholamines formed from tyrosine-C¹⁴ in brain. *J Pharmacol Exp Ther* 162:294–301
- Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, Someya Y, Sassa T, Sudo Y, Matsushima E, Iyo M, Tateno Y, Toru M (1997): Decreased prefrontal dopamine D₁ receptors in schizophrenia revealed by PET. *Nature* 385:634–636
- Owen F, Cross AJ, Crow TJ, Longden A, Poulter M, Riley GJ (1978): Increased dopamine-receptor sensitivity in schizophrenia. *Lancet* 2:223–226
- Owen F, Cross AJ, Waddington JL (1980): Dopamine-mediated behavior and 3H-spiperone binding to striatal membranes in rats after 9 months' haloperidol administration. *Life Sci* 26:55–59
- Rappaport MS, Sealfon SC, Prikhozhan A, Huntley GW, Morrison JH (1993): Heterogeneous distribution of D₁, D₂, and D₅ receptor mRNAs in monkey striatum. *Brain Res* 616:242–250
- Sedvall GC (1996): Neurobiological correlates of acute neuroleptic treatment. *Int Clin Psychopharmacol* 11:41–46
- Sedvall GC, Farde L (1995): Chemical brain anatomy in schizophrenia. *Lancet* 346:743–749
- Sedvall GC, Farde L, Barnett A, Hall H, Halldin C (1991): [¹¹C]-SCH 39166, a selective ligand for visualization of dopamine-D₁ receptor binding in the monkey brain using PET. *Psychopharmacology* 103:150–153
- Sedvall GC, Farde L, Nyback H, Pauli S, Persson A, Savic I, Wiesel F-A (1990): Recent advances in psychiatric brain imaging. *Acta Radiol Suppl* 374:113–115
- Sedvall GC, Farde L, Persson A, Wiesel F-A (1986): Imaging of neurotransmitter receptors in the living human brain. *Arch Gen Psychiat* 43:995–1005
- Sedvall GC, Pauli S, Karlsson P, Farde L, Nordström A-L, Nyberg S, Halldin C (1995): PET imaging of neuroreceptors in schizophrenia. *Eur Neuropsychopharmacol* 5:25–30
- Seeman P (1980): Brain dopamine receptors. *Pharmacol Rev* 32:229–313
- Seeman P, Lee T, Chau-Wong M, Wong K (1976): Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* 261:717–719
- Seeman P, Ulpian C, Bergeron C, Riederer P, Jellinger K, Gabriel E, Reynolds GP, Tourtelotte WW (1984): Bimodal distribution of dopamine receptor densities in brain of schizophrenics. *Science* 225:728–730
- Sunahara RK, Seeman P, Van Tol HHM, Niznik HB (1993): Dopamine receptors and antipsychotic drug response. *Br J Psychiat* 163:31–38
- Taylor LA, Tedford CE, McQuade RD (1991): The binding of SCH 39166 and SCH 23390 to 5-HT_{1C} receptors in porcine choroid plexus. *Life Sci* 49:1505–1511
- Wiesel F-A, Farde L, Nordström A-L, Sedvall G (1990): Central D₁- and D₂-receptor occupancy during antipsychotic drug treatment. *Prog Neuropsychopharmacol Biol Psychiat* 14:759–767
- Wiesel F-A, Nordström A-L, Farde L, Eriksson B (1994): An open clinical and biochemical study of ritanserin in acute patients with schizophrenia. *Psychopharmacology* 114:31–38
- Wong DF, Wagner HN Jr, Tune LE, Dannals RF, Pearson GD, Links JM, Tamminga CA, Broussolle EP, Ravert HT, Wilson AA, Toung JKT, Malat J, Williams FA, O'Touma LA, Snyder SH, Kuhar MJ, Gjedde A (1986): Positron emission tomography reveals elevated D₂-dopamine receptors in drug-naïve schizophrenics. *Science* 234:1558–1563
- Yamamoto T, Keabian JW (1989): [¹²⁵I]SCH23982 binds to a serotonin receptor (and not to a D-1 dopamine receptor) in the rat choroid plexus. *Biogen Amines* 6:241–246