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

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- Positron emission tomography and selective radioligands were used to determine D₁ and D₂ dopamine receptor occupancy induced by neuroleptics in the basal ganglia of drug-treated schizophrenic patients. In 22 patients treated with conventional dosages of classical neuroleptics, the D₂ occupancy was 70% to 89%. Patients with acute extrapyramidal syndromes had a higher D₂ occupancy than those without side effects. This finding indicates that neuroleptic-induced extrapyramidal syndromes are related to the degree of central D₂ occupancy induced in the basal ganglia. In five patients treated with clozapine, the prototype atypical antipsychotic drug, a lower D₂ occupancy of 38% to 63% was found. This finding demonstrates that clozapine is also "atypical" with respect to the central D₂ occupancy in patients. During treatment with clozapine, there is a low frequency of extrapyramidal syndromes, which accordingly may reflect the comparatively low D₂ occupancy induced by clinical doses of clozapine. Classical neuroleptics, like haloperidol or sulpiride, did not cause any evident D₂ occupancy, but the thioxanthene flupentixol induced a 36% to 44% occupancy. In four patients treated with clozapine, the D₂ occupancy was 38% to 52%. The D₂ occupancy induced by clozapine and flupentixol may contribute to the antipsychotic effect of these drugs.

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According to the dopamine hypothesis, the antipsychotic effect of neuroleptics is mediated by blockade of D₂ dopamine receptors.1-6 Using positron emission tomography (PET) and suitable radioligands, D₂ dopamine receptor occupancy has been determined previously in the basal ganglia of neuroleptic drug-treated patients. The dopamine hypothesis has been supported by consistent PET findings of a high D₂ dopamine receptor occupancy in patients treated with conventional clinical doses of all the chemically distinct classes of antipsychotic drugs.6,7

The D₂ dopamine receptor was the first of the dopamine receptor subtypes for which a biochemical effector system was described.10 Pharmacologic effects induced by drugs interacting with the D₂ dopamine receptor have been investigated extensively in experimental animals but so far not in man.11 Preliminary PET studies on D₂ dopamine receptor occupancy in neuroleptic drug-treated patients12,13 confirm the finding in vitro14 that some neuroleptics, but not all, interact with D₂ dopamine receptors.

The concept classical neuroleptics refers to drugs that induce antipsychotic effect and extrapyramidal syndromes (EPS) in man and have a cataleptic effect in animals.15,16 The ability to evaluate serum prolactin levels by blockade of D₂ dopamine receptors in the pituitary is another common property of classical neuroleptics.17 Most of the presently used antipsychotic drugs satisfy these criteria for a classical neuroleptic. Clozapine, however, is an antipsychotic drug with a very low incidence of EPS and only a slight and short-lasting effect on plasma prolactin levels.18-21 In addition, clozapine was recently demonstrated to be efficacious in some patients not responding to treatment with classical neuroleptics.22 Based on these observations, clozapine is often referred to as an antipsychotic with atypical effects. The clarification of how clozapine produces its atypical effects may provide guidelines for drug development and for clarifying the pathophysiologic features of schizophrenia.

Long before the advent of neuroleptic drugs, EPS were described in association with degenerative disorders of the basal ganglia. Neuroleptic-induced EPS are generally believed to be mediated by drug interference with dopamine transmission in the basal ganglia. A potential with PET is to relate central receptor binding quantitatively to pharmacologic effects induced in the same human subject. The performance of currently used PET camera systems allows determination of receptor binding in the human basal ganglia23-24 which is the proposed site of action for drug-induced EPS. It is accordingly of interest to examine the degree of central D₂ dopamine receptor occupancy and its relationship to EPS in patients treated with classical neuroleptics and clozapine.

The aim of this study was to examine if clozapine, besides its clinical effects, is also atypical with respect to biochemical factors in the human brain. Central D₁ and D₂ dopamine

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## Treatment Characteristics

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*EPS indicates extrapyramidal syndromes.
†No assay available for analysis.
‡Sample lost during transportation.

Receptor occupancy was determined by PET in patients treated with classical neuroleptics and clozapine. Extrapyramidal syndromes were recorded and related to the degree of D<sub>2</sub> dopamine receptor occupancy in the putamen.

**Subjects and Methods**

The study was approved by the Ethics and Radiation Safety Committees of the Karolinska Hospital, Stockholm, Sweden. The subjects participated after having given informed consent.

For the calculation of D<sub>2</sub> dopamine receptor occupancy, a control group was used that included 18 neuroleptic-naive first-hospital-admission schizophrenic patients (10 men and eight women) with an average age of 24.2 years (range, 18 to 29 years). This patient group has been described in detail previously. For the calculation of D<sub>2</sub> dopamine receptor occupancy, another control group was used that included 10 healthy subjects (seven male and three female) with an average age of 28.8 years (range, 22 to 37 years). They were healthy according to history and results of physical examination and blood and urine biochemistry studies. Exclusion criteria were as follows: organic mental disorder, alcohol or substance abuse or psychiatric disorder according to DSM-III, somatic disorder, history of head injury with loss of consciousness for more than 5 minutes or cranial fracture, and pregnancy.

For the determination of D<sub>2</sub> dopamine receptor occupancy, patients with a schizophreniform or schizophrenic disorder according to DSM-III and receiving monotherapy with a conventional dosage of an antipsychotic drug were selected. Patients should have been receiving neuroleptic drug treatment for at least 4 weeks. With the exception for schizophrenia, the exclusion criteria were those listed above for the healthy subjects.

Twenty-eight patients (18 male and 10 female) with an average age of 30.5 years (range, 18 to 49 years) were recruited at the Department of Psychiatry and Psychology, the Karolinska Hospital. Eighteen patients were treated with oral doses of a classical neuroleptic (Table). Five patients were treated with a depot formulation of a classical neuroleptic. Five patients were treated with clozapine because of a poor response to classical neuroleptics.

Concomitant medication for sedation was allowed with occasional doses of oxazepam (Sobril, 15 or 25 mg, Kabi, Stockholm, Sweden) or diazepam (Valium, 2 or 5 mg, Roche, Stockholm, Sweden). To treat EPS, biperiden hydrochloride (Akineton, 2 mg, Meda, Gothenborg, Sweden) was allowed but not during the 72 hours preceding the PET examination. Three of the patients with EPS had been given single doses and two repeated...
doses of biperiden during the month before the PET experiment. All the 28 patients had responded to neuroleptic drug treatment and within 1 month after the PET examination, 24 of them were outpatients. The other four patients were referred to units for intermediate care. At time of the PET examination, they had been receiving antipsychotic drug treatment with a fixed dosage for at least 4 weeks. Most patients had been treated for a short time. The median time receiving classical neuroleptics was 2 months, including time receiving other doses or other neuroleptics (range, 1 to 60 months). The median time receiving clozapine was 5 months (range, 2 to 69 months). In relation to the PET examination, all the patients were rated "much improved" or "very much improved" on the Clinical Global Impression Scale. Extra pyramidal syndromes were recorded immediately before the PET examination based on results of a neurologic examination and according to the rating scale for extrapyramidal side effects and the rating scale for drug-induced akathisia. The rater knew the drug and dosage used for the treatment but not the dopamine receptor occupancy. The severity of the akathisia indicated in the Table was at least "mild" according to the rating scale for drug-induced akathisia. In the patients with parkinsonism, at least one item indicating rigidity on the rating scale for extrapyramidal side effects was rated "2" or more.

In all the 28 drug-treated patients, a PET examination was made for the determination of D2 dopamine receptor occupancy. In 12 of them, an additional PET examination was performed for the determination of D1 dopamine receptor occupancy. In one of the patients, due to a computer malfunction, only D1 but not D2 dopamine receptor occupancy could be calculated. In the patients treated with oral formulations, the PET examinations were performed at 2 pm, ie, 6 hours after the morning dose was given. In patients treated with depot formulations, the PET examinations were performed at 2 pm 1 week after the last injection. In the patient treated with clozapine 300 mg × 2, two PET examinations were performed for determination of D2 dopamine receptor occupancy. The first was made at 3 hours and the second at 6 hours after clozapine administration.

**PET Determination of Dopamine Receptor Occupancy**

Radioligands for PET determination of D1 and D2 dopamine receptor occupancy were [11C]raclopride and [11C]SCH23390, respectively. They were prepared by methylation of the desmethyl precursor analogues using [11C]methyliodide. The specific activity was 4 to 50 GBq/µmol for [11C]raclopride and 8 to 60 GBq/µmol for [11C]SCH23390. The PET system (PC-384-7B, Scanditronix, Uppsala, Sweden) at the Department of Neuroradiology, Karolinska Hospital, Stockholm, was used to follow radioactivity in seven sections of the brain. Each study comprised 11 to 12 sequential scans during a period of 45 to 51 minutes. A plaster helmet was made for each individual and was used with a head fixation system both during computed tomography (CT) and PET. The head fixation system made transfer of the positioning from CT to PET feasible. To optimize and standardize the position of the caudate nucleus and the putamen within a PET section, Monsone's foramen was identified by CT. A level 3 mm above Monsone's foramen was chosen as the transaxial midpoint of the PET and the CT section 4.

Regions of interest were drawn for the cerebellum and the putamen. Regional radioactivity was measured for each sequential scan, corrected for [11C] decay and plotted vs time. Total radioactivity in the cerebellum, a region with negligible densities of D1 and D2 dopamine receptors, was used as an estimate of CO, the free radioligand concentration in brain. Specific binding in the putamen (CI), a region with a high density of D1 and D2 dopamine receptors, was defined as the difference between total radioactivity in the putamen (C) and the free radioligand concentration (C0).

The theory underlying calculation of dopamine receptor occupancy by PET has been presented in the ARCHIVES earlier. In summary, the ratio of specific binding (CI) to free radioligand concentration (C0) was calculated for each experiment at time of equilibrium. If a neuroleptic drug binds to the receptor population of interest, and thereby occupies a certain proportion of the receptors, this will be reflected in a reduced number of receptors available for radioligand binding. The reduction in number of available receptors is proportional to a reduction in the ratio C0/C1. Dopamine receptor occupancy (R) was expressed in percent and calculated according to the following equation: R = IC0/C1 (ref) - C0/C1 (drug)] × 100/C0/C1 (ref), where the reference value C0/C1 (ref) is the average ratio obtained in control subjects and C0/C1 (drug) is the individual ratio in a drug-treated patient.

**Statistics**

D3 dopamine receptor occupancy was determined in patients treated with classical neuroleptics (n = 22) with EPS (n = 11) and without EPS (n = 11) and in patients treated with clozapine (n = 5). The groups were normally distributed according to Shapiro-Wilk test indicating normality on the P < 0.01 level. Groups were compared by Student's t test for independent samples considering the different SDs using a specific program (Minutab) implemented in a computer (VAX).

**RESULTS**

After intravenous injection of [11C]raclopride into 18 neuroleptic-naive schizophrenic patients, there was a marked accumulation of radioactivity in the basal ganglia. This high uptake is illustrated by Figs 1, top, and 2, top. The average ratio, C0/C1, for [11C]raclopride binding in the 18 patients was 3.04 (SEM = 0.11; range, 2.3 to 4.3). After intravenous injection of [11C]SCH23390 into 10 healthy subjects, there was also a marked accumulation of radioactivity in the basal ganglia. The average ratio, C0/C1, for [11C]SCH23390 binding in the 10 subjects was 1.96 (SEM = 0.06; range, 1.7 to 2.3).

**Effect of Antipsychotic Drugs on D2 Dopamine Receptor Occupancy**

D3 dopamine receptor occupancy was determined in 27 antipsychotic drug-treated patients. After intravenous injection of [11C]raclopride into 22 patients treated with classical neuroleptics, there was a markedly reduced accumulation of radioactivity in the basal ganglia when compared with the control patients. The low accumulation in the neuroleptic-treated patients is illustrated by Figs 1, center, and 2, center. The ratio of specific [11C]raclopride binding to free radioligand concentration, C0/C1, ranged from 0.33 and 0.90 and the calculated D3 dopamine receptor occupancy ranged between 70% and 89% (78 ± 6, average ± SD) (Table).

In the five patients treated with the atypical neuroleptic clozapine, the D3 dopamine receptor occupancy was 38% to 63% (48 ± 11, average ± SD). This moderate occupancy is illustrated by Figs 1, bottom, and 2, bottom. This occupancy was lower than in any of the 22 patients treated with classical neuroleptics (P < .01). In one patient treated with clozapine 300 mg × 2, two PET experiments were performed 3 and 6 hours after clozapine administration, respectively. In the first experiment, the D3 dopamine receptor occupancy was 59% and in the second it was 63%.

**EPS and D3 Dopamine Receptor Occupancy**

Extra pyramidal syndromes were recorded in 11 of the 22 patients in whom D3 dopamine receptor occupancy was determined during treatment with classical neuroleptics (Table, Fig 3). The patients who had EPS had an average D3 dopamine receptor occupancy of 82% (SD = 4%). The 11 patients who did not have extrapyramidal side effects had an average occupancy of 74% (SD = 4%), which is lower (P < .001) than in the patients who exhibited EPS.

**Effect of Antipsychotic Drugs on D3 Dopamine Receptor Occupancy**

D3 dopamine receptor occupancy was determined in 12 antipsychotic drug-treated patients (Table). After intravenous injection...
of a ratio measured in a separate PET experiment in each patient before treatment introduces a small error in the calculation of D₂ dopamine receptor occupancy for each individual. The following example illustrates this error. If the measured ratio for [¹¹C]raclopride binding is 0.61 in a drug-treated patient, the calculated receptor occupancy will be 80% using the average ratio of 3.04. If the extreme values of 2.3 or 4.3 are used, the calculated receptor occupancy will be 74% or 86%, respectively. Five of the 28 patients had been examined by PET before treatment with neuroleptics. In none of the patients, the D₂ dopamine receptor occupancy calculated on the basis of the individual ratio was more than 3% different from the occupancy based on the average ratio.

No effect of sex has been reported on central D₂ dopamine receptor density (Farde et al, unpublished data, 1990). A nonlinear negative effect of age on D₂ dopamine receptor binding has been reported for spiperone derivatives.³⁷,³⁸ The mean age was 24.3 years (median, 24 years; range, 18 to 29 years) for the 18 control patients of the present study and 31.6 years (median, 29 years; range, 20 to 43 years) for the neuroleptic drug-treated patients. For the control patients, a linear regression analysis of the Cₚ/Cₚ ratio vs age gave a negative regression coefficient of −0.09. Analysis of the confidence interval for this regression coefficient indicated a statistically significant age effect (P = .014).³⁹ For some patients, D₂ dopamine receptor occupancy values would be lower with correction for this age effect. We have not applied an age correction since the regression coefficient calculated is based only on a linear analysis of a narrow interval in the low age range. The age-corrected D₂ dopamine receptor occupancies would be lower in particular for the clozapine-treated patients who had a comparative high mean age of 41 years. The statistically significant difference between clozapine-treated patients and those treated with classical neuroleptics would thus be even more significant if a negative effect of age on the D₂ receptor binding was considered.

A 30% to 70% upregulation of D₂ dopamine receptor densities has been demonstrated consistently in animal experiments after administration of classical neuroleptic drugs.⁴⁰-⁴² It has also been suggested that elevated D₂ dopamine receptor densities found in schizophrenic brains post mortem may have been caused by neuroleptic drug treatment during lifetime.⁴³,⁴⁴ We have reported previously a high D₂ dopamine receptor density with a ratio Cₚ/Cₚ of 4.6 as measured by PET in a patient 2 weeks after withdrawal from sulpiride treatment.²⁵ Seven weeks later, the ratio was 3.1, which is close to the average value of 3.04 in controls. These findings suggest upregulation of the receptor density during clinical treatment with neuroleptic drugs. If the value for Cₚ/Cₚ of 4.6 obtained in this patient is used in the example in the previous paragraph, the "true" D₂ dopamine receptor occupancy will be 87% instead of 80%. This example indicates that D₂ dopamine receptor occupancy is underestimated in patients with a neuroleptic-induced upregulation of the D₂ dopamine receptor density. Upregulation is in all probability a dose-dependent effect, i.e., more marked in patients treated with high doses and with high D₂ dopamine receptor occupancy. If that is the case, D₂ dopamine receptor occupancy will be more underestimated in patients with high occupancy. The demonstrated significant differences in D₂ dopamine receptor occupancies between classical neu-

**TECHNICAL COMMENTS**

In this study, an average ratio Cₚ/Cₚ of 3.04 (range, 2.3 to 4.3) for [¹¹C]raclopride binding in untreated schizophrenic patients was used to calculate D₂ dopamine receptor occupancy. This use of an average ratio instead
roleptics and clozapine as well as between patients with EPS and those without side effects are accordingly more significant if upregulation occurs.

An effect of endogenous dopamine on the binding of tritiated raclopride has been demonstrated by Seeman.45 Classical neuroleptics increase the extracellular concentration of dopamine in the rat striatum as demonstrated with brain dialysis.46 The increase is dose dependent and at most twofold following both single and repeated administration of a neuroleptic.47 This twofold increase is low compared with the 40-fold maximal increase demonstrated after administration of amphetamine to rats.48 In a yet-unpublished study (L. Farde and C. Hallidin, unpublished data), [11C]raclopride binding was examined before and 90 minutes after oral administration of 30 mg of amphetamine sulphate to three healthy subjects. There were evident pharmacologic effects, but [11C]raclopride binding was only reduced by 6%, 10%, and 16%. It is thus not likely that the comparatively small increase in dopamine concentration following neuroleptic drug treatment will have a major effect on [11C]raclopride binding.

For [11C]SCH23390 binding to D1 dopamine receptors, the reference ratio C0/C1 was the average ratio calculated from 10 healthy subjects, 1.96 (range, 1.7 to 2.3). If the measured ratio for [11C]SCH23390 binding is 1.18 in a drug-treated patient, the calculated dopamine receptor occupancy will be 40% using the average ratio of 1.96. If the extreme values of 1.7 and 2.3 were used, the calculated receptor occupancy will be 31% or 49%, respectively. This uncertainty in determination of D1 dopamine receptor occupancy has to be considered when comparing classical neuroleptics and clozapine with respect to D1 occupancy values (Table).

The control group used to calculate D2 dopamine receptor occupancy consisted of neuroleptic-naive schizophrenic patients. To calculate D2 dopamine receptor occupancy, healthy subjects were used as the control group, since we have so far not determined D2 dopamine receptor densities in a larger sample of neuroleptic-naive schizophrenic patients. The conclusion drawn in this article on differences between drugs with regard to D2 dopamine receptor occupancy should be valid also based on the average ratio from healthy control subjects; however, the calculated values for D2 dopamine receptor occupancy would be systematically different if D2 dopamine receptor densities in schizophrenic patients were different from those of healthy subjects. From preliminary data in three neuroleptic-naive schizophrenic patients, D2 dopamine receptor densities are markedly different from those in healthy subjects.

Extrapyramidal syndromes were recorded immediately before the PET examination. The rater knew the drug and dosage used for the treatment but not the dopamine receptor occupancy. This procedure may introduce bias if high doses were related to EPS. Using equipotency factors, the daily doses of the present study were expressed in chlorpromazine equivalents.49-51 The average daily dose was 290 (SD = 95) for patients without EPS and 295 (SD = 135) for patients with EPS. The doses used in the present study could thus not be used to predict D2 dopamine receptor occupancy and EPS and thereby introduce bias in the rating of EPS.

**COMMENT**

We and other PET groups have previously reported a high D2 dopamine receptor occupancy in patients treated with conventional doses of all the chemically distinct classes of antipsychotic drugs.29 This was a consistent finding also in the present extended series of schizophrenic patients treated with classical neuroleptics. In these patients the D2 dopamine receptor occupancy ranged between 70% and 89%.

Since some of the these patients exhibited EPS, it was pos-

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**Fig 2.**—Regional radioactivity in two brain regions after intravenous injection of 100 MBq [11C]raclopride into a healthy volunteer (left), a patient treated with haloperidol 2 mg × 2 (center), and a patient treated with clozapine 250 mg × 2 (right). Circles indicate putamen; squares, cerebellum.

**Fig 3.**—D2 dopamine receptor occupancy in relation to extrapyramidal syndromes (EPS) in schizophrenic patients treated with classical neuroleptics and clozapine. Open bars indicate classical neuroleptics, no EPS; solid bars, classical neuroleptics, EPS; and hatched bars, clozapine.
sible to compare D2 occupancy in these patients with those who did not show any side effects. The patients who had EPS had a significantly higher D2 dopamine receptor occupancy than those who had not (P < .001). This finding is the first direct demonstration that EPS are quantitatively related to central D2 dopamine receptor occupancy.

The patients who did not have EPS had a relatively lower D2 dopamine receptor occupancy. Yet, they were clinical responders to neuroleptic drug treatment. There may be thresholds in terms of D2 dopamine receptor occupancy both for EPS and for the antipsychoytic effect. The results of the present study indicate that there is a threshold for EPS between 74% and 82% D2 occupancy (Fig 3) which seems to be higher than a threshold for the antipsychoytic effect, since the patients with occupancy below 74% were clinical responders. This hypothesis of distinct thresholds has implications for optimal dose finding in clinical neuroleptic drug treatment. The hypothesis has to be tested in controlled clinical studies designed for identification of sigmoid-shaped occupancy-response relationships.

Five patients were treated with the atypical antipsychotic clozapine. These five patients had a significantly lower D2 occupancy than the 22 patients treated with classical neuroleptics (P < .01). This difference was not caused by the dose levels used since the dosages and serum concentrations were in the higher clinical range for clozapine and in the low to moderate range for the classical neuroleptics (Table). 41,52

All patients had been treated for at least 4 weeks and were in pharmacokinetic steady-state conditions. The PET examinations were performed 6 hours after administration of the morning dose. Compared with classical neuroleptics, clozapine has a relatively short half-life of about 6 hours. 53,54 The D2 dopamine receptor occupancy of clozapine may accordingly be higher shortly after drug administration than after 6 hours. In one patient treated with clozapine 300 mg × 2, two PET experiments were performed 3 and 6 hours after clozapine administration, respectively. The D2 dopamine receptor occupancy was 59% in the first experiment and 63% in the second. These results indicate that not even during the early phase after drug administration did the clozapine-induced D2 occupancy approach the high D2 dopamine receptor occupancy of classical neuroleptics.

The finding of a low occupancy strongly indicates that clozapine is "atypical" not only with respect to pharmacologic effects but also with respect to the central D2 dopamine receptor occupancy induced in the basal ganglia of neuroleptic drug-treated patients. Clozapine is known to induce a very low frequency of EPS. 18,19 A simplistic explanation of this low frequency of EPS is that clinically used doses of clozapine do not induce the high D2 dopamine receptor occupancy demonstrated in the basal ganglia of patients with neuroleptic-induced EPS (Fig 3).

The doses and D2 occupancy values in the clozapine-treated patients of the present study can be used to calculate the dose of clozapine that produces an occupancy likely to induce EPS. Such a calculation, according to the equations for receptor-ligand interaction, indicates that a daily dose of clozapine higher than 2000 mg is required to induce an occupancy higher than 80%. 55 Safety and tolerability precautions preclude the analysis of drug effects of clozapine at such doses. Pharmacologic effects in man have not yet been reported for selective drug interaction with the D1 dopamine receptor. As shown in this study, several neuroleptics in conventional clinical doses did not interact significantly with D1 dopamine receptors, indicating that blockade of this subtype is not a prerequisite for the medication of antipsychotic effect. However, this does not preclude the potential of D1 dopamine receptor blockade as a mechanism per se for induction of antipsychotic effects.

In experiments in vitro on human brain tissue, clozapine has been demonstrated to have affinities of the same order for the D1 and the D2 dopamine receptor. 56 In experiments in vivo on animals, Andersen 57 reported an equal effect of clozapine on the two subtypes. In agreement with these characteristics, clozapine-treated patients in the present PET study were found to have a D1 dopamine receptor occupancy of 38% to 52%, which is similar to the D2 occupancy of 38% to 63%. High D1 dopamine receptor occupancy was also found in single patients treated with the classical neuroleptics flupentixol and thioridazine, compounds demonstrated to have some affinity for the D1 dopamine receptor in vitro and in vivo. 11,58 The D1 dopamine receptor occupancy induced by clozapine is thus not a unique property of this compound. However, the combination of a comparatively low D2 and high D1 occupancy is a unique property of clozapine as compared with classical neuroleptic drugs representing all the chemical classes used today. This pharmacologic uniqueness may be related to the atypical clinical effects of clozapine.

This study has focused on D1 and D2 dopamine receptor occupancy in the basal ganglia and EPS. To our knowledge, this is the first demonstration that EPS can be related to the degree of D2 dopamine receptor occupancy in the basal ganglia and that clozapine is atypical in this respect. The study was not designed for examination of dopamine receptor occupancy in relation to the antipsychotic effect. Recently, several new dopamine receptor subtypes have been cloned. A D3 dopamine receptor seems to be found predominantly in the nucleus accum-bens, 59 a limbic brain region of particular interest for the antipsychotic effect. 59 Clozapine has recently been reported to have high affinity for cloned D1 dopamine receptors for which the distribution in the human brain has not yet been clarified. 60 With the new generation of PET systems with improved resolution and with new selective radioligands, it will be possible to determine binding to dopamine receptor subtypes both in the basal ganglia and in some other brain regions which have been suggested as site of action for the antipsychotic effect.

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