Central D2-Dopamine Receptor Occupancy in Schizophrenic Patients Treated With Antipsychotic Drugs

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• Using positron emission tomography and the carbon 11–labeled ligand raclopride, central D2-dopamine receptor occupancy in the putamen was determined in psychiatric patients treated with clinical doses of psychoactive drugs. Receptor occupancy in drug-treated patients was defined as the percent reduction of specific carbon 11–raclopride binding in relation to the expected binding in the absence of drug treatment. Clinical treatment of schizophrenic patients with 11 chemically distinct antipsychotic drugs (including both classic and atypical neuroleptics such as clozapine) resulted in a 65% to 85% occupancy of D2-dopamine receptors. In a depressed patient treated with the tricyclic antidepressant nortriptyline, no occupancy was found. The time course for receptor occupancy and drug levels was followed after withdrawal of sulpiride or haloperidol. D2-dopamine receptor occupancy remained above 65% for many hours despite a substantial reduction of serum drug concentrations. In a sulpiride-treated patient, the dosage was reduced in four steps over a nine-week period and a curvilinear relationship was demonstrated between central D2-dopamine receptor occupancy and serum drug concentrations. The results demonstrate that clinical doses of all the currently used classes of antipsychotic drugs cause a substantial blockade of central D2-dopamine receptors in humans. This effect appears to be selective for the antipsychotics, since it was not induced by the antidepressant nortriptyline.

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The antipsychotic effect of neuroleptic drugs has been well established.[1,2] The individual response to treatment is highly variable, however, and in some patients severe side effects have been recorded. Reduction of the risk of side effects by the titration of the minimal antipsychotic dosage in each patient is a demanding clinical procedure. For these reasons, there is a need for useful measures to guide the dose-finding procedure.

During the past 20 years, techniques have been available for the measurement of drug concentrations in serum and other body fluids. The assumption motivating such measurements in neuroleptic-treated patients is that the drug concentration in body fluids reflects the concentration in the synaptic cleft close to the target neuroreceptors.[3] Despite a large number of studies on the relationships between serum drug concentrations and antipsychotic effects, no consistent relationships have been generally confirmed.[4]

It is widely accepted that the therapeutic effect of neuroleptic drugs is related to their ability to antagonize the action of the neurotransmitter dopamine by blockade of central dopamine receptors.[5-8] This hypothesis is supported by the demonstration of a linear correlation between drug affinity for central D2-dopamine receptors in animals and antipsychotic potency in humans, while no such correlation has been demonstrated for any other central receptor.[9] Previously, it had not been possible to test this hypothesis in humans. The development of positron emission tomography (PET) has now made it feasible to study drug interaction with receptors in the living human brain.[10-14] The determination of central D2-dopamine receptor blockade in neuroleptic-treated patients should offer a measure that is closer to the assumed target for antipsychotic drug action than the serum drug concentration.

Using the highly selective D2-dopamine receptor antagonist raclopride, labeled with carbon 11 (^{11}C), we have developed a PET method for the quantitative measurement of D2-dopamine receptor characteristics in the putamen of living human subjects.[13,15] In an earlier study, this method was applied to determine the degree of D2-dopamine receptor occupancy in patients treated with four chemically distinct neuroleptics. Clinical treatment with all four drugs resulted in a D2-dopamine receptor occupancy of approximately 80%.[12]

The present study was performed to examine how an extensive series of classic and atypical neuroleptic drugs in clinical doses affect central D2-dopamine receptor occupancy in psychiatric patients. Treatments with clinical doses of all of the major chemical classes of antipsychotics were examined and compared with a clinical dose of the antidepressant drug nortriptyline. For the two antipsychotic drugs haloperidol and sulpiride, we also examined the relationship between D2-dopamine receptor occupancy in the brain and drug concentration in the serum during drug withdrawal.

SUBJECTS AND METHODS

To study various antipsychotic drugs, 14 patients who satisfied *DSM-III* criteria for a schizophrenic disorder (ages 19 to 51 years) were recruited after giving their informal consent. Patients with an organic brain disorder (*DSM-III*) or somatic disease or who abused alcohol or other drugs were excluded. The patients had all been receiving treatment with conventional dosages of one of 11

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antipsychotic drugs for at least one month. Only one antipsychotic drug had been given during the month preceding the experiment. One 58-year-old patient with a major affective disorder (*DSM-III*) who had been treated with the tricyclic antidepressant nortriptyline chloride for two months was also recruited. In all of these patients, D2-dopamine receptor occupancy was determined in a PET experiment performed at steady-state conditions six hours after the last dose intake.

As a reference group for the determination of receptor occupancy, 15 drug-naive schizophrenic patients (*DSM-III*) 18 to 30 years of age were used.[16]

Two schizophrenic patients (*DSM-III*) (19 and 39 years of age, respectively) were recruited for an analysis of the relationship between serum drug concentration and central D2-dopamine receptor occupancy at several points in time after treatment withdrawal. One of these patients had been treated with sulpiride (600 mg twice daily) for seven weeks. Treatment was withdrawn and PET experiments were made 3, 6, and 27 hours after the last dose was given. The other patient had been treated with haloperidol (6 mg twice daily) for three months. Positron emission tomography experiments were performed 6, 30, and 53 hours after administration of the last dose. In both patients, repeated blood samples were taken to follow serum drug concentrations after drug withdrawal.

One 31-year-old schizophrenic patient (*DSM-III*) was selected to examine the effect of dosage on the serum drug concentration and D2-dopamine receptor occupancy. This patient had been treated with sulpiride (800 mg twice daily) for two years. The dosage was reduced successively in four steps (800, 600, 400, 200, and 0 mg twice daily). To assure steady-state conditions at each dosage, at least one week elapsed between a dosage reduction and the day of the next PET experiment. Each PET experiment was performed six hours after the last dose intake.

PET Determination of D2-Dopamine Receptor Occupancy

Raclopride ^{11}C was prepared by methylation of the desmethyl precursor analogue using methyliodide ^{11}C.[15] The specific activity of raclopride ^{11}C was 110 to 800 Ci/mmol. The PET system (Scanditronix, Uppsala, Sweden, PC-384) at the department of Neuroradiology, Karolinska Hospital, Stockholm, was used to follow radioactivity in seven sections of the brain. Each study comprised ten sequential scans during a 51-minute period.[15] A plaster helmet was made for each subject and was used with a head-fixation system both during computed tomography (CT) and PET.[17] The head-fixation system made transfer of the positioning from CT to PET feasible. To optimize and standardize the positioning of the caudate nucleus and the putamen within a PET section, Monroe's foramen was identified by CT. A level 3 mm above Monroe's foramen was chosen as the midpoint of section 4 of the PET and CT scans.

Regional radioactivity was measured for each sequential scan, corrected for ^{11}C decay, and plotted vs time. Specific binding in the putamen (B*) was defined as the difference between radioactivity in the putamen, a region with a high density of D2-dopamine receptors, and the cerebellum, a region with a negligible density of D2-dopamine receptors. The total radioactivity in the cerebellum was used as an estimate of the free radioligand concentration in the brain (F*).[13] The relationship between B* and F* is expressed by the following hyperbolic (curvilinear) function:

$$B^* = \frac{B_{max} \times F^*}{K_d^* + F^*} \qquad \text{Equation 1}$$

where B_{max} is the density of receptors available for ligand binding and K_d^* is the equilibrium dissociation constant of the labeled ligand. After the injection of a tracer dose of raclopride ^{11}C (2.7 mCi; specific activity: >200 Ci/mmol), F* is less than 0.20 pmol/cc.[15] This value for F* is much lower than the K_d value of 7.1 nM (picomoles per cubic centimeter) found for raclopride ^{11}C binding in vivo in healthy controls and schizophrenic patients.[16] At this concentration of F*, the effect, according to the law of mass action, is negligible; after rearrangement of terms, equation 1 can be simplified as follows:

$$\frac{B^*}{F^*} = \frac{B_{max}}{K_d^*} \qquad \text{Equation 2}$$

D2-Dopamine Receptor Occupancy in Patients Treated With Psychoactive Drugs*

Drug	Dosage, mg	Receptor Occupancy, %
Phenothiazines		
Chlorpromazine	100	80
Thioridazine	100	75
Trifluoperazine hydrochloride	5	80
Perphenazine	4	79
Thioxanthenes		
Flupentixol	5	74
Butyrophenones		
Haloperidol	4	84
Melperone	100	70
Diphenylbutyls		
Pimozide	4	77
Dibenzodiazepines		
Clozapine	300	65
Substituted benzamides		
Sulpiride	400	82
	400	73
	400	68
Raclopride tartrate	4	72
	3	65
Tricyclic antidepressants		
Nortriptyline hydrochloride	25	−3

*Receptor occupancy was defined as the percent reduction of specific carbon 11–labeled raclopride binding in relation to the expected binding in the absence of drug treatment. All drugs were administered twice daily, with the exception of melperone, which was given three times a day.

In experiments where one radiolabeled ligand and one unlabeled ligand compete for the same binding site, the complete equation should be as follows[18]:

$$\frac{B^*}{F^*} = \frac{B_{max}}{K_d^*(1 + F/K_d) + F^*} \qquad \text{Equation 3}$$

F and K_d indicate the free concentration and the equilibrium dissociation constant of the unlabeled ligand, respectively. In the presence of an unlabeled ligand, the ratio B*/F* will be reduced, when compared with the ratio in the absence of an unlabeled ligand (equation 2). The reduction in the ratio B*/F* is proportional to the reduction in the number of available receptors caused by binding of the unlabeled ligand.

The concentration of unlabeled ligand cannot be determined by PET. The ratio F/K_d can, however, be calculated from equation 3. If a tracer dose of radiolabeled ligand is injected and if the receptor occupancy is 80%, the ratio F/K_d will be 4. Assuming a receptor occupancy of 80% ($F/K_d = 4$) and a raclopride ^{11}C concentration in the brain of 0.2 pmol/mL (see above), a receptor occupancy of 79.4% will be obtained, according to equation 3. The 0.6% difference from the true value of 80% is due to competition for binding sites caused by this comparatively small, but yet not "true," tracer dose of raclopride ^{11}C.

In the present study, the expected ratio B*/F* in the absence of drug treatment was calculated from the mean value in 15 drug-naive schizophrenic patients (mean = 3.55, SD = 0.63; range = 2.7 to 5.0).[16] Receptor occupancy in the drug-treated patients was expressed as the percent reduction of B*/F* from the value 3.55. If, for example, the measured ratio B*/F* is 0.71, the calculated receptor occupancy will be 80% when the mean value 3.55 is used. If 2.7 and 5.0, the extreme values for the range of B*/F* obtained in the drug-naive schizophrenic patients, are used, the calculated receptor occupancies will be 74% and 86%, respectively.

Determination of Serum Drug Concentrations

Sulpiride and haloperidol concentrations were measured by high-performance liquid chromatography.[19,20]

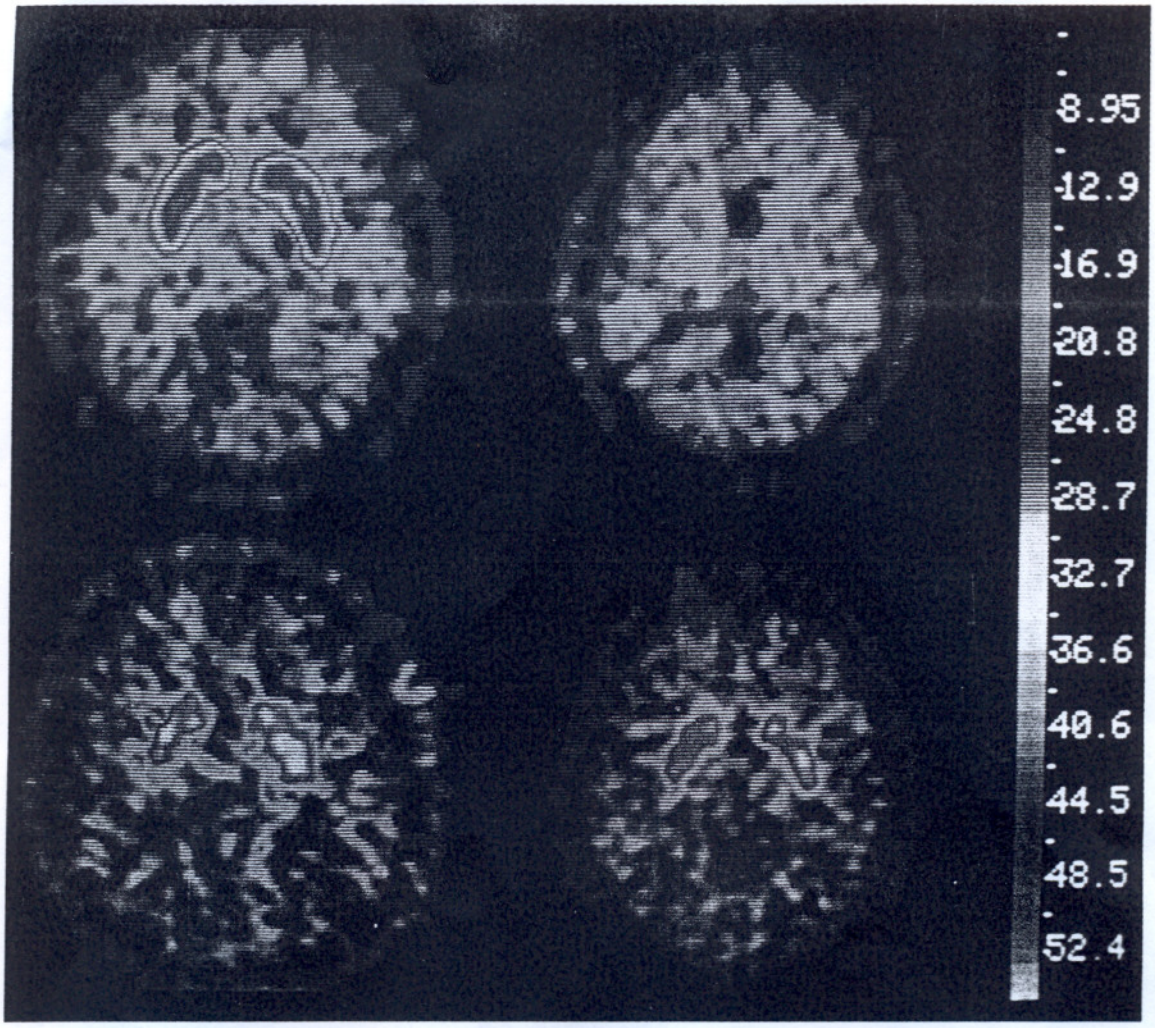

Fig 1.—Positron emission tomography images through caudate/putamen level of one healthy volunteer (top left) and three schizophrenic patients treated with haloperidol (top right), clozapine (bottom left), and raclopride (bottom right), respectively.

RESULTS

In each of the patients treated with one of the 11 chemically distinct antipsychotic drugs, there was a marked reduction of radioactivity in the putamen when compared with the mean value previously obtained in the drug-naive schizophrenic patients (Table; Fig 1).[16] The ratio B*/F* of specifically bound raclopride ^{11}C to the free concentration varied from 0.58 to 1.24, and the D2-dopamine receptor occupancy calculated for the different antipsychotic drug treatments varied between 65% and 85% (Table). In the patient treated with the tricyclic antidepressant nortriptyline, the ratio B/F was 3.65, corresponding to a receptor occupancy of −3%.

In the patient treated with sulpiride (600 mg twice daily), receptor occupancy and serum drug concentrations were followed for 27 hours after withdrawal. The D2-dopamine receptor occupancy remained above 65% during 27 hours despite a substantial reduction in the serum concentration (Fig 2).

In the patient from whom haloperidol (6 mg twice daily) was withdrawn, receptor occupancy and serum drug concentrations were followed for 54 hours. There was only a reduction of a few percent in the D2-dopamine receptor occupancy despite a substantial reduction of the haloperidol serum concentration (Fig 3).

In the patient treated with sulpiride (800 mg twice daily), the dosage was reduced stepwise. Nine days to three weeks elapsed between each dosage reduction. The reduction in D2-dopamine receptor occupancy in relation to dosage followed a curve with a hyperbolic (curvilinear) shape (Fig 4), while the reduction of the serum concentration of sulpiride was linear.

COMMENT

In the present study, PET was used to examine D2-dopamine receptor occupancy in psychiatric patients treated with conventional doses of 11 chemically distinct antipsychotic drugs and one antidepressant drug. Each of the antipsychotic drugs induced a greater than 65% occupancy of D2-dopamine receptors in the putamen when binding was compared with the mean value in drug-naive schizophrenic patients. In the patient treated with the tricyclic antidepressant nortriptyline, no significant interaction with D2-dopamine receptors was obtained. Animal studies have demonstrated that most of the antipsychotic drugs used in the present study have affinity in vitro for several types of central neuroreceptors.[21] The substituted benzamides, however, are relatively selective for the D2-dopamine receptor.[22-24] The latter receptor is also the only central receptor that all classes of antipsychotic drugs have been shown to have affinity for in vitro. This common affinity is the basis for the dopamine hypothesis of the mechanism of action for the antipsychotic drugs.[5,7-9] The lack of appropriate methodology has previously precluded

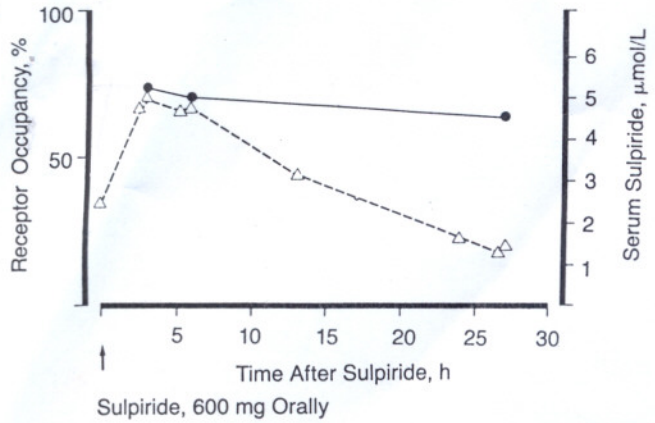

Fig 2.—D2-dopamine receptor occupancy in putamen and sulpiride concentration in serum of schizophrenic patient after withdrawal of sulpiride treatment. Solid line indicates receptor occupancy; broken line, sulpiride concentration.

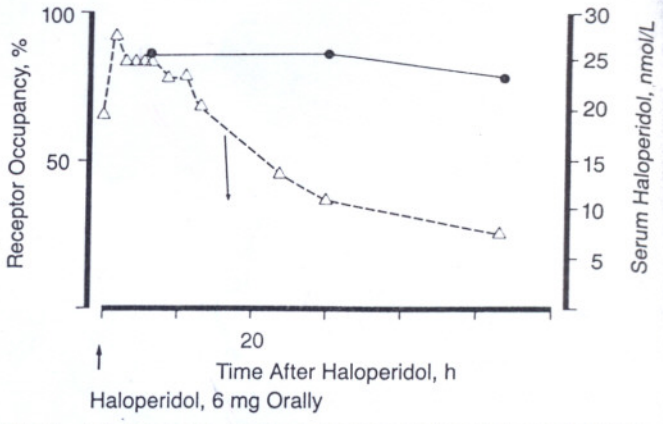

Fig 3.—D2-dopamine receptor occupancy in putamen and haloperidol concentration in serum of schizophrenic patient after withdrawal of haloperidol treatment. Solid line indicates receptor occupancy; broken line, haloperidol concentration.

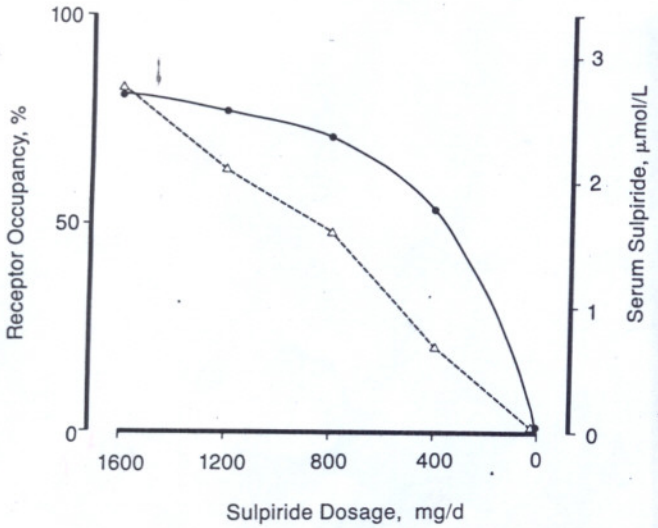

Fig 4.—D2-dopamine receptor occupancy in putamen (solid line) and drug concentration in serum (broken line) of sulpiride-treated patient. Dosage was successively reduced from 800 to 0 mg twice daily.

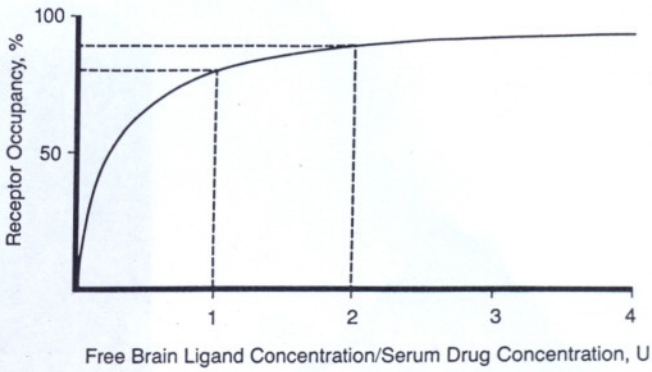

Fig 5.—Theoretical binding hyperbola showing curvilinear relationship between free ligand concentration in brain (or serum) and degree of receptor occupancy. At high degree of receptor occupancy, as during antipsychotic drug treatment, twofold increase in free ligand concentration, as indicated by broken lines, will only give small increase in receptor occupancy.

the direct evaluation of this hypothesis in patients. Thus, the degree of D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs has previously been unknown. Our finding that clinical doses of all 11 chemically distinct antipsychotic drugs induce a 65% to 85% occupancy of the central D2-dopamine receptors, but that an antidepressant drug did not, represents evidence in living patients that the mechanism of action of antipsychotic drugs is indeed related to a substantial degree of D2-dopamine receptor occupancy.

In animal studies, an induction of D2-dopamine receptors has been demonstrated after long-term administration of neuroleptic drugs.[25-27] It is possible that the B_{max} values in drug-treated schizophrenic patients may be higher than in drug-naive patients.[28] If the B_{max} values in antipsychotic drug–treated patients are higher than the values in the drug-naive schizophrenic patients, the calculated receptor occupancy during clinical antipsychotic treatment should have been even higher than the values presented in the Table.

This study was not designed to examine prospectively the detailed relationships between the degree of D2-dopamine receptor occupancy and drug effects. However, it is of interest that all of the patients with receptor occupancy between 65% and 85% had responded well to the treatments. Only one of the patients had observable extrapyramidal side effects despite the marked blockade of striatal D2-dopamine receptors. This patient had akathisia when treated with 6 mg of haloperidol twice daily. His D2-dopamine receptor occupancy was then 86% (Fig 5), the highest level recorded in the present series. He was subsequently treated with 4 mg of haloperidol twice daily; an antipsychotic effect was maintained without extrapyramidal side effects. At this time, the patient's receptor occupancy was 84% (Table). The low frequency of extrapyramidal side effects in all the neuroleptic-treated patients and the observations in this haloperidol-treated patient indicate that a lower receptor occupancy may be required for the antipsychotic effect than the occupancy required for extrapyramidal side effects. However, it cannot be excluded that the antipsychotic effect and the extrapyramidal side effects

are mediated by qualitatively different receptor mechanisms.

Antipsychotic drugs have been subdivided into classic and atypical neuroleptics.[29] The concept *atypical* refers to drugs that do not produce catalepsia in animals and that have a low frequency of extrapyramidal side effects in humans. Clozapine, thioridazine, sulpiride, and melperone have been discussed as drugs with atypical profiles.[22,29,30,31] From animal experiments, it has been suggested that classic neuroleptics, such as haloperidol, have preference for striatal dopamine receptors, whereas the atypical neuroleptics should have a preference for limbic dopamine receptors.[30,32] Interestingly, in the present study all of the classic, as well as the atypical, neuroleptics, including clozapine, thioridazine, sulpiride, and melperone, induced a marked occupancy of D2-dopamine receptors in the striatum. In the present limited series of patients, the atypical neuroleptics might have induced a lower degree of D2-dopamine receptor occupancy in the putamen than the classic drugs (Table). However, since conventional but not clinically equivalent doses were used in the present study and since the B_{max} value of each individual patient was unknown, future studies with a greater number of patients are required to determine whether classic and atypical neuroleptics differ with regard to D2-dopamine receptor occupancy.

In the two patients studied after withdrawal of haloperidol or sulpiride, there was a substantial reduction of serum drug concentrations with time. However, the D2-dopamine receptor occupancy was only slowly reduced and remained at a high level many hours after withdrawal (Figs 2 and 3). Two hypotheses can be formulated to explain this finding of a discrepancy between the time courses of receptor occupancy in brain and drug concentrations in plasma.

1. The drug bound to the receptor dissociates at a slower rate than the rate by which the concentration of free drug is reduced.

2. There is a curvilinear relationship between specific binding and free drug concentration.

Receptor binding in vitro follows the law of mass action for enzyme-substrate interactions as adapted to receptor-ligand interaction.[33,34] Previously, we performed a saturation analysis of raclopride ^{11}C binding in healthy volunteers and demonstrated a curvilinear relationship between specific binding and free drug concentration in the brain, as described by equation 1 (see "Subjects and Methods" section).[13] The hypothetical hyperbola for drug binding to receptors is shown in Fig 5. The receptor occupancy of 65% to 85% that was calculated in the present study in drug-treated schizophrenics indicates that the horizontal part of the hyperbola is approached during antipsychotic drug treatment. At this part of the hyperbola, a change of the free drug concentration will only be reflected in a minor change of receptor occupancy.

The experiment with the successive dose reductions of sulpiride (Fig 4) was undertaken to examine the two hypotheses formulated above. The measurements of D2-dopamine receptor occupancy were made at steady-state conditions at each dosage level. At least one week elapsed between the dosage reductions, providing enough time for the receptor-drug complex to dissociate and adjust to the new steady-state condition. Two weeks after the complete withdrawal of treatment, D2-dopamine receptor occupancy was reduced to zero, indicating the complete dissociation of drug binding to D2-dopamine receptors. Moreover, the relationship was curvilinear (Fig 4). These findings support the second hypothesis. When a high degree of central D2-dopamine receptor occupancy is encountered, as occurs during antipsychotic drug treatment, the horizontal part of the binding hyperbola is approached; ie, a major change in free drug concentration is only reflected in a minor change in receptor occupancy. This explanation, according to the second hypothesis, is sufficient to explain the discrepancy in the time course for receptor occupancy and serum drug concentration, as demonstrated in Figs 2 and 3. However, a certain influence from a slow dissociation rate cannot be ruled out.

By relating D2-dopamine receptor occupancy to antipsychotic effect, it may be possible to define a "threshold occupancy" for antipsychotic effect. In this way, a principally new measure could be obtained to guide the selection of optimal doses for antipsychotic drug treatment. In several studies, similar antipsychotic effects have been reported with widely different dosages and concentration levels of neuroleptic drugs in schizophrenic patients.[35-40] This marked variation of dosages and concentrations that give a similar effect may be expected if the clinical dosages are high enough to give a receptor occupancy that approaches the horizontal part of the hyperbola. An increased or reduced dosage at this part of the hyperbola will only give a small alteration of receptor occupancy at the already nearly saturated D2-dopamine receptors (Fig 5). Positron emission tomography may be a rapid and efficient procedure for defining the minimal individual dosage that gives sufficient occupancy for antipsychotic effect with a minimum of side effects.

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