Eleven healthy subjects (10 men, 1 woman; 23–34 years) and nine neuroleptic naive schizophrenic patients (8 men, 1 woman; 21–28 years) (DSM-IV) were recruited according to previously formulated criteria [2]. MRI was performed to exclude brain pathology. Two PET experiments were performed in each subject. In each experiment 200–300 MBq of the ^{11}C-labelled selective D_1-receptor antagonist SCH 23390 was injected IV as a bolus. In the first a high (321–2061 Ci/mmol) and in the second a low specific radioactivity (2.3–4.3 Ci/mmol) was injected. Radioactivity was measured for 33–63 min using the Scanditronix PC2048-15B PET-system. Anatomical delineations for regions of interest (ROI's) for the caudate nucleus and putamen were made on all MRI sections where these structures appeared. For the cerebellum ROI's were drawn on the 2 middle sections. The ROI's were transferred to the corresponding PET sections. The total radioactivity in each structure was measured for each sequential scan, corrected for decay and plotted as a function of time. For the quantitative analysis the cerebellum was used as reference region to estimate the free radioligand concentration in the brain. Specific [^{11}C]SCH 23390 binding was defined as the difference of radioactivity concentration in the caudate/putamen and that in the cerebellum. An equilibrium analysis was performed to determine B_{max} (density) and K_d (affinity) values for [^{11}C]SCH 23390 binding in the caudate and putamen [2].

There was no difference between the group means of the B_{max} and K_d values in the caudate and putamen (Fig). There was a significantly greater variability both in the B_{max} and K_d values of the putamen in the patient group (Fig.). There was also a significantly greater variability in the K_d values of the caudate in the patients ($p < 0.01$). The Bound/Free ratio (binding potential) in the putamen tended to be lower in the patient group ($p = 0.1$) (Fig.).

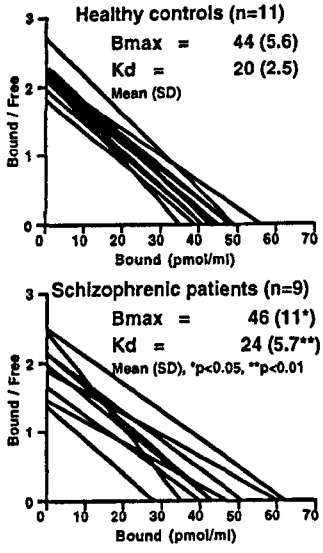

Fig. Scatchard plot of [^{11}C]SCH 23390 binding in the putamen measured by PET

The larger variability of [^{11}C]SCH 23390 binding may reflect a disturbed D_1-dopamine receptor activity in some schizophrenic patients.

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5HT2 RECEPTOR MEASUREMENT IN SCHIZOPHRENIA BY PET

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An involvement of the serotoninergic system has been hypothesized in schizophrenia: some post-mortem studies reported abnormalities of the 5-HT2 receptor numbers in the prefrontal cortex of schizophrenic patients. Furthermore, many antipsychotic drugs (APD) have a high affinity for these receptors and it has been proposed that this ability might be involved in some of their therapeutic effects. We used positron emission tomography and 18-F Setoperone, a high affinity radioligand of cortical 5-HT2 receptors, in order to study: 1/ the in vivo frontal cortex 5-HT2 receptor density in a group of untreated schizophrenic patients and 2/ the effect of conventional dosages of various antipsychotic drugs on the binding of 18-F setoperone to these receptors.

Preliminary analysis in a group of 14 untreated schizophrenics did not demonstrate change in the frontal cortex 18-F setoperone specific binding. However, when compared with the untreated group, patients receiving chronic treatments by clozapine (CZP) but also by chlorpromazine (CPZ) had a marked reduction of the specific binding of 18-F setoperone in the frontal cortex. In the CPZ group, this reduction correlated with oral and plasma dosages of the drug, and total saturation of the cortical 5-HT2 receptors was reached for oral doses equal or superior to 800 mg/d. In the CZP group, usual therapeutic doses induced at least 80% occupancy of these receptors and saturation was reached at 500 mg/day. Patients treated by amisulpride, a specific dopaminergic receptors antagonist, did not differ from untreated patients. In the basal ganglia, interaction with the 18F Setoperone binding was less marked with CZP than with CPZ.

These results suggest that both CZP and a typical neuroleptic such as CPZ produce at therapeutic dosages a significant effect on the cortical serotoninergic system in schizophrenic patients. This effect appears to be neither specific to atypical APD nor common to all neuroleptics.

THE IMPACT OF IN VIVO RECEPTOR PET MEASUREMENT ON NEUROPHARMACOLOGY

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Positron emission tomography (PET) is a direct, quantitative approach to explore relationships among central neuroreceptor occupancy, psychotropic drug blood levels and clinical effects. In the development of new drugs PET may be used to define dose-response relationships and to explore mechanisms of atypical effects. We have used the radioligands [^{11}C]raclopride and [^{11}C]NMSP to study antipsychotic drug binding to central D_2- and 5-HT_2 receptors in man. Clinical treatment with classical neuroleptics induces a uniformly high (70–90%) D_2 receptor occupancy. The risk of extrapyramidal side-effects was significantly increased in patients with D_2 receptor occupancy above 80%, whereas patients with low (below 50%) occupancy were less likely to receive antipsychotic effect. Receptor occupancy was high already at low drug plasma concentrations. Schizophrenic patients in remission treated with haloperidol decanoate had only an intermittently high (> 70%) occupancy during a 4-week injection interval. A continuously high D_2 receptor occupancy may thus not be required to prevent schizophrenic relapses. Our observations point to the need to re-evaluate dose-response char-

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