Beyond the striatum: The extrastriatal binding characteristics of Clozapine. A PET study with [^{18}F]Fallypride in schizophrenic patients

Gerhard Gründer[1], Christian Landvogt[2], Ingo Vernaleken[1], Hans-Georg Buchholz[2], Thomas Siessmeier[2], Sebastian Härtter[1], Peter Stoeter[3], Christoph Hiemke[1], Frank Rösch[4], Peter Bartenstein[2]

Departments of Psychiatry[1], Nuclear Medicine[2], Institute of Neuroradiology[3], and Institute for Nuclear Chemistry[4], University of Mainz, Mainz, Germany

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Introduction:

Until very recently, the occupancy of D_2-like dopamine receptors by antipsychotic drugs was determined in striatal structures (caudate nucleus, putamen) only. With the availability of D_2/D_3-selective high affinity ligands such as [^{11}C]FLB 457 for PET or [^{123}I]epidepride for SPECT it became possible to determine the binding characteristics of antipsychotics in extrastriatal regions also. However, the first studies in drug-treated schizophrenic patients performed with these ligands revealed controversial results with regard to differential occupancy of striatal vs. extrastriatal regions, which has been attributed to trace characteristics and methodological pitfalls. Due to its fluorine-18 label, [^{18}F]fallypride is an ideal tracer for the study of both striatal and extrastriatal receptors in a single PET scan. The purpose of this PET study with [^{18}F]fallypride as the radiotracer was to determine the striatal and extrastriatal binding characteristics of the prototypic "atypical" antipsychotic clozapine in schizophrenic patients.

Methods:

D_2-like dopamine receptors were quantified with positron emission tomography and [^{18}F]fallypride ([^{18}F]FP) in 13 patients suffering from schizophrenia (DSM-IV). Time activity curves were generated after normalization using a template for cerebellum, caudate nucleus, putamen, temporal and frontal cortices, thalamus, amygdala, pituitary, colliculi, and substantia nigra. Binding potentials were calculated by means of the simplified reference tissue model. Receptor occupancy was calculated as percent reduction in binding potential where unblocked values were taken from six normal volunteers. Clozapine plasma concentrations were determined immediately before injection of the radiotracer. Plasma concentrations and percent binding data were fit to a simple one-site ligand binding model by nonlinear regression.

Results:

Mean D_2/D_3 receptor occupancy was statistically significantly higher in cortical than in striatal regions (putamen 43%, caudate 50%, medial frontal and inferior temporal cortex 62%, $p < 0.01$ for all comparisons). Occupancy in both the pituitary and the substantia nigra was significantly lower than in striatum (pituitary 38%, substantia nigra 19%, $p < 0.01$ for all comparisons). Preliminary nonlinear regression analysis revealed an E_{max} of 65% in striatal regions and of 100% in cortical regions.

Conclusions:

We could demonstrate a significant preferential cortical binding of the prototypic "atypical" antipsychotic clozapine as compared to its striatal binding. The fact that even at the highest plasma concentrations the striatal occupancy did not exceed 67% is an excellent explanation for the clinical observation that clozapine does not induce extrapyramidal side effects. In contrast, cortical binding exceeded 90% in some cases. We conclude from these findings that the extrastriatal binding of clozapine might be more closely related to its antipsychotic actions.