HIGH STRIATAL OCCUPANCY OF D_2-LIKE DOPAMINE RECEPTORS BY AMISULPRIDE IN BRAIN OF SCHIZOPHRENIC PATIENTS: IMPLICATIONS FOR ATYPICAL ANTIPSYCHOTIC MECHANISM OF ACTION

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Introduction: The "atypical" clinical properties of amisulpride, a substituted benzamide antipsychotic selective for D_2-like dopamine receptors, have been attributed to preferential extrastriatal binding. The aim of this PET study in amisulpride treated schizophrenic patients was to relate striatal occupancy by amisulpride to plasma levels and to compare these findings to previous PET studies that used other radiotracers and analytical methods, respectively.

Methods: Nine patients under subchronic treatment with amisulpride and twelve healthy volunteers serving as control group were studied with PET and [^{18}F]desmethoxyfallypride as the radiotracer. Data analysis was carried out using two noninvasive methods. Receptor occupancies 4 hours after last drug administration were non-linearly correlated with corresponding plasma levels, choosing a volume of interest analysis as well as a voxel-wise approach using SPM99.

Results: Striatal D_2-like dopamine receptor binding of amisulpride ranged from 43 to 90 %. Plasma amisulpride concentrations at time of tracer injection were significantly non-linearly correlated to occupancy levels. While the maximal attainable receptor occupancy E_{max} was similar in caudate nucleus and putamen, occupancy was lower in caudate at lower amisulpride plasma concentrations (Table 1). The voxel-wise SPM analysis confirmed significant non-linear correlations between plasma-concentrations and receptor occupancies in dorsal putamen.

Conclusions: Our data are not consistent with findings of low striatal binding of amisulpride as measured with a high affinity ligand. The calculated maximal attainable occupancy in striatum is similar to values in temporal cortex that were reported previously. However, region-specific different steepness of the concentration/occupancy curve suggests a concentration-depending preferential extrastriatal binding with higher differences at lower amisulpride concentrations..

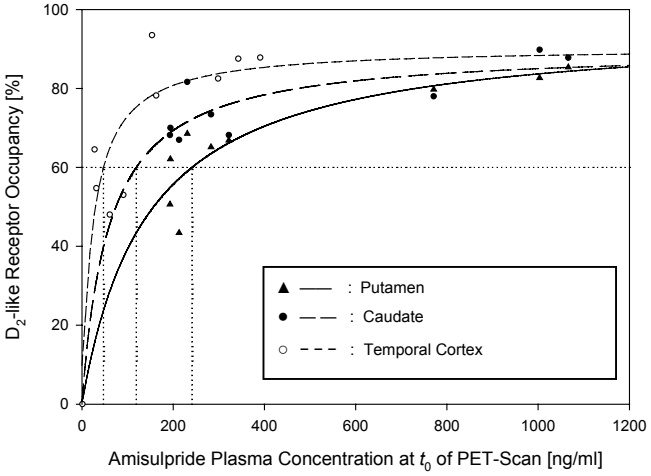

Figure 1: Relationship between amisulpride plasma concentration at t_0 of PET scan and D_2-like dopamine receptor occupancy in putamen, caudate nucleus and temporal cortex (data from Xiberas et al., 2001)[a]

[a] Non-linear curve fitting was performed following the assumption of one site ligand binding. Drop lines characterize the concentrations and receptor binding at Occ_{60} (see also table 1).

Reference: Xiberas X, et al.: In vivo extrastriatal and striatal D_2 dopamine receptor blockade by amisulpride in schizophrenia. J Clin Psychopharmacol 2001; 21: 207-214

Region	E_{max} [a]	ED_{50} [b]	Occ_{60} [c]	Occ_{80} [d]
Putamen	95.70	143.55	241.29	731.64
Caudate Nucleus	90.10	59.85	119.29	473.95
Temporal Cortex	90.47	24.06	47.37	183.74

Table 1: Fitted pharmacokinetic parameters of D_2-like dopamine receptor occupancy in putamen and caudate nucleus compared to data of temporal cortex adapted from Xiberas et al. (2001).

[a] E_{max} is the maximum attainable receptor occupancy [%]; [b] EC_{50} is the plasma concentration [ng/ml] predicted to provide 50% occupancy of E_{max}; [c] O_{cc60} is defined as plasma concentration [ng/ml] predicted to provide 60% occupancy of all D_2-like receptors; [d] O_{cc80} is defined as plasma concentration [ng/ml] predicted to provide 80% occupancy of all D_2-like receptors.