High Striatal Occupancy of D_2-like Dopamine Receptors by Amisulpride in Brain of Patients with Schizophrenia

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Introduction: The substituted benzamide amisulpride is of high interest for understanding "atypicality". It acts specifically on D_2-like receptors and is not binding to receptor being discussed as target for "atypicality". The atypical features of amisulpride have been attributed to preferential extrastriatal binding. Previous neuroimaging studies revealed different extents of striatal amisulpride binding due to varying radiotracers and methods of analysis. Because of these conflicting previous results regarding striatal D_2-occupancies the present PET study wants to relate striatal D_2-receptor occupancy by amisulpride with plasma levels and to compare these findings to previous findings. We use [^{18}F]desmethoxyfallypride-PET with simplified reference tissue model; previous studies have validated the results of this methodological approach.

Methods: We examined 9 patients suffering from acute schizophrenia or schizoaffective psychosis with predominantly positive symptoms aged 19-53 years (mean ± SD 35.9 ± 12.5). They received stable amisulpride treatment with daily doses ranging from 200 to 1200 mg (622 ± 323 mg/d). Patients were avoid of dopaminergic or serotonergic co-medication. The mean PANSS score was 76.0.
Amisulpride plasma concentrations were measured at 8 a.m., before drug intake, and during the PET-Scan (4-5h after drug intake). As a control group we examined 12 healthy volunteers aged 24-60 years (mean 35.4 ± 15.9). They underwent dynamic PET scans over a duration of 124 min (30 time frames) after bolus injection of 157-308 MBq DMFP. Scans were performed using a Siemens ECAT EXACT Scanner with FWHM of 5.4 mm.

The analysis was carried out VOI-based (Caudate Nucleus (NC), Putamen; Cerebellum as reference region) using the simplified reference tissue model (SRTM). All PET scans were motion corrected, coregistered with T1 weighed MRI and normalized to SPM coordinates.

Results: We found 43-85% (putamen) and 67-90% (caudate) D_2-like receptor occupancy. Plasma amisulpride concentrations at time of tracer injection but not administered doses were significantly non-linearly correlated to occupancy levels (putamen: r_S=0.88, p=0.0017; caudate: r_S=0.78, p=0.0127). The maximal attainable D_2 receptor occupancy (Emax) in putamen (96%) and caudate (90%) was very similar to the Emax value in temporal cortex (91%) calculated from the data reported by Xiberas et al. (2001), but occupancy levels were lower in caudate at lower amisulpride plasma concentrations. Calculated plasma levels to attain 60 to 80% receptor occupancy range from 119 to 474 ng/ml (caudate) and from 241 to 732 ng/ml (putamen). No linear correlation could be found between D_2-like dopamine receptor occupancy and side effects as assessed by the SAS rating scale

Conclusions: Our data show high striatal D_2-like receptor occupancies at higher plasma levels. Maximal attainable striatal occupancies were similar to previously reported temporal values. However, region-specific different steepness of the concentration/occupancy curve suggests a concentration-dependent preferential extrastriatal binding with higher differences at lower amisulpride concentrations. This may partly explain amisulpride's "atypical" properties. There is a broad range of plasma levels leading to striatal occupancies below the EPS border of 80% although extrastriatal occupancies of more than 60% can be expected.

Reference :

Xiberas X, Martinot J-L, Mallet L, Artiges E, Canal M, Loc'h C, Mazière B, Paillere-Martinot M-L (2001). In vivo extrastriatal and striatal D2 dopamine receptor blockade by amisulpride in schizophrenia. Journal of Clinical Psychopharmacology 21: 207-14

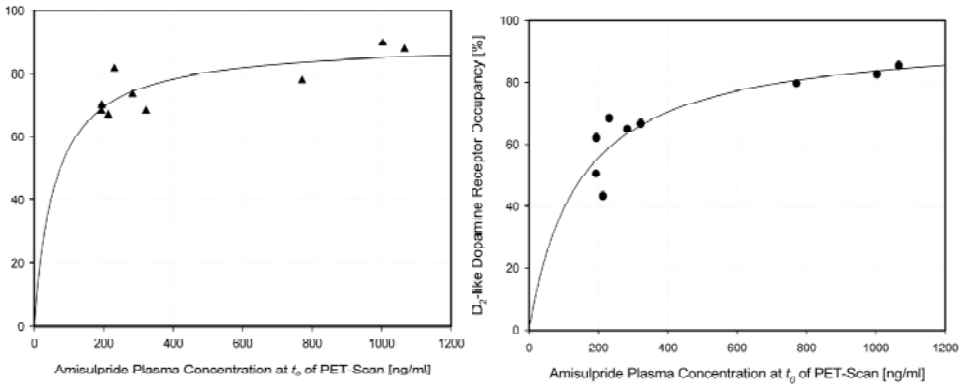

Fig.1:

Relationship between amisulpride plasma concentrations and D2R receptor occupancies in putamen [left] and caudate nucleus [right].