D_2-like dopamine receptor occupancy in amisulpride-treated schizophrenic patients in relationship to plasma levels and side-effects: A PET-study using [^{18}F]desmethoxyfallypride

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Introduction: The selective D_2-like dopamine receptor antagonist amisulpride (ASP) is an atypical antipsychotic agent frequently used in European countries. Receptor occupancy studies using [^{76}Br]FLB-457 and a simplified binding index method published recently found preferential antagonism in extrastriatal regions, while comparably low receptor occupancies in striatal areas were observed. Aim of this investigation was to determine receptor occupancies in amisulpride-treated schizophrenic patients in relationship to plasma levels and side-effects by positron emission tomography with several established analytical methods. We used the substituted benzamide [^{18}F]desmethoxyfallypride as the radioligand, which has been proven to be a suitable agent for D_2-like dopamine receptor mapping, although its' moderate affinity does not reliably allow quantification of extrastriatal dopamine receptors.

Methods: Nine patients suffering from DSM-IV diagnosis of schizophrenia or schizoaffective disorder were included. All patients received a long-term amisulpride-treatment with stable oral daily doses (1 x 200 mg/d; 3 x 400 mg/d; 1 x 600mg/d; 2 x 800 mg/d; 1000 mg/d). Benzodiazepines in low doses were allowed as concomitant medication. Eleven healthy and drug-free volunteers served as control group. PET-Scans were started approximately four hours after the last drug-ingestion on a Siemens ECAT EXAT whole-body scanner (FWHM: 5.4 mm; 47 slices). 165-308 MBq [^{18}F]DMFP was injected intravenously as a bolus, followed by a scanning-period of 124 min (30 time-frames). Most patients underwent arterial plasma sampling for determination of plasma input function and labeled metabolites. After movement correction, coregistration with a T1-weighted MRI and subsequent normalization, polygonal volumes of interest were defined according to the anatomical structures. Time activity curves were plotted for caudate nucleus, putamen, medial thalamus und cerebellum. Data analysis was carried out using pseudoequilibrium method, graphical methods, simplified reference tissue model and compartmental models as well as analysis via parametric spectral analysis. Plasma levels of amisulpride were determined closely before the last ingestion of amisulpride and during the scan-period in 30 minute-intervals. Additionally, side-effect ratings, psychopathological ratings and neuropsychological tests were conducted.

Results: Control subjects show binding potentials (BP) in putamen between 2.19 ± 0.32 (pseudoequilibrium method) and 2.44 ± 0.40 (Logan-plot), depending on the analytical method. Caudate nucleus yielded lower BPs between 1.61 ± 0.34 (Logan plot with reference region) and 1.80 ± 0.41 (2-compartment model). All methods were significantly correlated with each other. Preliminary data analysis (pseudoequilibrium method) in amisulpride-treated patients revealed BPs between 0.36 and 2.18 for the putamen and between 0.12 and 1.27 for caudate nucleus, respectively. From the comparison with BPs of the control group occupancy-rates between 13% and 83% were calculated (putamen), which were significantly correlated with extrapyramidal side effect rating scores (Simpson-Angus-Scale). Morning plasma levels of ASP ranged from 67 ng/ml to 426 ng/ml, mean intra-scan-levels ranged from 177 ng/ml to 608 ng/ml. No correlation could be found between plasma levels and receptor occupancy. During the 124 min. lasting scanning procedure a considerable decline of plasma levels could be observed in most cases (up to 41%).

Conclusions: The D2-receptor selective DMFP is a suitable tracer for D2-like receptor mapping in striatal regions. The highly significant correlations between various analytical methods show that the applied methods reveal valid and reliable binding potentials. In contrast to previous investigations we found much higher D2 receptor occupancies in putamen (average occupancy: 49 ± 23 % under mean dose of 622 ± 291 mg/d), with blockade even exceeding 80% in one subject. This is in accordance with the significant correlation with extrapyramidal side effect-scores. These differences to previously reported data may be due to a more accurate methodological approach in comparison to static calculation of a binding index, which is being used by others. Although DMFP does not provide estimates of extrastriatal D2 receptor densities, our results question the hypothesis of the preferential extrastriatal action of amisulpride. Furthermore, the marked decline of plasma levels during the scan is noteworthy. Thus, when reporting relationships between plasma levels and receptor occupancies, the time of blood sampling for determination of plasma levels as well as the time of last drug-intake in relation to time of PET scanning are of critical importance. Finally, the absence of significant correlations in our sample between occupancy and morning plasma level or daily dose, respectively, may be critically considered when providing dichotomic dosing-recommendations.

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