Evaluation of P-Glycoprotein Modulation of [^{18}F]Fallypride

Piel, Markus[1]; Schmitt, Ulrich[2]; Bausbacher, Nicole[3]; Buchholz, Hans-Georg[3]; Hiemke, Christoph[2]; Rösch, Frank[1]
[1]Institue of Nuclear Chemistry, Johannes Gutenberg-University Mainz, 55128 Mainz, Germany; [2]Department of Psychiatry and Psychotherapy, Universitätsmedizin Mainz, 55131 Mainz, Germany; [3]Department of Nuclear Medicine, Universitätsmedizin Mainz, 55131 Mainz, Germany.

Introduction: P-gp is a member of the highly conserved superfamily of ATP-binding cassette (ABC) transporter proteins and acts as an active efflux pump for a wide range of compounds, including a number of drugs and steroid hormones. P-gp at the BBB thus regulates intracerebral concentrations and may affect the PET imaging of ligands that are substrates of this transporter [1]. Therefore, we examined possible interactions between P-gp and [^{18}F]fallypride, which is a routinely used high affinity ligand to determine the D2-receptor status *in vivo* [2].

Experimental: [^{18}F]fallypride was synthesised as described elsewhere [3] and formulated in isotonic saline solution containing 10% ethanol. 25-30 MBq of the tracer were then applied to Sprague Dawley rats. Half of them were treated with the P-gp inhibitor cyclosporine A (50 mg/kg i.p.) 30 min before injection of [^{18}F]fallypride. In a second experimental series, P-gp KO (mdr1a/b -/-) and wild type mice, with or without cyclosporine A treatment, were used in ex vivo biodistribution studies to determine the brain uptake of [^{18}F]fallypride.

Results: In Sprague Dawley rats, µPET imaging showed the same trend in uptake kinetics of [^{18}F]fallypride for both groups (cf. Figure 1). In the control group, a BP of 13.7 and a SUV of 2.5 at 60 min was observed in the striatum, while the blockade group gave a BP of 8.7 and a SUV of 4.2 in the striatum. In the mouse models the determined brain uptake resulted in 2.62 %ID/g in KO, 2.29 %ID/g in treated and 1.68 %ID/g in untreated wild type mice.

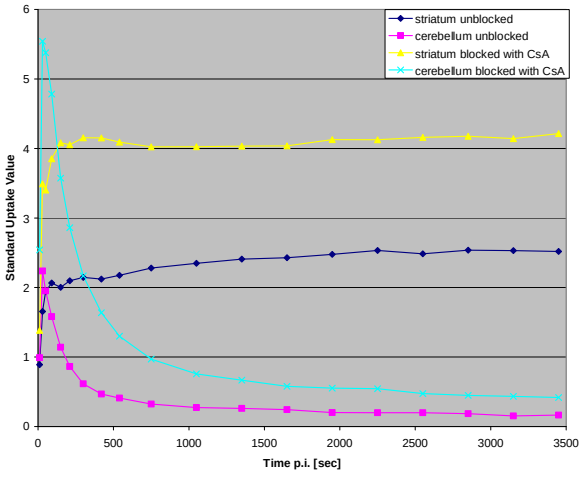

Figure 1. Plot of striatal and cerebrellar [^{18}F]Fallypride uptake for blocked and unblocked Sprague Dawley rats

Conclusions: In the rat model, the treated animals showed a reduction of the BP compared to the untreated animals, due to an increased unspecific uptake in the cerebellum (cf. Figure 2). Besides, generally higher SUVs were found which result from a global increase of radioactivity in the brain under blockade conditions. In mice, a similar effect showed an increasing uptake from wild type to treated and KO mice. It is assumed that not all P-gp transporters could be blocked by cyclosporine A, resulting in an additionally increased uptake in KO mice. These results indicate that [^{18}F]fallypride is a substrate of P-gp and therefore its uptake is modulated by this efflux pump.

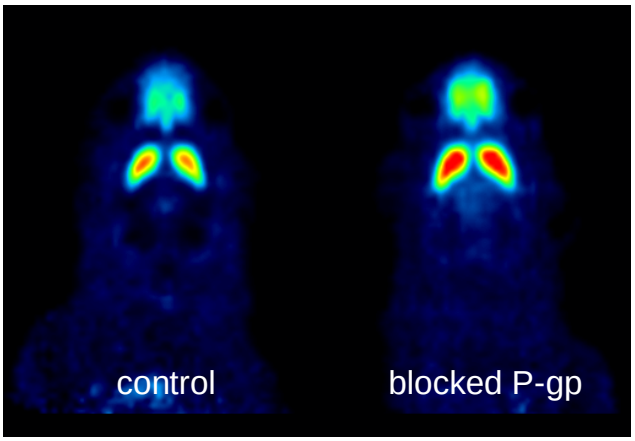

Figure 2: [^{18}F]Fallypride sum images (0-60 min p.i.) of untreated (left) and with cyclosporine A treated (right) Sprague Dawley rats.

References

[1] Uhr M, Tontsch A, Namendorf C, Ripke S, Lucae S, Ising M, Dose T, Ebinger M, Rosenhagen M, Kohli M, Kloiber S, Salyakina D, Bettecken T, Specht M, Pütz B, Binder E B, Müller-Myhsok B, Holsboer F (2008) Polymorphisms in the Drug Transporter Gene ABCB1 Predict Antidepressant Treatment Response in Depression, Neuron 57: 203-209.

[2] Mukherjee Y, Yang Z-Y, Das M K, Brown T (1995) Fluorinated benzamide neuroleptics—III. Development of (*S*)-*N*-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-[^{18}F]fluoropropyl)-2,3-dimethoxybenzamide as an improved dopamine D-2 receptor tracer, Nucl. Med. Biol. 22: 282-296.

[3] Siessmeier T, Zhou Y, Buchholz HG, Landvogt C, Vernaleken I, Piel M, Schirrmacher R, Rösch F, Schreckenberger M, Wong DF, Cumming P, Grunder G, Bartenstein P (2005) Parametric mapping of binding in human brain of D-2 receptor ligands of different affinities, J. Nucl. Med. 46: 964-972.

[4] Schmitt U, Abou El-Ela A, Guo1 L J, Glavinas H, Krajcsi P, Baron J M, Tillmann C, Hiemke C, Langguth P, Härtter S (2006) Cyclosporine A (CsA) affects the pharmacodynamics and pharmacokinetics of the atypical antipsychotic amisulpride probably via inhibition of P-glycoprotein (P-gp), J. Neural Transm. 113: 787-801.