Is the brain uptake of the 5-HT_{2A} Ligand [^{18}F]MH.MZ affected by the P-glycoprotein ?

Ulrich Schmitt, Fabian Debus, Dianne E. Lee, Katrin M. Kirschbaum, Matthias M. Herth, Marcus Piel , Hans-Georg Buchholz, Matias Schreckenberger, Frank Roesch and Christoph Hiemke

Institute of Nuclear Chemistry, Johannes Gutenberg-University Mainz, Mainz, Germany
Molecular and Cellular Pharmacology, Stony Brook University, Stony Brook, New York

Introduction: P-glycoprotein (P-gp) belongs to the superfamily of ATP-binding cassette transport proteins in the blood brain barrier. P-gp functions as an efflux pump limiting the access of xenobiotics into the CNS compartment. This efflux pump has been shown to oppose passive diffusion of many antipsychotic and antidepressant drugs (Doran et al., 2005). The transport activity of P-gp can be blocked by a substrate, such as cyclosporine A, enhancing accumulation of the therapeutic drug in the brain, due to competitive inhibition between both substrates for the efflux transporter. MDL 100907, a derivative of MH.MZ, is a potent $5HT_{2A}$ receptor antagonist (Ki = 0.68-1.4 nM) shown to be an effective drug to treat schizophrenia (Sorensen et al., 1993). Many studies have evaluated [^{11}C]MDL 100907 as a valid PET imaging agent. Recently, we developed an ^{18}F-labeled version as a PET radioligand. Because another $5HT_{2A}$ antagonist, ^{18}F-Altanserin similar in structure, is a substrate for P-gp[1] we tested [^{18}F]MH.MZ in P-gp KO and wild type mice to assess its vulnerability to P-gp transport in both brain and plasma.

Experimental: Male mdr1a/1b double-knockout mice and male WT controls (20 - 28 g) were used. The radiotracer [^{18}F]MH.MZ was synthesized and applied IP (~ 12 MBq) to P-gp KO (n=3) and wildtype (n=4) mice. Following a 45 min awake uptake period, mice were anaesthetised with chloral hydrate (7%) by i.p. injection of 6 mL/kg. and a 10 min static scan ensued. Images were reconstructed by a 3D maximum a posteriori (MAP) algorithm. Tomographic images were analyzed with pixel-wise modeling computer software (PMOD; Zurich, Switzerland). Region of interest (ROI) template was applied and included 5 regions; frontal cortex, thalamus, hippocampus, hypothalamus and cerebellum. Data was normalized for whole brain uptake and compared between groups (P-gp KO vs. wild type) using $P < 0.05$ significance threshold.

Results: We observed a global increase of [^{18}F]MH.MZ uptake qualitatively in P-gp KO vs. wild type mice (Fig. 1). ROI results (Fig. 2) show the greatest change in the frontal cortex (~20% increase) and hypothalamus (~25% decrease). Further, statistically significant increases occurred in the thalamus (~ 15 %) and hippocampus (~15 %); however, no significant change was observed in the cerebellum.

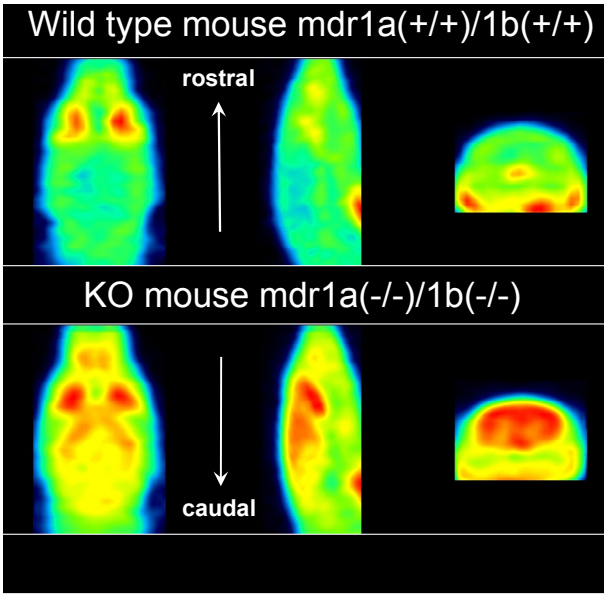

Fig.1: Mean normalized PET images. An enhancement of [^{18}F]MH.MZ uptake is clearly visible in P-gp deficient mice

Conclusion: Our *in vivo* data revealed a increase in uptake of the radiolabeled tracer in P-gp KO compared to wild type animals, specifically in regions of the brain that would have had limited access to the ligand due to its binding properties to the efflux transporter. The uptake profile was in agreement with regions of the brain known to have the riches $5HT_{2A}$ receptors with the highest relative change in the frontal cortex (~ 20 %) and no change in the cerebellum devoid of $5HT_{2A}$.

References

[1] Palner et al. (2007); The effects of a P-Glycoprotein inhibitor on rat brain uptake and binding of [^{18}F]Altanserin: A microPET study, Journal of Cerebral Blood Flow and Metabolism, 27 (SUPPL. 1), pp. PO05-05U