In vivo evaluation of [^{18}F]MH.MZ via PET

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Introduction: Serotonin is a neurotransmitter that has been linked to a number of physiological processes and diseases, including appetite, emotion, changes in mood, depression, Alzheimer's disease and the regulation of the sleep/wake cycle. In particular, serotonergic 5-HT_{2A} receptors have been implicated in the beneficial effects of some antidepressants as well as antipsychotics. Most but not all hallucinogens, including LSD, function as agonists at 5-HT_{2A} receptors, while all clinically approved atypical antipsychotic drugs are potent 5-HT_{2A} receptor antagonists. Therefore *in vivo* studies of 5-HT_{2A} receptor occupancy would provide a significant advance in the understanding of the mentioned disorders and conditions. Positron emission tomography (PET) is an appropriate tool to measure *in vivo* directly, non-invasively and repetitively the binding potential of radio tracers for neuroreceptors.

Aim: Recentyl, we have reported the syntheses, first *in vitro* and *ex vivo* evaluation studies of an ^{18}F-analog of MDL 100907, [^{18}F]MH.MZ with the aim to create a ligand combining the reported better selectivity of MDL 100907 as compared to altanserin and the superior isotopic properties of [^{18}F]fluorine as compared to [^{11}C]carbon.
Our results justified further experiments like *in vitro*, *ex vivo* and *in vivo* small animal PET studies. Therefore, we want to report and verify the potential of our new 5-HT_{2A} imaging ligand, herein.

Results:

Dynamic microPET data and Kinetic Modeling

[^{18}F]MH.MZ were determined. Figure 1 shows a time-activity curve (TAC) of the [^{18}F]M.HMZ binding. The graph shows results of a total binding study (n = 3). Results are given as the standardized uptake value (SUV). Uptake of radiotracer in near equilibrium state (t > 2000 sec) is more than 50% higher in cortical regions than in the cerebellum.

PET

Images of [^{18}F]MH.MZ frontal cortex were displayed relative to cerebellum binding. The binding potential of [^{18}F]MH.MZ was calculated using PMOD software and a four parameter reference tissue model. BP was determined to be 1.45 for the uptake in the frontal cortex region.

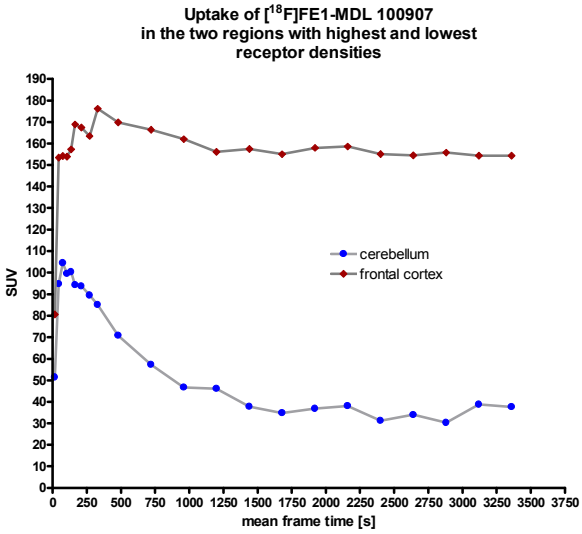

Figure 1: Time-activity curve (TAC) of micro positron emission tomography experiments with [^{18}F]MH.MZ. Uptake of radiotracer in equilibrium state (t > 2000sec) is more than 50% higher in cortical regions than in the cerebellum.

The cortex to cerebellum ratio was determined to be 4.4 after ~30 min., which is strikingly close to the data published by Lundkvist et al.[1]. According to the time-activity curves (TAC) displayed in figure 1, equilibrium appears to be reached between 28 to 35 minutes post injection. The fact that the equilibrium state seems to be reached earlier than observed by Lundkvist et al. is not too surprising given the tremendously faster metabolism of rodents as compared to primates. Once equilibrium binding is reached the specific binding stays on almost the same level for a relatively long time, which promises to enable even scans as long as 120 min.

Conclusion: All together, new auspicious results concerning the biological behavior of [^{18}F]MH.MZ both in *in vivo* and in *ex vivo* experiments are reported. Therefore, a toxicology study is planned and provided that it will result in a non-toxicity of the tracer first human PET studies in healthy volunteers would be possible.

References

[1] Lundkvist et al..(1996); Life Science 58: 187