Pharmacological characterisation of [^{18}F]PR04.MZ and [^{11}C]PR04.MZ in papio Anubis baboons: A promising DAT-ligand for low-concentration imaging

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Introduction: The presynaptic dopamine transporter DAT has attracted a veritable interest due to its role in psychiatric and movement disorders. With respect to molecular imaging, cocaine derived, phenyltropanes have emerged as the most frequently considered imaging agents for this purpose. N-(4-fluorobut-2-yn-1-yl)-2β-carbomethoxy-3β-(4'-tolyl)nortropane (PR04.MZ) is a novel candidate for the non-invasive exploration of the neuronal dopamine transporter (DAT). It offers convenient labelling sites for both, carbon-11 to form [^{11}C]PR04.MZ and fluorine-18 [^{18}F]PR04.MZ. We were interested in a comparative pharmacological characterisation of both tracers in papio anubis baboons.

Experimental: An adult female *papio anubis* baboon was studied using a test-retest protocol with [^{11}C]PR04.MZ and [^{18}F]PR04.MZ. The injected doses ranged from 5.44 mCi to 0.51 mCi. Dynamic PET was conducted on a Siemens ECAT HR+ PET camera. Automated blood sampling was performed throughout the studies for plasma input and metabolite analysis. Metabolite-corrected plasma input functions were derived from the blood samples. The initial frames of the dynamic PET data were summed for coregistration with [^{18}O]H_2O cerebral perfusion images and the obtained transformations (PET-PET) were used for coregistration of the individual dynamic PET data with the LONI-MR-atlas of the baboon brain. Regions of interest were drawn onto the anatomical MR-image and copied into the dynamic PET data. Time-activity curves and distribution volumes (DVs) were derived for the putamen, the caudate nucleus, the nucleus accumbens, the midbrain and the cerebellum. Distribution volumes (DV) for various brain regions were obtained from Logan-plot analysis and binding potentials were calculated according to the two compartment simplified-reference-tissue-model (SRTM). The test-retest reliability was calculated from the time activity curves for the specifically bound tracers.

Results: [^{11}C]PR04.MZ and [^{18}F]PR04.MZ show a rapid, relatively high uptake into the DAT-containing brain regions inside and outside the striatum and low non-specific binding. Both the striatal as well as the extra-striatal DAT-populations are clearly visualised. Both tracers are rapidly metabolised, however, rodent studies did not indicate brain uptake of any metabolite.

Conclusion: In conclusion, PR04.MZ displays good test-retest reliability and visualises all DAT-containing brain regions in the primate brain. A long term scan with [^{18}F]PR04.MZ showed reasonable washout after 90-120 min which is beneficial for the routine application of the tracer in molecular diagnostics. The visualisation of the extra-striatal DAT in the midbrain might contribute to a more detailed, more sensitive exploration of neurodegenerative disorders with PET. Furthermore, the former facilitates the quantitative investigation of extrastriatal contributions to a variety of psychiatric diseases.

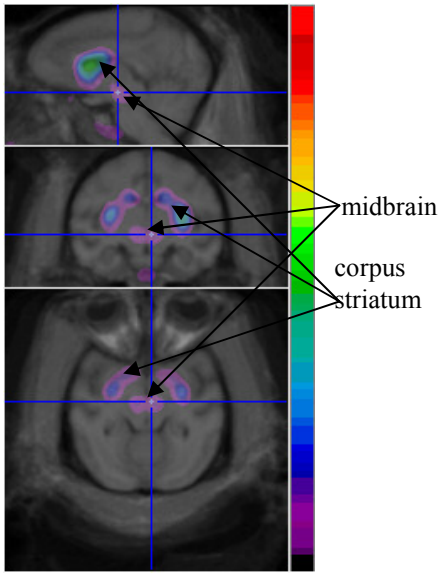

Figure 1: PET/MR-Fusion images of [^{11}C]PR04.MZ in a female papio anubis baboon

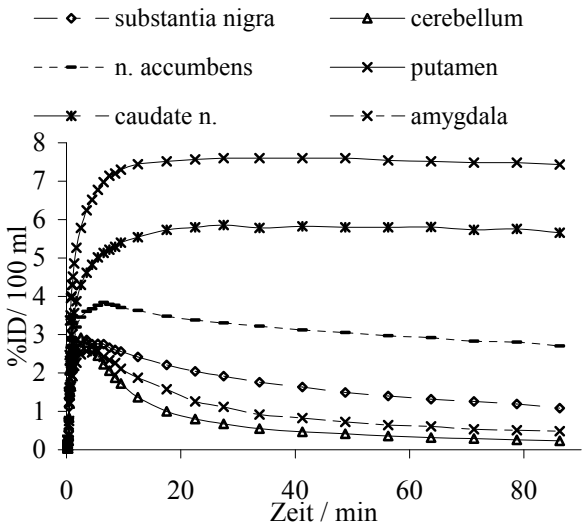

Figure 2: Time activity curves of various brain regions with [^{11}C]PR04.MZ in a female papio anubis baboon

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