

Impact of the P-glycoprotein inhibitor Tariquidar on brain uptake of the Serotonin 5-HT_{1A} Antagonist [¹⁸F]-MPPF in Rats

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INTRODUCTION

The activity of the multidrug transporter P-glycoprotein (P-gp) in the blood-brain barrier can impede the attainment of effective therapeutic brain concentrations of diverse medications, potentially contributing to pharmacoresistance. Corresponding to this, the net cerebral uptake of many tracers for positron emission tomography (PET) is influenced by P-gp. Therefore we established a microPET assay for the uptake and binding of the 5-HT_{1A} antagonist [¹⁸F]-MPPF in rat brain, and determined the dose-response of this uptake to the P-gp inhibitor Tariquidar (TQD).

MATERIAL & METHODS

Animal Treatment:

Female Sprague Dawley rats received Tariquidar (5mg, 15mg or 30mg/kg) and Glucose 5% via tail vein 1h before PET imaging with an interval of one week between PET sessions.

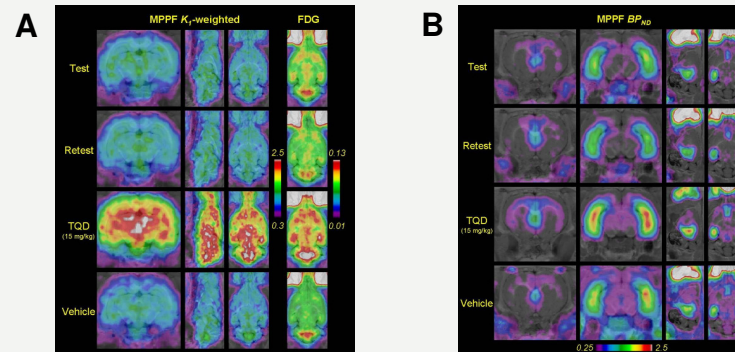
PET imaging

A 60min dynamic emission recording was initiated upon intravenous bolus injection of 45.6 ± 4.2 MBq [¹⁸F]-MPPF. Followed by a transmission scan using a rotating [⁵⁷Co] point-source. Following the [¹⁸F]-MPPF recording, 47.6 ± 6.0 MBq [¹⁸F]-FDG was injected as an intravenous bolus upon which a 45 minute long dynamic emission recording was obtained.

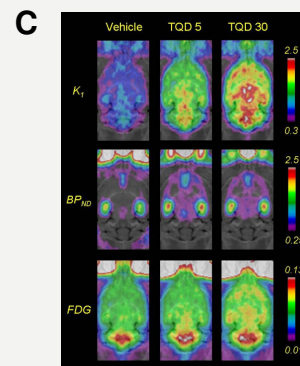
Image analysis

Summation images of the initial two minutes (K₁-weighted), were validated as a surrogate marker for the physiological blood-brain clearance (K₁; ml g⁻¹ min⁻¹). Parametric maps of the [¹⁸F]-MPPF binding potential (BP_{ND}) were calculated from the entire 60 minute emission recordings using conventional reference tissue methods.

RESULTS



Mean K₁-weighted summation images of [¹⁸F]-MPPF and [¹⁸F]-FDG images (A) and mean parametric maps of [¹⁸F]-MPPF (BP_{ND}) binding potential (B). Treatment with TQD clearly increased the uptake of [¹⁸F]-MPPF and [¹⁸F]-FDG into the brain.



Treatment with TQD shows a dose dependent increase of the K₁ weighted uptake of [¹⁸F]-MPPF for 5mg and 30mg/kg TQD (C).

All images are superposed on the rat brain histological atlas (grey scale), in identical coronal (Z = 13), sagittal (X = -7.4) and transversal (Y = 8.9) planes.

SUMMARY

K₁-weighted summation images

- The Test-retest-variability of K₁-weighted-uptake was 25%.

- TQD-medication evoked a global dose-dependent increase in K₁-weighted summation, suggesting an IC₅₀ of 5 mg/kg, and a maximal 250% increase in the condition of complete P-gp blockade.

Binding Potential

- All TQD-doses increased the apparent [¹⁸F]-MPPF BP_{ND} in hippocampus by 30–40%, a bias apparently arising due to increased free [¹⁸F]-MPPF concentrations in brain.

CONCLUSION

P-gp activity can be analyzed in vivo by [¹⁸F]-MPPF PET in combination with the third generation P-gp inhibitor Tariquidar.

ACKNOWLEDGEMENT

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