

P-glycoprotein modulation at the rat blood-brain barrier studied with (R)-[¹¹C]-Verapamil PET

C. Kuntner ¹, J. Bankstahl ⁵, A. Abraham ^{1,2}, R. Karch ³, J. Stanek ¹, T. Wanek ¹, M. Zsebedics ¹, W. Wadsak ⁴, K. Kletter ⁴, M. Müller ², W. Löscher ⁵, O. Langer ^{1,2}

Departments of

- ¹ Radiopharmaceuticals & microPET Imaging, Austrian Research Centers GmbH-ARC, Seibersdorf, Austria
- ² Clinical Pharmacology, Medical University of Vienna, Austria
- ³ Medical Computer Sciences, Medical University of Vienna, Austria
- ⁴ Nuclear Medicine, Medical University of Vienna, Austria
- ⁵ Pharmacology, Toxicology & Pharmacy, School of Veterinary Medicine Hannover, Germany

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 201380.

P-glycoprotein modulation at the rat blood-brain barrier studied with (R)-[¹¹C]-Verapamil PET

Research Objective: study the functional activity of P-glycoprotein at the BBB with tariquidar and (R)-[¹¹C]-Verapamil microPET

Imaging system(s): Focus 220

System Parameters: 350-750 keV, 6 ns timing

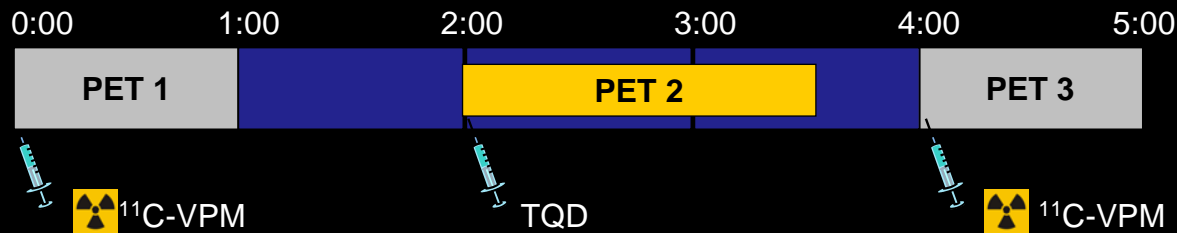
Animal Model: rat (female, Wistar Unilever)

Animal Size: 220-250 g

Imaging Protocol: paired scans with ¹¹C-VPM (scans 1 and 3), 60 min dynamic scan 2, 90 min dynamic at tariquidar (TQD) administration

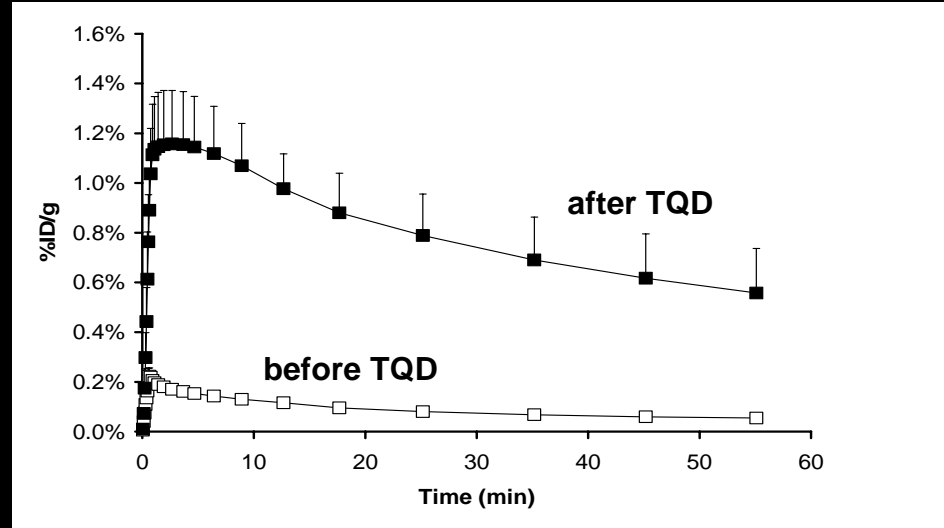
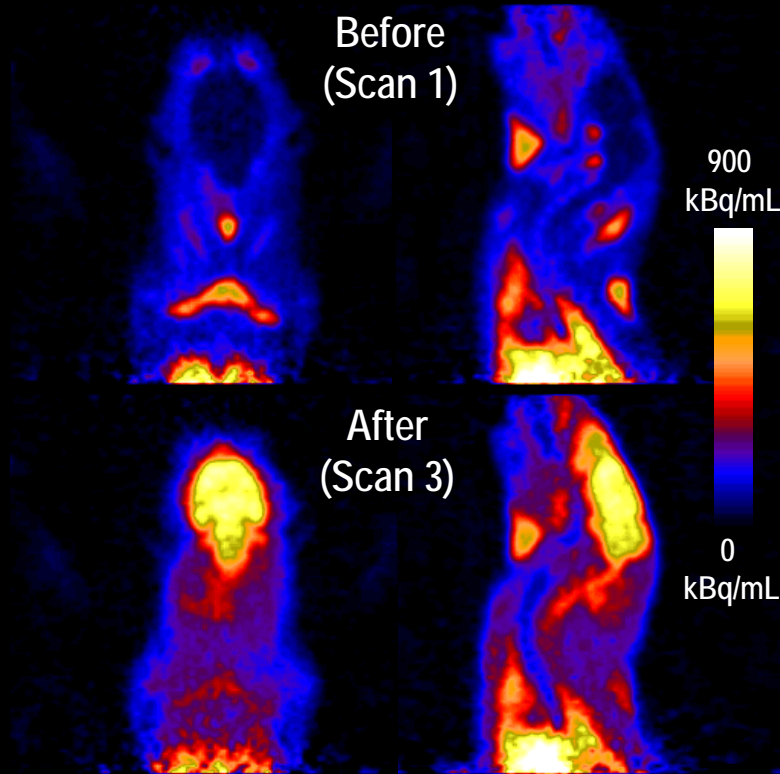
Biomarker or Contrast Agent: (R)-[¹¹C]-Verapamil (VPM)

Activity, volume, concentration, injected: 1-2 mCi (37-74 MBq) in 500 μL over jugular vein



P-glycoprotein modulation at the rat blood-brain barrier studied with (R)-[¹¹C]-Verapamil PET

(R)-[¹¹C]-Verapamil μ PET before and after tariquidar (TQD, 15 mg/kg)

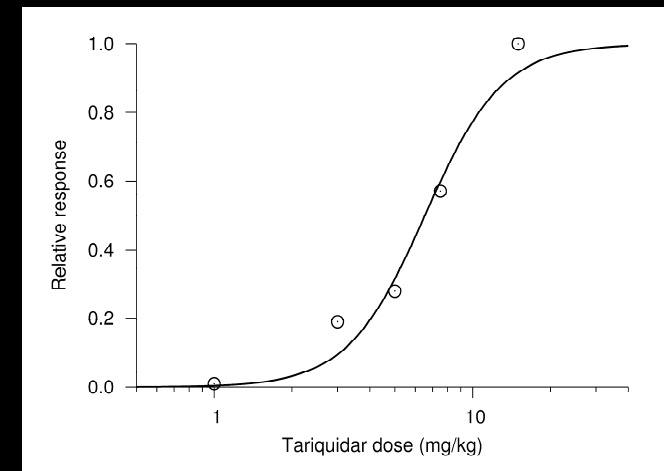
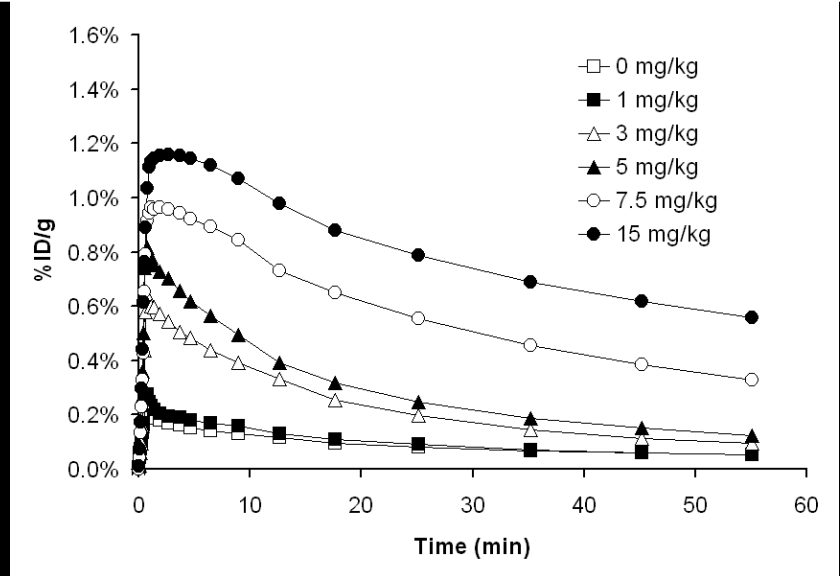
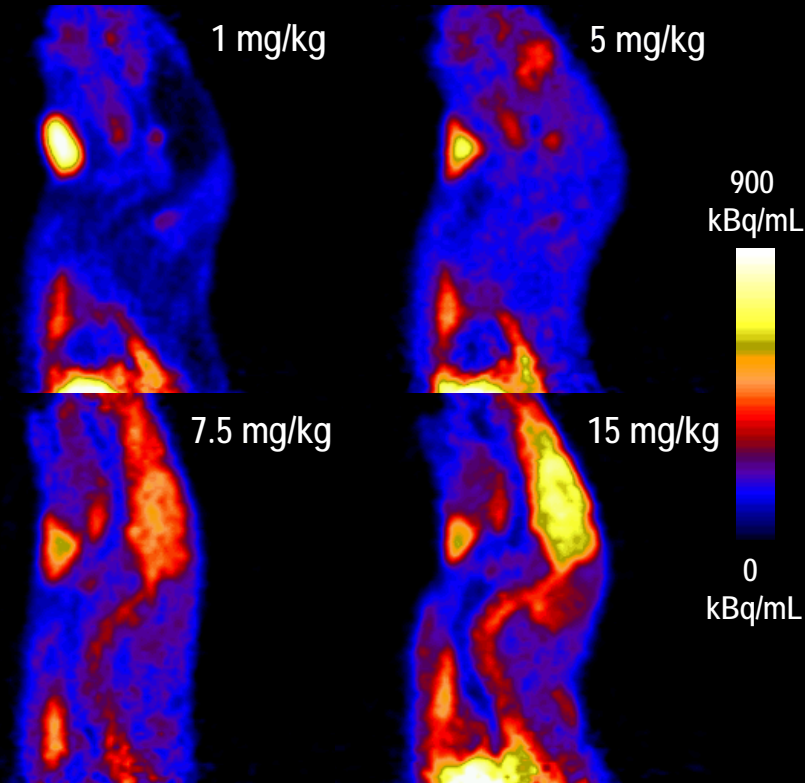


Parameter	Before TQD	After TQD	% Δ
K_1	0.07 \pm 0.03	0.58 \pm 0.20	+711
k_2	0.34 \pm 0.06	0.27 \pm 0.07	-23
k_3	0.29 \pm 0.22	0.37 \pm 0.17	+27
k_4	0.73 \pm 0.29	0.66 \pm 0.49	-9
DV	0.30 \pm 0.08	3.68 \pm 0.81	+1,137

Claudia Kuntner et al.

P-glycoprotein modulation at the rat blood-brain barrier studied with (R)-[¹¹C]-Verapamil PET

Dose-response assessment of tariquidar



P-glycoprotein modulation at the rat blood-brain barrier studied with (R)-[¹¹C]-Verapamil PET

Discussion:

Among all parameters of the 2T4K model, the influx rate constant K1 and the distribution volume DV were most markedly affected following tariquidar administration. The about 8-fold increase of K1 caused by P-gp inhibition is in line with the concept that P-gp acts a “gatekeeper” at the BBB and prevents substrates from diffusing across the luminal endothelial cell membrane.

Our data suggest that tariquidar is a fast acting P-gp inhibitor with relatively low plasma clearance as reflected by the slow decline of activity following peak uptake as observed in the figure below.

In the preliminary dose-response evaluation a highly significant correlation between tariquidar dose and the measured distribution values of (R)-[¹¹C]-Verapamil was found ($r=0.94$; $p<0.001$). The fitted parameters from the sigmoidal dose-response curve were as follows: ED_{50} : 8.4 ± 9.5 mg/kg, E_{max} : 4.5 ± 3.8 mg/kg and n : 1.9 ± 2.0 .

Our data demonstrate that (R)-[¹¹C]-Verapamil PET combined with tariquidar administration is a useful approach for assessment of P-gp function at the BBB. It holds great promise for a future translation to animal models of drug resistance as well to studies in healthy volunteers and patients.

Brain TACs for PET scan 2 recorded from time 0-90 min following administration of vehicle (open squares, $n=2$) or 15 mg/kg of tariquidar (filled squares, $n=5$). PET scan 2 measured the remainder of circulating activity from scan 1.

