

# Increased brain uptake of (R)-[<sup>11</sup>C]-verapamil in rats following administration of the P-glycoprotein inhibitors elacridar and tariquidar quantified with small animal positron emission tomography



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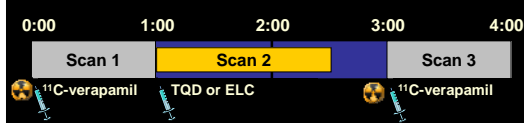
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## Purpose

- ❖ Multidrug efflux transporters like P-glycoprotein (Pgp) at the blood-brain barrier (BBB) are believed to play an important role in resistance to antiepileptic drug treatment.
- ❖ Recently, we have shown changes in Pgp expression 48 h after status epilepticus (SE) in rats. [J.P. Bankstahl and W. Löscher (2008) *Epilepsy Research* 82(1): 70-85]
- ❖ In the present study, we evaluated whether  $\mu$ PET-imaging with the Pgp substrate (R)-[<sup>11</sup>C]-verapamil after Pgp modulation by tariquidar and elacridar could be used to quantify changes in Pgp function in the brain.

## Methods

### PET setup



- ❖ Focus 220  $\mu$ PET-Scanner, 350-750 keV, 6 ns timing
- ❖ Tracer: (R)-[<sup>11</sup>C]-verapamil
- ❖ Paired dynamic scans
- ❖ Pgp-inhibitors: tariquidar (TQD) and elacridar (ELC)
- ❖ Blood-sampling: A. femoralis catheter
- ❖ Application: V. femoralis catheter
- ❖ Radioactivity uptake into the brain was expressed as the area under the time activity curve (AUC) normalized for injected <sup>11</sup>C-activity

### SE model

- ❖ Female Sprague Dawley rats
- ❖ Fractionated LiCl-pilocarpine model
- ❖ SE for 90 min, interrupted by diazepam (10 mg/kg IP, up to 3 injections)
- ❖ Decapitation 48 h after onset of SE

### Pgp expression

- ❖ Immunohistochemical staining of coronal brain sections (14  $\mu$ m) for quantification of Pgp (using the antibody C219 and DAB).
- ❖ Computer-assisted image analysis of Pgp staining

## Results Changes in (R)-[<sup>11</sup>C]-verapamil uptake (white arrows) after 3 mg/kg TQD in naïve rats and 48 h post SE

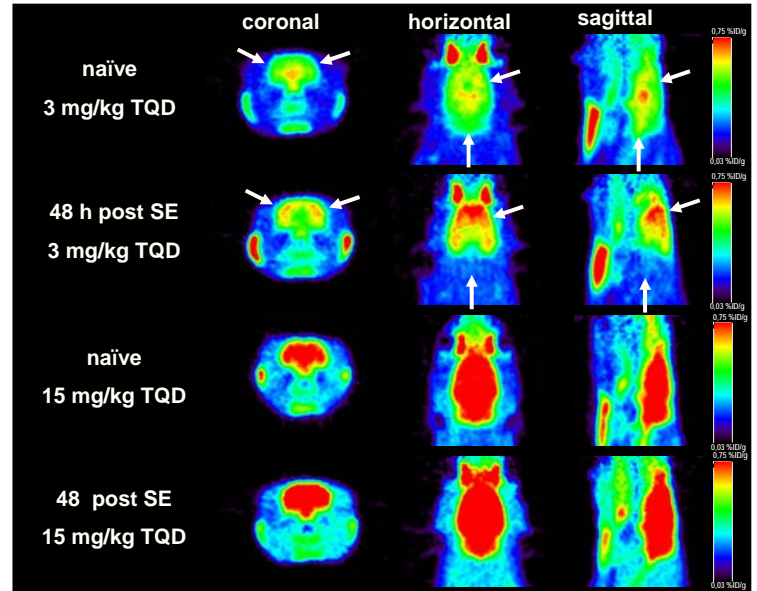
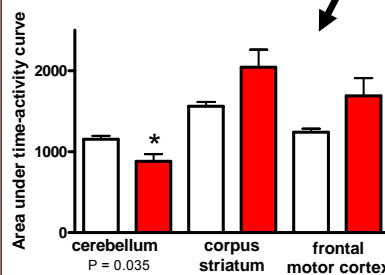


Fig.: Coronal, horizontal and sagittal PET summation images (0–60 min) recorded 2 h after administration of TQD (3.0 + 15.0 mg/kg) (scan 3).



### Increased Pgp expression in cerebellum

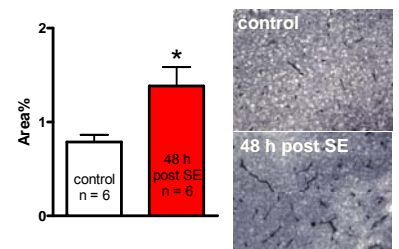


Fig.: Area under time-activity curve (0–60 min) recorded 2 h after administration of TQD (3.0 mg/kg) (scan 3) in control rats (n=4) and 48 h post SE (n=4). Student's t-test, \* indicates significant changes ( $p \leq 0.05$ ).

### Time course of tariquidar and elacridar function

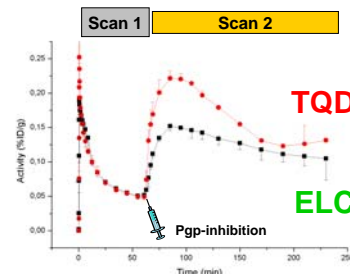


Fig.: Brain time-activity curves for PET scan 1 and 2 before and after administration of tariquidar (15 mg/kg) and elacridar (5 mg/kg). PET scan 2 measured remainder of circulating activity from scan 1. Activity concentration is expressed as mean percentage injected dose per gram (mean  $\pm$  SD).

## Results

### Dose-response assessment of tariquidar and elacridar

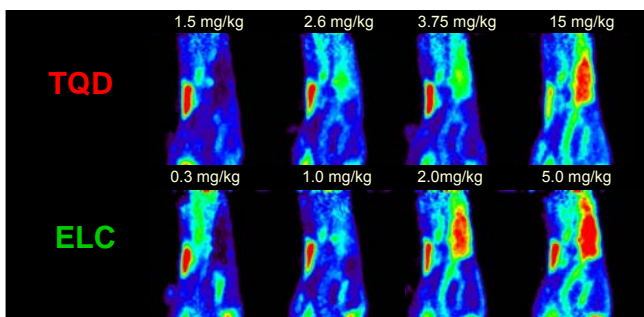


Fig.: Sagittal PET summation images (0–60 min) recorded 2 h after administration of TQD and ELC (scan 3).

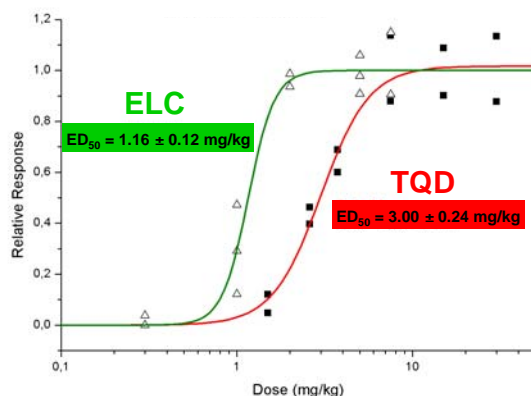


Fig.: Dose-response curve after administration of TQD (1.5–30.0 mg/kg) and ELC (0.3–7.5 mg/kg)

## Conclusion / Outlook

- ❖ Both elacridar and tariquidar are potent inhibitors of Pgp at the BBB.
- ❖ (R)-[<sup>11</sup>C]-verapamil  $\mu$ PET combined with Pgp inhibition is a promising tool for quantifying Pgp function at the BBB.
- Next steps:
  - ❖ This setup will be used to quantify Pgp expression in rat models of drug resistant epilepsy.
  - ❖ In parallel to the animal studies this approach will be translated to healthy volunteers and epileptic patients.

## Acknowledgements

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