

PGP action in temporal lobe epilepsy explored with [¹⁸F]MPPF: Intermediate results after blockade of PGP with cyclosporine A

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Introduction

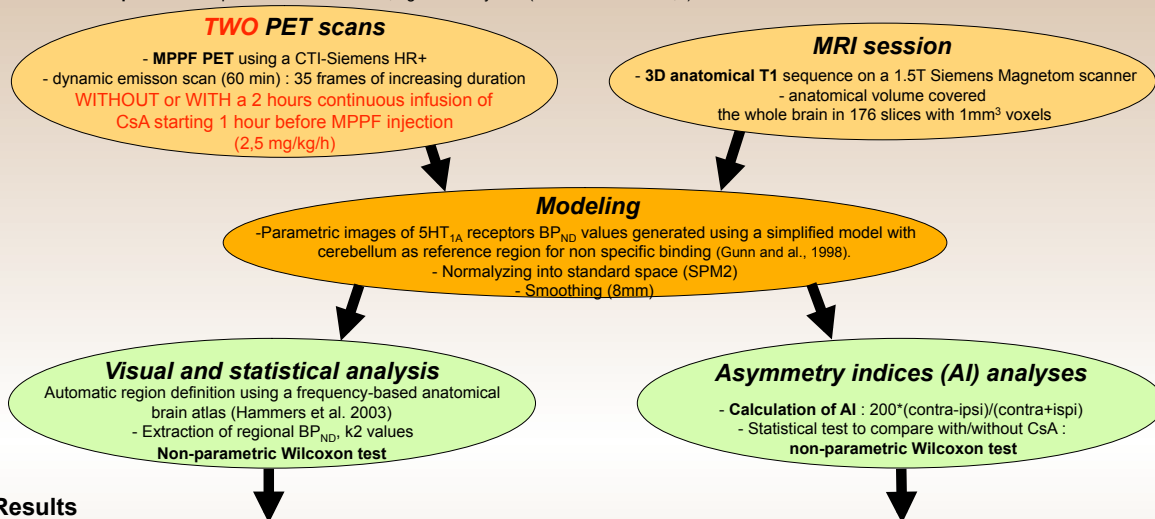
Despite the introduction of numerous antiepileptic drugs (AEDs) in the last 15 years, the proportion of patients with pharmacoresistant focal epilepsies is virtually unchanged (Kwan & Brodie, 2000). Mechanisms of pharmacoresistance are incompletely understood. They include an overexpression of multiresistance proteins (multidrug transporter : MDT). Most AEDs are substrates for MDTs. The MDT that has been best characterised is P-glycoprotein (PGP). In epilepsy patients, PGP protein levels were increased compared to tissue further from the focus (Sisodiya et al., 2002) and compared to autopsy controls (Aronica et al. 2004). [¹⁸F]MPPF is a radiotracer antagonist of 5-HT_{1A} receptors, but also a substrate for PGP.

Previous studies have shown major asymmetries of [¹⁸F]MPPF binding potential (BP_{ND}) in temporal lobe epilepsy (TLE) (Merlet et al. 2004; Didelot et al. 2008) Cyclosporine A (CsA) blocks PGP.

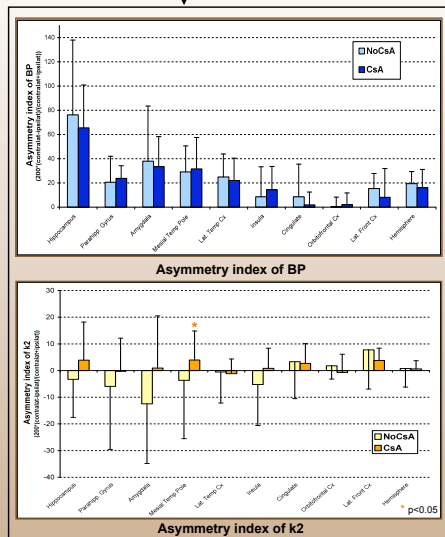
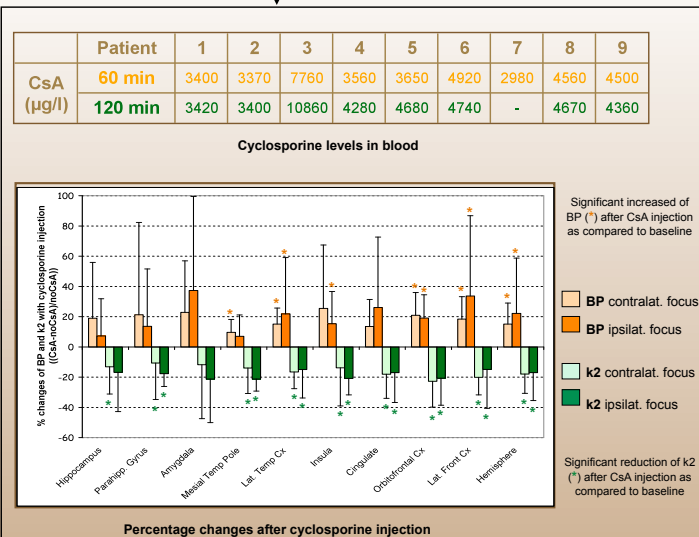
Our Aim : to establish [¹⁸F]MPPF as an *in vivo* tool for the study of mechanism of pharmacoresistance in patients with TLE, based on the hypothesis that CsA will decrease hippocampal asymmetries of [¹⁸F]MPPF BP_{ND}.

Methods

- 9 patients with pharmacoresistant TLE, aged 32-51 years (mean ± SD : 44 ± 6,3)



Results



Conclusions

In this PET study, we have shown that the concurrent infusion of Cyclosporine, a blocker of Pgp, is associated with:

- A significant **REDUCTION** of [¹⁸F]MPPF k2 in the majority of brain regions, except the epileptic hippocampus and both amygdala
- A significant **INCREASED** [¹⁸F]MPPF BP_{ND} in fewer regions, excluding most temporolimbic regions
- No impact on [¹⁸F]MPPF BP_{ND} and K2 ASYMMETRY INDEX, but in the mesial temporal pole due a bigger variation of ipsilateral k2
- A large interindividual variability that might obscure specific blockade of overexpressed Pgp in the epileptic focus of a subgroup of patient

Altogether, these data suggest that cyclosporine has a significant impact on the brain efflux of [¹⁸F]MPPF that could allow demonstrating the presence of Pgp overexpression. However, there was no clear indication of such an overexpression being restricted to the epileptogenic temporal lobe in our patients population. A larger population needs to be scanned to further evaluate this issue.

References
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