In vivo evaluation of a hybrid nanoparticle for molecular imaging of amyloid aggregation

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In vivo evaluation of a hybrid nanoparticle for molecular imaging of amyloid aggregation

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Introduction

Amyloid-β (Aβ) fibrillization is described as a central event in the pathogenesis of Alzheimer's disease (AD). Amyloid imaging is expected to play a pivotal role in early and differential diagnosis of dementias, and in the evaluation of anti-Aβ treatments. Luminescent conjugated oligothiophenes (LCO) have been proposed as optical biomarkers of protein fibrillation [1]. In this paper, we evaluated a fluorescent magnetic hybrid nanoprobe (HNP5011), based on gadolinium fluoride nanoparticles functionalized with luminescent conjugated polythiophenes moieties (Fig. 1). The aim of this study was to investigate its potential for molecular imaging in a rat model bearing intracerebral pre-aggregated Aβ peptides.

Methods

Recombinant human $A\beta_{1-42}$ peptides were agitated at 200µM and 37°C. Resulting fibrils were characterized by transmission electron microscopy (TEM) and spectrofluorometry with thioflavine T (ThT). Rats were stereotaxically injected with 5µl of fibrils on one hippocampus and with PBS on the contralateral side. Blood brain barrier (BBB) integrity was evaluated with magnetic resonance imaging (MRI) after gadolinium injection and with histology after Bleu Evans injection. Macrophage recruitment was highlighted on in vivo MRI and ex vivo Synchrotron Radiation X-ray phase contrast CT (SR-PCT) after ultrasmall superparamagnetic iron oxide injection. The capacity of HNP5011 to detect amyloid fibrils was investigated after stereotaxic (140µM, 2.5µl) or intravenous (14mM, 75µmol Gd/kg) injection of the nanoparticles. Brain sections were used for fluorescence microscopy.

Results

Pre-aggregated Aβ peptide injection caused transient BBB disruption and macrophage recruitment as well as few complications such as petechial hemorrhage and inflammatory oedema around the injection site. HNP5011 was visible on MRI and SR-PCT after stereotaxic injection (Fig. 2) but not visible after intravenous injection. Post-mortem fluorescence on brain tissue without MRI detection could also be explained by in vivo dissociation of HNP5011.

Conclusion

This preliminary evaluation highlighted the need to bring the HNP5011 solution at a higher concentration to reach MRI detection threshold after intravenous injection. Biostability of the nanoparticle deserves further studies.

References

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Figures

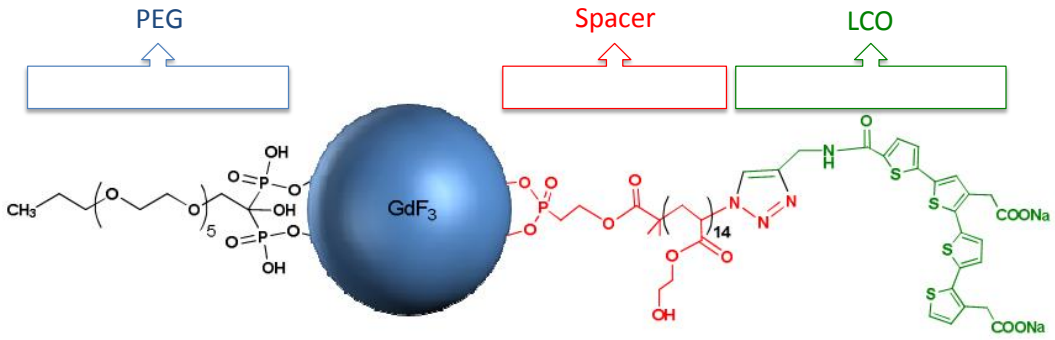

Figure 1. Hybrid nanoparticle 5011.

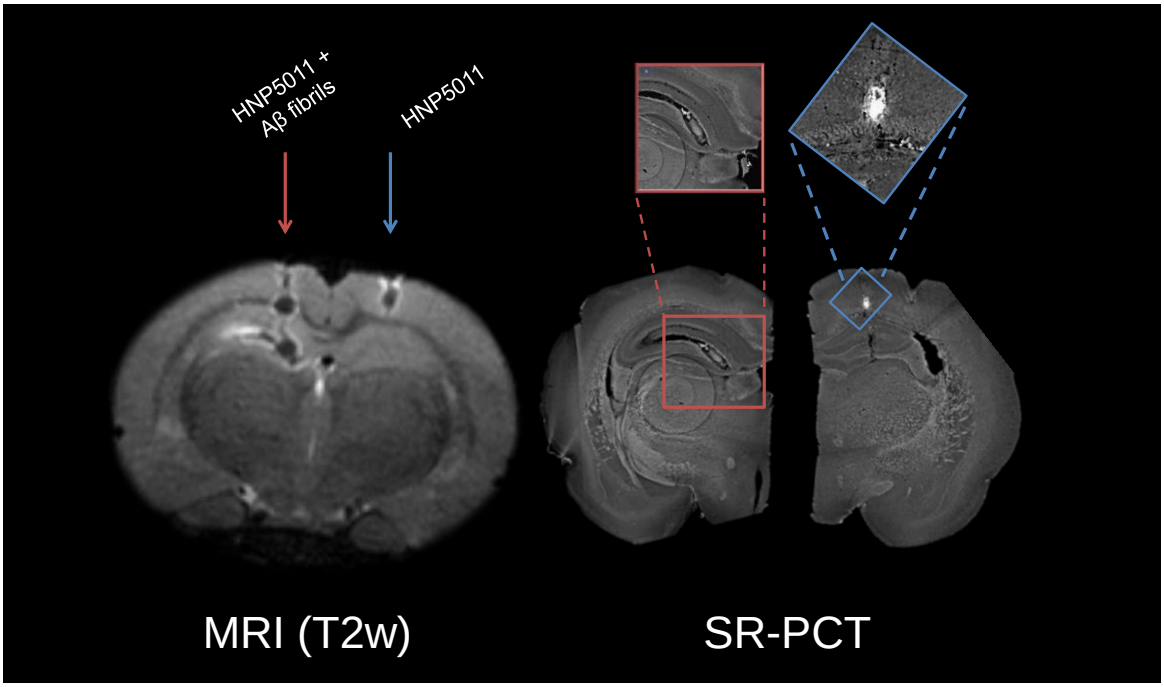

Figure 2. Back-to-back MRI and SR-PCT detection of intra-cerebral hybrid nanoparticle 5011 injected in right (red) and left (blue) hippocampi after stereotaxic injection of pre-aggregated amyloid fibrils (in left hippocampus only).