Vectorization of Iron Oxide Nanoparticles with a Neuron-penetrating RVG Peptide: An Attempt to Cross the Blood Brain Barrier

Jean-Marie Colet[2], Sophie Laurent[1], Sebastien Boutry[1], Zehra Kahvecioglu[2], Luce Vander Elst[1], **Robert N. Muller**[1], *[1]NMR and Molecular Imaging Laboratory, University of Mons, Mons, Belgium; [2]Human Biology and Toxicology, University of Mons, Mons, Belgium. Contact e-mail: robert.muller@umh.ac.be*

Introduction: Neurotropic viruses cross the BBB to infect brain cells. Amongst those, rabies virus shows a high degree of neurotropism in vivo through very well characterized cellular mechanisms. As recently demonstrated by Kumar et al. (Nature, 448, 39, 2007), a short 29-amino-acid peptide from rabies virus glycoprotein (RVG) interacts specifically with the nicotinic acetylcholine receptor (AchR) on endothelial and neuronal cells to enable viral entry into the brain. USPIO are ultrasmall superparamagnetic iron oxide nanoparticles presenting a prolonged plasma half-life. In the brain, they are restricted to the vascular space due to their physico-chemical properties that prevent them to cross the BBB. In this study, USPIO were vectorized with the 29-amino-acid peptide from RVG to promote their way through the BBB. Materials and Methods: USPIO were functionalized with the short RVG peptide and then with an amino-PEG 750 to avoid rapid elimination. The particles were fully characterized by relaxometry and magnetometry. Imaging of anaesthetized mice brain was performed on a Bruker Avance machine at 4.7T. Images were acquired with the TURBO-RARE sequence (TR = 3090 ms / TE = 42.1 ms / Tacq = 13.1 min.) before and 0.5, 4, and 22h after i.v. administration of either USPIO at a single dose of 300 µmol of iron/kg of body weight. Results: 30 minutes after the administration of RVG-USPIO, a 37% reduction in signal intensity was reproducibly observed in brain sub-regions. 22h post-RGV-USPIO injection, a signal reduction of 18% was still measured, as compared to a 8% signal reduction with naked USPIO. Conclusions: In this study, we have successfully developed new vectorized nanoparticles with the RVG peptide known to allow crossing of BBB. Preliminary in vivo imaging assessment of mouse brain showed sustained (>22h) reduction of signal intensity, suggesting that a fraction of the injected particles effectively crossed the BBB. Pharmacokinetics properties of the RVG-coated particles and brain distribution using histochemistry and FITC-RVG-particles are under investigations.

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