ENHANCED BRAIN TARGETING OF ENGINEERED SOLID LIPID NANOPARTICLES

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The blood-brain barrier (BBB) plays an important role in maintaining the homeostasis of the central nervous system and in protecting the brain from potentially harmful endogenous and exogenous compounds. Nevertheless it represents also the major obstacle for the diagnosis and therapy of brain diseases. One of the most promising strategies to overcome the limited BBB penetration of drugs and contrast agents is based on nanoparticles (NP). Lipid based NP, basically liposomes and solid lipid nanoparticles (SLN), have several advantages in terms of biocompatibility, non-immunogenicity, non-toxicity; they can be used as carrier systems [1], and they have a high blood circulation residence time [2]. Moreover their surface can be easily modified with ligands which mediate a site-specific targeting. Here we evaluated the ability to cross the BBB and reach the brain district of SLN, radiolabelled or loaded with different fluorescent dyes, covalently coupled by DSPE-PEG(2000)- Maleimide with the monomer of ApoE-residues (141-150) [3] and functionalized with phosphatidic acid (Aβ ligands) [4]. SLN cell uptake was monitored by confocal-laser-scanning microscopy and quantified by radiochemical techniques [5]. The ApoE monomer mediated an efficient cellular uptake of SLN within cultured human cerebral microvascular endothelial cells (hCMEC/D3). SLN without surface-located peptide displayed less membrane accumulation and cellular uptake. In order to assess the ability of ApoE monomer to enhance SLN transcellular transport we employed an in vitro BBB model, based on hCMEC/D3. With respect to the un-functionalized SLN, the presence of monomer ApoE significantly enhanced their permeability through the cell monolayer (PE = 0.6 • 10-5 cm/min vs PE = 6.95 • 10-5 cm/min, respectively; Student's t-test, p value<0.05). The biodistribution of SLN, loaded with DiR (fluoroprobe strictly associated to SLN), was evaluated by means of in vivo Fluorescent Microscopy Tomography (FMT 1500, Perkin Elmer). Our results confirmed the role of monomer ApoE in sustaining the delivery of SLN to the central nervous system, and allowed us to identify the intratracheal administration route (IT) as promising to enhance SLN biodistribution within the brain. Taken together these results suggest that the SLN formulation herein analyzed is a suitable tool for sustaining drug delivery to the brain.

References:

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