An in vivo study with polymeric nanoparticles for innovative drug brain delivery

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Nanoparticles are rapidly revolutionizing many areas of medicine and technology and they are recognized as promising and powerful tools to fight against the human brain diseases such as multiple sclerosis orAlzheimer's disease. The development of new drug nanodelivery systems to increase drug bioavailability and reduce adverse effects has been claimed as a good option.Considering that optimization and further validation of these systems is needed, the design of novel fluorescent polymeric nanoparticles to target brain tissues and follow their in vivo distribution is proposed in this study. As far as polymeric nanoparticles are concerned, two innovative fluorescent nanospheres were designed: ethylcyanoacrylate-made nanospheres coated with polysorbate 80 and human serum albumin-made nanospheres. Ethylcyanoacrylate-made nanospheres were prepared by emulsion polymerization method while human serum albumin-made nanospheres by coacervation method and chemical cross-linking with glutaraldehyde. Nanospheres were characterized in terms of dimensional analysis, polydispersity and Zeta potential, morphology, encapsulation efficacy and loading capacity. Ethylcyanoacrylate- and albumin-made nanospheres were produced with good yields (65% and 80%, respectively). Both nanospheres were suitable for the intraperitoneal administration (mean diameter ≤300 nm; Polydispersity index: 0.2), had a sphere-like shape and a good encapsulation efficacy (≈98%). Intracerebrally injected ethylcyanoacrylate- and albumin-made nanospheres into the nucleus basalis magnocellularis of anesthetized rats didn't induce any glial reaction and inflammatory response. Differently from albumin-made fluorescent nanospheres that remained in loco 24 hours and one week after the intracerebral administration, ethylcyanoacrylate-made fluorescent nanospheres mobilized from the injection site and distributed unilaterally in the injected hemisphere. Preliminary experiments demonstrate that, one week after injection, ethylcyanoacrylate-made fluorescent nanospheres were detected in the brain parenchyma within blood vessels, microglial and neuronal cells indicating their passage through the cell membranes in addition to endothelial cells.

Intraperitoneally administered ethylcyanoacrylate- (400 and 200 mg/kg) and albumin-made (200 and 100 mg/kg) fluorescent nanospheres to young C57BL/6 mice, weighing about 20 g, were detected in the brain parenchyma one hour after administration, indicating their cross through the blood brain barrier. A subchronic intraperitoneal administration (two weeks) of ethylcyanoacrylate- (200 mg/kg/die) and albumin-made (100 mg/kg/die) fluorescent nanospheres in young C57BL/6 mice did not result in any side effects, impairments in locomotor activity and cognitive deficits in the 'step down' inhibitory avoidance test ($p<0.001$) and object recognition test (Discrimination Score > 0.05), as compared to vehicle (PBS) treated mice.

In conclusion our in vivo study demonstrates that these nanovectors are able to cross the blood brain barrier and to distribute within the brain parenchyma, thus they may provide innovative drug delivery tools for Alzheimer's disease treatment. Supported by University of Florence.