Brain Delivery of Drugs and Transport across the BBB by Nanoparticles: Application to Anticancer drugs, NGF for Stroke Treatment and Alzheimer/Parkinson Models

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Abstract

The blood-brain barrier (BBB) represents an insurmountable obstacle for the delivery of a large number of drugs to the central nervous system (CNS). One of the possibilities to overcome this barrier is drug delivery to the brain using nanoparticles. Drugs that have been transported into the brain and led to a pharmacological effect after intravenous injection using this carrier include the hexapeptide dalargin, the dipeptide kyotorphin, loperamide, tubocurarine, doxorubicin, and the NMDA receptor antagonists MRZ 2/576 and MRZ 2/596. To achieve a significant transport across the blood-brain barrier the coating of the nanoparticles with polysorbate 80 (Tween® 80) was a key factor.

Poly(butyl cyanoacrylate) nanoparticles coated with polysorbate 80 enabled the delivery of nerve growth factor (NGF, MW ~ 130 kDa) into the brain of mice after intravenous injection. The poly(butyl cyanoacrylate) nanoparticles yielded considerably enhanced NGF levels in the brain with a peak after 45 min whereas the injection of the NGF solution in saline or in polysorbate 80 solution as well as uncoated nanoparticles did not alter the NGF concentration in the CNS. These results were accompanied by pronounced and prolonged pharmacological effects: The polysorbate 80-coated nanoparticles with bound NGF were able to totally reverse the scopolamine-induced amnesia and improved the recognition and memory in an acute amnesic mouse model as shown by the passive avoidance reflex (PAR) test. In addition, in a number of Parkinson's disease models these particles significantly reduced the basic symptoms of Parkinsonism such as oligokinesia, rigidity, and tremor.

Experiments with the extremely aggressive glioblastoma 101/8 transplanted intracranially showed a long term survival for 6 months of up to 40 % of the rats after intravenous injection of the polysorbate 80-coated nanoparticle preparation. The surviving animals showed a total remission by histological investigation. Untreated controls died within 10 - 20 days, the animals in the doxorubicin control and uncoated doxorubicin nanoparticle groups died between 10 – 50 days.

The mechanism of the drug transport across the blood-brain barrier with the nanoparticles appears to be endocytotic uptake by the brain capillary endothelial cells followed either by release of the drugs in these cells and diffusion into the brain or by transcytosis. After injection of the nanoparticles, apolipoproteins A-I or E adsorb on the particles surface promoting the interaction with receptors on the endothelial cells followed by endocytosis and thus would the uptake of naturally occurring lipoprotein particles. This hypothesis was supported by the achievement of a antinociceptive effect with loperamide-loaded albumin nanoparticles with covalently bound apo E and by electron microscopy.

The cardiac, and testicular toxicity of doxorubicin was very significantly reduced by binding the drug to Poly(butyl cyanoacrylate) and even more considerably by binding to human serum albumin nanoparticles. In addition the haematological and liver toxicity could be reduced. Coating of PBCA nanoparticles with polysorbate 80 contributed to the reduction of the toxicity. The lower toxicity of the nanoparticle formulations can be most probably explained by the altered biodistribution of the drug mediated by the nanoparticles. Indication of short-term neurotoxicity, such as increased apoptosis in areas distant from the tumor, increased expression of GFAP or ezrin on distant astrocytes or degenerative morphological changes of neurons, were entirely absent in the rats on day 12 as well as in long-term survivors.
References:


