NEUROTHERAPEUTIC NANOPARTICULATE
DRUG DELIVERY SYSTEMS

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Drug Targeting. The inhibition of the caspase-3 enzyme is reported to increase neuronal cell survival following cerebral ischemia. The peptide Z-DEVD-FMK is a specific caspase inhibitor, which significantly reduces vulnerability to the neuronal cell death. However, this molecule is unable to cross the blood-brain barrier (BBB) and to diffuse into the brain tissue. Thus, the development of an effective delivery system is needed to provide sufficient drug concentration into the brain to prevent cell death. Using the avidin (SA)-biotin (BIO) technology, we describe here the design of chitosan (CS) nanospheres conjugated with poly(ethylene glycol) (PEG) bearing the OX26 monoclonal antibody whose affinity for the transferrin receptor (TfR) may trigger receptor-mediated transport across the BBB. These functionalized CS-PEG-BIO-SA/OX26 nanoparticles (NPs) were characterized for their particle size, zeta potential, drug loading capacity, and release properties. Fluorescently labeled CS-PEG-BIO-SA/OX26 nanoparticles were administered systemically to mice in order to evaluate their efficacy for brain translocation. The results showed that an important amount of nanoparticles were located in the brain, outside of the intravascular compartment. These findings, which were also confirmed by electron microscopic examination of the brain tissue, indicate that this novel targeted nanoparticulate drug delivery system was able to translocate into the brain tissue after iv administration. Consequently, these novel nanoparticles are promising carriers for the transport of the anticaspase peptide Z-DEVD-FMK into the brain.

Drug Delivery. Mitoxantrone (MTZ) has potent in vitro activity against malignant glioma cell lines, but it cannot be used effectively as a systemic agent for the treatment of brain tumors because of its poor central nervous system penetration. However, MTZ-loaded poly(lactide-co-glycolide) (PLGA) microspheres may be injected into the peritumoral area and into tumor tissue to provide effective and sustained local drug concentrations without causing systemic side effects. No tumor formation was observed when glioma cells and MTZ-loaded PLGA microspheres were implanted concomitantly (n = 6). No systemic side effects or parenchymal inflammatory infiltration were observed in either group of rats. Brain MTZ concentration was highest at the injection site and declined with time and distance from the injection site and with time. These data demonstrate that MTZ-loaded PLGA microspheres can deliver therapeutic concentrations of drug to the tumor and prevent glioma growth without causing side effects. This treatment method may increase the efficiency of antineoplastic therapy and positively impact survival.

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