Dendrimer-based targeted systemic therapies for neuroinflammation in CNS disorders

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ABSTRACT SUMMARY

Neuroinflammation, caused by activated microglia and astrocytes, plays a key role in the pathogenesis of cerebral palsy (CP), retinal degeneration, and other debilitating neurodegenerative disorders. Engineering and reprogramming the microglial response, to achieve targeted attenuation of neuroinflammation, can be a potent therapeutic strategy. However, drug delivery to the central nervous system is strongly restricted for most drugs by the blood-brain-barrier, making treatment of diffuse neuroinflammation a challenge. We take advantage of the unique, intrinsic, pathology-dependent, biodistribution patterns of dendrimers in diseases models of neurodegeneration. For example, dendrimers are transported to the periventricular region of the brain of newborn rabbit kits with cerebral palsy (CP), whereas little brain uptake is seen in healthy animals. Interestingly, they further localize selectively in activated microglia and astrocytes in animals with CP. Building on these findings, we have designed and synthesized dendrimer-N-acetyl cysteine (NAC) nanodevices, taking advantage of their rich surface functionality using appropriate linking chemistry. They can deliver and release the drug in the targeted tissue in a tailored and sustained manner. We show that a single intravenous dose of dendrimer-drug conjugate, administered after birth to rabbit kits with CP, results in significant improvement in motor function along with decrease in neuroinflammation and oxidative/neuronal injury, followed by improved myelination, by 5 days of age.1 These studies suggest that attenuation of ongoing neuroinflammation, achieving by appropriate engineering of the glial response, can have significant positive consequences in these and other debilitating neurodegenerative diseases.

Application of this approach to designing dendrimer-based targeted therapeutic platforms is being explored in a variety of systemic inflammation and neuroinflammation-associated disorders.1

INTRODUCTION

Cerebral palsy (CP) is a broad term encompassing a group of disorders involving variable degrees of motor, sensory and cognitive impairment, that occur due to an injury/insult to the developing fetal or infant brain. Maternal intrauterine infection and inflammation are risk factors for the development of CP in the neonate, mediated by activation of microglia and astrocytes in the developing brain. Microglia are normal immune cells in the brain that play an important role in remodeling and growth during development, in the fetal and postnatal brain. Activation of these cells can result in uncontrolled inflammation with formation of free radicals, excitotoxic metabolites, and pro-inflammatory cytokines, leading to brain injury. Targeted attenuation of microglia and astrocytes may be highly beneficial. Such an approach was attempted in this study, with poly(amidoamine) dendrimers, and NAC as the drug. The anti-inflammatory and anti-oxidant properties of NAC, along with an good safety profile in the perinatal period are utilized.

EXPERIMENTAL METHODS

Hydroxyl-terminated PAMAM dendrimer-NAC (D-NAC) conjugates were prepared with a disulfide linker between the drug and the dendrimer, enabling intracellular GSH based release.1 Pregnant rabbits in the endotoxin group underwent laparotomy at gestational day 28, and L-PS was administered along the uterus. The kits were born 3 days later. Littermates born to endotoxin-exposed mothers were randomized
for intravenous treatment with 200 µl of PBS (negative control), 10 mg/kg or 100 mg/kg of free NAC, or 1 or 10 mg/kg of NAC as D-NAC. The protocols for assessing improvement upon treatment, on neurobehavior, oxidative stress, inflammatory response, and neuronal response are described previously.¹

RESULTS AND DISCUSSION

Systemic administration of hydroxyl-terminated PAMAM dendrimer to animals with CP resulted in selective accumulation of these dendrimers in activated microglia and astrocytes in the brain. In contrast, minimal uptake of the dendrimer was seen in the brains of healthy kits. Intravenous administration of a single dose of D-NAC resulted in a significant improvement in motor function in CP kits, suggesting the importance of targeted drug delivery in the treatment of ongoing neuroinflammation (Figure 1).

Our results show that a decrease in inflammation and glial response in the brain accompanies improved motor function in rabbits treated with D-NAC. A dose response was seen with NAC and D-NAC for all outcome measures. However, a significant improvement in motor function was not seen with the free drug, even at a high dose of 100 mg/kg. The dramatic improvement in motor function upon D-NAC treatment was consistent with improvements at the inflammation, oxidative stress, and the neuronal injury.¹

CONCLUSION

This study demonstrates that targeted postnatal therapy for a prenatal insult, using a dendrimer-based approach can result in improved cellular and functional outcomes in CP. The efficacy of the dendrimer-drug construct, even without a targeted ligand, suggests that accumulation in microglia and astrocytes is sufficient to produce therapeutic benefits for this challenging disorder. These results also provide insights into the importance of timely attenuation of neuroinflammation in neurodegenerative disorders. Using dendrimers to deliver drugs to activated microglia and astrocytes may eventually provide a versatile platform for the treatment of other neuroinflammatory/neurodegenerative disorders such as autism and age-related macular degeneration.²

REFERENCES


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