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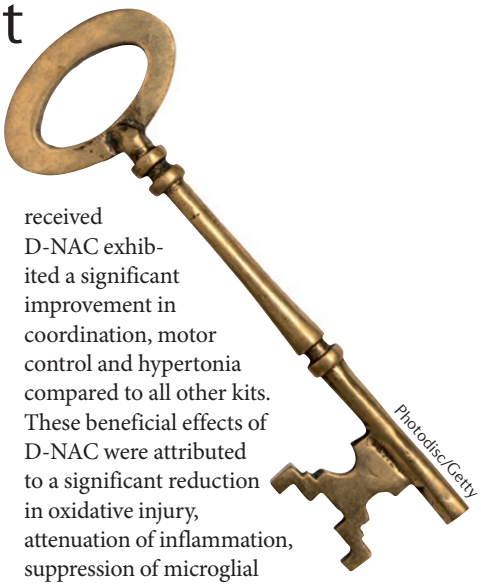
NEUROLOGICAL DISORDERS

Nanoparticle opens door to cerebral palsy treatment



Cerebral palsy (CP) refers to a group of chronic, non-progressive disorders of the developing brain that are associated with variable degrees of motor impairment. There is currently no cure for CP and treatment relies on physical therapy to improve quality of life. Now, writing in *Science Translational Medicine*, Sujatha Kannan and Rangaramanujam M. Kannan and colleagues demonstrate the use of polyamidoamine (PAMAM) dendrimers to effectively deliver an anti-inflammatory drug to the brain of a rabbit CP model, resulting in improved motor function.

Although the precise cause of CP is often unknown, several key risk factors have been identified. Indeed, intrauterine infection and inflammation are associated with the development of periventricular leukomalacia — a disorder of the immature white matter, characterized by focal necrosis around the ventricles as well as diffuse microglial and astrocyte activation — which is the major pathophysiological correlate of CP. As microglia and astrocytes are involved in neuroinflammation and scar formation, respectively, Kannan and colleagues hypothesized that specifically targeting these cell types may improve symptoms in an animal model of CP.

To investigate their hypothesis, Kannan and colleagues chose the antioxidant and anti-inflammatory drug *N*-acetylcysteine (NAC), which is currently in clinical trials for neuroprotective effects in various disorders. They conjugated NAC to PAMAM dendrimers (D-NAC) to facilitate delivery of the drug across the blood–brain barrier into cells associated with neuroinflammation. To enable intracellular release of NAC, disulphide linkers that are cleavable by glutathione — a major intracellular antioxidant in the brain — were used to conjugate the drug to the dendrimer. Importantly, previous studies had demonstrated that when PAMAM dendrimers were injected into the subarachnoid space of neonatal rabbits with a CP phenotype, they were localized in activated microglia and astrocytes.

The authors then tested the effects of D-NAC in a neuroinflammation rabbit model with newborn motor deficits similar to those found in human CP, which were generated by injecting *Escherichia coli* endotoxin into the uterus of pregnant rabbit dams at approximately 90% term gestation. Within 6 hours of birth, kits were intravenously administered a single dose of D-NAC, free NAC, dendrimer alone or vehicle control. From day 1 to day 5, those kits that received D-NAC exhibited a significant improvement in coordination, motor control and hypertonia compared to all other kits. These beneficial effects of D-NAC were attributed to a significant reduction in oxidative injury, attenuation of inflammation, suppression of microglial activation, increased myelination and normalization of neuronal cell counts in the brain.

In summary, this study demonstrates that an anti-inflammatory drug delivered with a nanoparticle can dramatically improve CP symptoms in an animal model, which may have implications for the postnatal treatment of babies who are at risk of developing CP. Moreover, this approach may have broader applications, given the role of neuroinflammation in the pathogenesis of several neurological disorders.

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ORIGINAL RESEARCH PAPER Kannan, S. *et al.* Dendrimer-based postnatal therapy for neuroinflammation and cerebral palsy in a rabbit model. *Sci. Transl. Med.* **4**, 130ra46 (2012)