BIOMEDICINE

Nanoparticle Treatment Reverses Cerebral Palsy in Rabbits

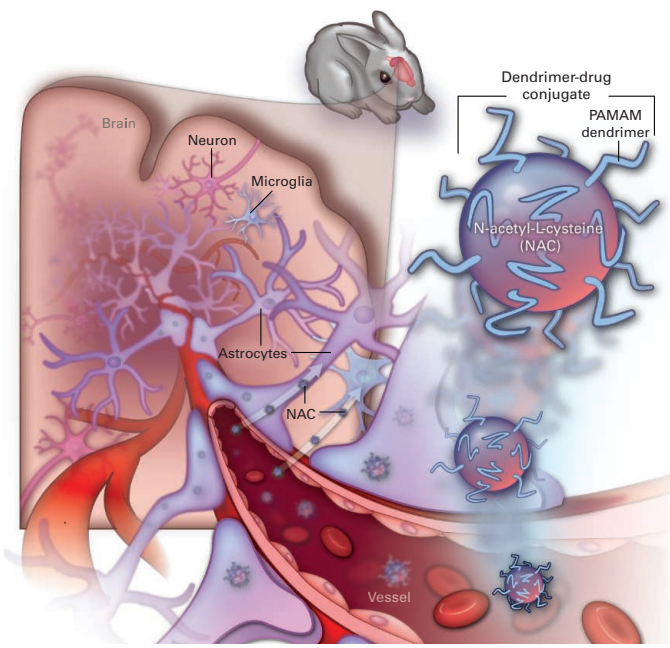
By the time a child is diagnosed with cerebral palsy, typically around the age of 2, it's too late to figure out exactly what caused the neurological damage. Cerebral palsy affects roughly three in 1000 babies, and a far greater percentage of those born prematurely. It can result from genetic causes, infection and ensuing inflammation, a disruption in the brain's oxygen supply, or a combination of these. The injury to the brain happens before birth, but its impact persists for a lifetime, causing rigid muscles, a lack of coordination, and other permanent movement difficulties.

Or maybe not so permanent. This week in *Science Translational Medicine* (http://scim.ag/SKannan), researchers describe a treatment that restores nearly normal movement to rabbits with an induced form of cerebral palsy when given a few hours after birth. The therapy consists of an injection of an anti-inflammatory drug bound to nanoparticles that ferry the drug into the brain and deliver it to specific cells. The treatment's developers acknowledge it's not ready for clinical trials in humans, but they and others say the findings raise the possibility of a preventive treatment that could be given to high-risk infants soon after they're born.

"The big question is how late could you give that injection and still see an improvement in the outcome," says Janice Brunstrom-Hernandez, a pediatric neurologist specializing in cerebral palsy at Washington University in St. Louis in Missouri. In contrast to the current standard of care, which includes physical therapy and medications that improve mobility and reduce other symptoms, the new study suggests it may be possible to reduce the underlying brain damage, Brunstrom-Hernandez says: "We have to have more research like this."

While at Wayne State University in Detroit, Michigan, chemical engineer Rangaramanujam Kannan and his wife Sujatha Kannan, a pediatric critical care physician, developed the new therapy, whose key ingredient is an anti-inflammatory and antioxidant drug called *N*-acetyl-L-cysteine (NAC). The drug is already used to prevent liver damage in people who overdose on the painkiller acetaminophen, and its neuroprotective effects are being tested in clinical trials for conditions as diverse as autism and Alzheimer's disease. The Kannans reasoned that NAC might also have potential for treating cerebral palsy.

They and colleagues, including Roberto Romero of the Eunice Kennedy Shriver National Institute of Child Health and Human Development in Detroit, first tested this idea by injecting NAC alone into rabbits with cerebral palsy–like symptoms. These animals, whose mothers had been given a shot containing toxin from *Escherichia coli* bacteria 3 days before giving birth, exhibit abnormally rigid muscles and movement problems similar to those of children with cerebral palsy. Unlike healthy rabbit kits, they could barely walk and were unable to hop. NAC alone had only a barely discernible effect on these symptoms, however.



Brain defense. Drug-carrying nanoparticles (*top right*) injected into rabbits target microglia and astrocytes in the brain and reduce symptoms of cerebral palsy.

Rangaramanujam Kannan, who specializes in nanomedicine, knew that drugs coupled to nanoparticles have shown promise in treating cancer and other disorders, because they help target the drug where it's needed (see p. 292). So he chemically attached NAC to nanoparticles called dendrimers that branch out from the center to form tiny spheres. When given an injection of the dendrimer-coupled NAC a few hours after birth, kits with cerebral palsy showed improved muscle tone and were walking and hopping nearly as well as healthy animals within 5 days, which is as long as the researchers followed them in this study.

Exactly how the NAC-nanoparticle treatment works is not yet clear—the dendrimers alone don't have any effect—but follow-up experiments by the Kannans and their colleagues provide several clues. In rabbits with cerebral palsy, the nanoparticles seem to deliver their payload of NAC specifically to two types of cells in the brain: immune system cells called microglia, and multifunctional support cells called astrocytes. The treatment decreased several molecular markers of potentially harmful inflammation and oxidative stress, decreased the loss of neurons, and improved myelination, the fatty insulation on neurons that's essential for neural signaling.

"To my knowledge, this is the first demonstration that such a dendrimer-based approach is doable and efficient to protect the neonatal brain," says Pierre Gressens, a child neurologist at the French biomedical research agency INSERM in Paris. It's especially impressive, Gressens adds, that the nanoparticle treatment was effective at doses 100 times lower than those tried with NAC alone.

"This is on the threshold of something big," says Sidhartha Tan, a neonatologist at NorthShore University HealthSystem in Evanston, Illinois. Tan notes that although some clinical trials with nanoparticle therapies are already under way, the particular type of dendrimers used in the new study has not yet been approved for human use. More work will be needed to establish that they are safe, he says.

Other questions remain as well, says Zena Vexler, a neuroscientist who studies perinatal brain injury at the University of California, San Francisco. "The results are quite striking, but they need to follow up for much longer" to see if the benefits last longer than a few days and whether side effects develop, Vexler says. The Kannans, who have since moved to Johns Hopkins University in Baltimore, Maryland, say these experiments are already under way.

–GREG MILLER

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Published by AAAS