Scientists discover window of opportunity to prevent cerebral palsy

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Researchers at the Perinatology Research Branch of the National Institutes of Health, located at the Wayne State University School of Medicine and the Detroit Medical Center, have demonstrated that a nanotechnology-based drug treatment in newborn rabbits with cerebral palsy (CP) enabled dramatic improvement of movement disorders and the inflammatory process of the brain that causes many cases of CP. The findings strongly suggest that there may be an opportunity immediately after birth for drug treatment that could minimize CP.

The study is the first to show that an anti-inflammatory drug delivered with a nanodevice can dramatically improve CP symptoms in an animal model.

The report, "Dendrimer-Based Postnatal Therapy for Neuroinflammation and Cerebral Palsy in a Rabbit Model," was published April 18 in the prestigious journal Science Translational Medicine, published by the American Association for the Advancement of Science.

"The key finding of this work is that early identification of neuroinflammation allows postnatal treatment," said Roberto Romero, M.D., D.Med.Sci., chief of the Perinatology Research Branch and an author of the study. "This suggests that there is a window of opportunity to prevent cerebral palsy, and that the condition may be preventable."

Cerebral palsy is a disorder of the developing brain that affects motor

skills and muscle coordination, often not diagnosed until the age of two or three years in children. The United Cerebral Palsy Foundation, a national advocacy and support group, estimates that 764,000 children and adults in the United States have CP. According to the U.S. Centers for Disease Control and Prevention, 100,000 babies born in the U.S. develop CP annually. A 2009 report by the CDC indicated the prevalence of the condition at 3.3 per 1,000 births. Worldwide, the CDC estimates the prevalence of CP births to range from 1.5 to 4 for every 1,000 births.

Risk factors for the condition include low birth weight and premature birth. Children born before the 32nd week of pregnancy are at high risk for developing CP. Intrauterine infection and/or inflammation is a major risk factor for CP.

Microglia - immune cells in the brain - play an important role in remodeling and growth during fetal and postnatal periods. Activation of these cells can cause an exaggerated inflammatory response, leading to brain injury and CP. Treatment is problematic because inflammation and the resulting injury can be spread throughout the brain's white matter. Transporting drugs across the blood-brain barrier also represents a challenge.

The PRB team hypothesized that it was possible to deliver a drug using a tiny device (or nanodevice) that would cross the blood-brain barrier and target the activated cells (microglia and astrocytes) in the brain involved in neuroinflammation.

The researchers used a rabbit model of congenital CP because it replicates the type of neuroinflammation found in human brains and the resulting motor deficits observed in children with the condition. The method consisted of exposing fetal rabbits to endotoxin (a component of bacteria). Endotoxin induced inflammation of the fetal brain but did not

induce the onset of labor. When the rabbits were born, they had great difficulties walking or hopping. The experiment consisted of treating affected rabbits intravenously with either a saline solution, a drug known as NAC (N-acetyl-L-cysteine) or a dendrímer coupled with NAC, also known as a D-NAC conjugate. Rabbits with CP treated with D-NAC on the first day of life showed a dramatic improvement and, within five days, were able to walk and hop. Rabbits treated with the NAC conjugate also showed a higher neuron count and lower evidence of inflammation compared to untreated animals.

NAC is an antioxidant and anti-inflammatory agent. It is being explored in several ongoing clinical trials to test its potential in autism spectrum disorders, pregnant women for the treatment of maternal and fetal inflammation, and Alzheimer's disease. Dendrimers are synthetic biomimics of globular polymers of the amino acid alanine. Researchers are exploring their use as a vehicle to target drug delivery, a science known as nanotechnology.

The authors believe that conjugating NAC with dendrimers allows delivery of the drug directly to the cells involved, providing greater effectiveness.

"One of the challenges of the 21st century is to rebuild brains injured during fetal or neonatal life, and to prevent not only cerebral palsy, but also other brain disorders," Dr. Romero said.

The CDC estimates that the lifetime cost to care for a person with CP amounts to nearly $1 million (in 2003 dollars). The estimated combined lifetime cost for all Americans born with CP in 2000 is expected to total $11.5 billion in direct and indirect costs.

While still in preclinical testing in animals, the dendrimer-drug conjugate shows promise for postnatal treatment of babies suspected of

having CP.

The therapy described by the PRB researchers also holds promise for possible future treatments of some neurological disorders, including multiple sclerosis. The brain, for the most part, can be divided into gray and white areas. Neurons are located in the gray area, and the white parts are where the neurons send their axons -- similar to electrical cables carrying messages -- to communicate with other neurons or muscles. Oligodendrocyte cells manufacture a cholesterol-rich membrane called myelin that coats the axons. The myelin's function is to insulate the axons, much like the plastic coating on an electrical cable. In addition, the myelin speeds communication along axons and makes that communication much more reliable. Patients with multiple sclerosis display neuronal loss and myelin abnormalities that reduce the myelin coating.

The PRB team found that D-NAC therapy also improved the production of myelin and reduced the neuroinflammation associated with the loss of myelin. In fact, by the fifth day after treatment with D-NAC, the CP rabbits demonstrated a significant increase in myelin that nearly matched healthy control animals.

"This is certainly an exciting breakthrough and it certainly points toward new hope for those affected by cerebral palsy," said Rangaramanujam M. Kannan, Ph.D., a chemical engineer and a member of the PRB research team and an author of the study. "We found that the administration of the anti-inflammatory agent coupled with the dendrimers allowed the drug to not only cross the blood-brain barrier but also to target the cells that cause the neuroinflammation in CP. Of course, this approach and these compounds are not yet approved for testing in humans, and further studies are required to find the optimal dose, duration of treatment and establish safety. More questions need to be answered, but the potential is immense."

"The use of a rabbit model is a unique aspect of the work, since this model mimics the phenotype of CP as seen in humans. This also illustrates the potential of research collaborations across disciplines in advancing and translating novel technologies for the treatment of debilitating childhood disorders," said Dr. Sujatha Kannan, a pediatrician and first author of the study.

Dr. Kannan said the work was made possible by the development of an animal model of cerebral palsy, the implementation of molecular imaging to detect neuroinflammation at the time of birth and the coupling of the nanodevices (dendrimers) with NAC. The significance of the work is that it opens avenues for the treatment of neuroinflammation, a mechanism of disease not only for cerebral palsy, but for other conditions such as meningitis, encephalitis and multiple sclerosis.

"This is tremendous recognition of the research breakthroughs and the power of the partnership between Wayne State University, the Detroit Medical Center and the Perinatology Research Branch," said Valerie M. Parisi, M.D., M.P.H., dean of the Wayne State University School of Medicine. "This study has the potential to pull back a curtain that has shrouded a medical challenge not just in relation to cerebral palsy, but with other conditions that affect millions around the world."

DMC President and CEO Michael Duggan said that the publication of the PRB study marked "a hugely important step forward in the decades-old struggle to protect infants and their parents from the immense suffering caused by cerebral palsy.

"As a healing institution with a passionate commitment to medical research, having Dr. Romero's PRB team working on our campus daily for the past 12 years has been extraordinarily gratifying," Duggan said. "For all of us at the DMC, this is a deeply rewarding moment."

Provided by Wayne State University