

Potential Nutritional Therapy for Childhood Neurodegenerative Disease

August 01, 2013 |

Researchers at the University of California, San Diego School of Medicine have identified the gene mutation responsible for a particularly severe form of pontocerebellar hypoplasia, a currently incurable neurodegenerative disease affecting children. Based on results in cultured cells, they are hopeful that a nutritional supplement may one day be able to prevent or reverse the condition.

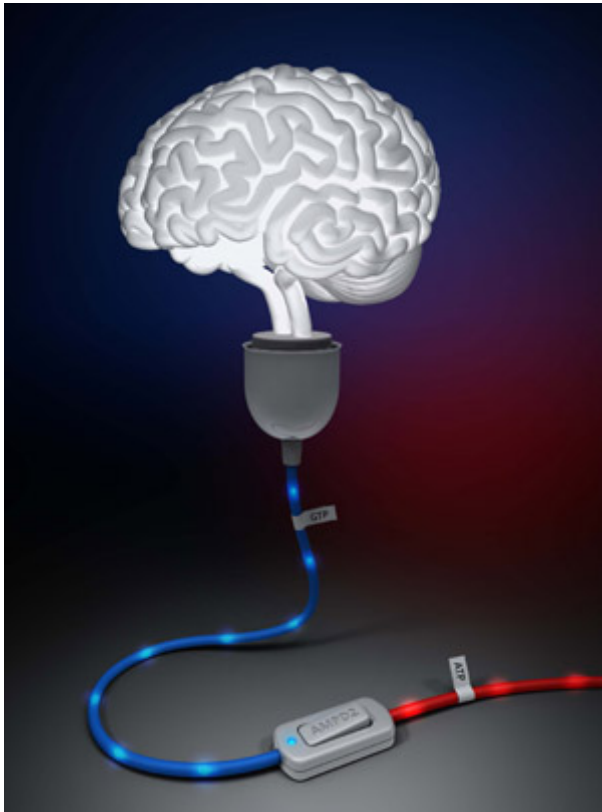
The study, from a team of international collaborators led by Joseph G. Gleeson, MD – Howard Hughes Medical Institute investigator and professor in the UCSD Departments of Neurosciences and Pediatrics and at Rady Children’s Hospital-San Diego, a research affiliate of UC San Diego – will be published in the August 1 issue of the journal *Cell*.

Pontocerebellar hypoplasia is a group of rare, related genetic neurological disorders characterized by abnormal development of the brain, resulting in disabilities in movement and cognitive function. Most patients do not survive to adulthood.

Gleeson and colleagues identified a specific gene mutation that causes pontocerebellar hypoplasia and linked it to an inability of brain cells to generate a form of energy required to synthesize proteins. Without this ability, neurons die, but the researchers also found that bypassing this block with a nutritional supplement restored neuronal survival.

“The goal is to one day use this supplement to prevent or reverse the course of neurodegeneration in humans, and thus cure this disease,” said Gleeson.

Nucleotides are the main energy source of cells. They exist in two forms: ATP and GTP. While ATP fuels most energy requirements, GTP is the source for protein synthesis. Mutations in the gene *AMPD2* lead to the accumulation of ATP, and the subsequent depletion of GTP. The result, said Gleeson, is an imbalance in the cell’s energy source, which



Healthy brains require a balance of two energy sources – ATP and GTP – regulated by the gene AMPD2. A mutation in the gene can result in pontocerebellar hypoplasia, a neurodegenerative disease afflicting children. Illustration courtesy of Evgeny Onutchin, Buryat Studio.

prevents protein synthesis and causes neurodegeneration.

“These patients have what is described in medical textbooks as an untreatable disease, yet show mutations in a neuronal pathway that should be amenable to medication,” said study co-author Naiara Akizu, PhD, a member of Gleeson’s lab. “We chose to bypass this block using AICAR, a substance known to improve exercise endurance.”

The researchers tested their AICAR-based treatment in genetic models of the disease and in human cells. The next step, said Gleeson, will be to test AICAR in a mouse model of pontocerebellar hypoplasia that his lab has created, followed by human trials.

“We don’t know if AICAR will work in mice or humans yet, but our work in cells definitely points in that direction,” said co-author Vincent Cantagrel, PhD. “This rare disorder might be one of the first treatable neurodegenerative diseases in humans.”

Other co-authors include Jana Schroth, Na Cai, Keith Vaux, Ali G. Fenstermaker, Jennifer L. Silhavy, Emily Spencer, Rasim Ozgur Rosti, Eric Scott, Douglas McCloskey, Robert K. Naviaux, Jeremy Van Vleet, UCSD Departments of Neurosciences, Bioengineering, Medicine, Pediatrics, Pathology and Glycotechnology Core Resource; Edward W. Holmes, Sanford Consortium for Regenerative Medicine; Judith S. Scheliga Sanford-Burnham Medical Research Institute; Keiko Toyama, Hiroko Morisaki and Takayuki Morisaki, Osaka University; Fatma Mujgan Sonmez and Figen Celep, Turgut Ozal University and Karadeniz Technical University, Turkey; Azza Oraby and Maha S. Zaki, Cairo University Children’s Hospital, and National Research Center, Egypt; Raidah Al-Baradie, Eissa Faqeh and Mohammed Saleh, King Fahd Specialist Hospital and Children’s Hospital, Kingdom of Saudi Arabia; Elizabeth Nickerson and Stacey Gabriel, The Broad Institute of MIT and Harvard University.

Funding for this research came, in part, from the National Institutes of Health (grants HD070494, NS048453), the Howard Hughes Medical Institute, California Institute for Regenerative Medicine, UCSD Christini Fund, Jane Botsford Johnson Foundation, Broad Institute, Center for Inherited Disease Research and Simons Foundation Autism Research Initiative.

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