MedicalXpress

Exercise provides clue to deadly ataxia

November 3 2011

When Dr. John Fryer and Dr. Huda Zoghbi prescribed mild exercise for mice with a neurodegenerative disorder called spinocerebellar ataxia 1 (SCA1), they did not know what to expect.

Fryer, then a postdoctoral associate in the lab of Zoghbi, the Baylor College of Medicine researcher who co-discovered the gene for the disorder, was disappointed when the exercise did not affect the mice's gait or walking ability. However, he and Zoghbi decided to put them back in their cages and see what would happen. What they found was the mice that exercised lived longer than those that had not. A report on their research appears online today in the journal *Science*.

The result was important because spinocerebellar ataxia 1 is a devastating inherited disorder with no cure. The disease occurs when a mutation in the gene for a protein called ataxin1 causes numerous repeats of the DNA sequence CAG (cytosine, adenine, guanine), the genetic code for an amino acid called glutamine. SCA1 first affects gait and motor skills, then swallowing, speech and cognition and eventually kills the person who has it.

Brief period of exercise

"What surprised us was that a brief period of exercise in early life had a long-term effect on survival," said Zoghbi, professor of molecular and human genetics, pediatrics, neurology and neuroscience and director of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital.

"That exercise extended the mice's survival surprised me," said Fryer, now an assistant professor of molecular neuroscience at the Mayo Clinic in Jacksonville, Florida. The finding sparked Fryer's interest and he then began to explore what happened within the neurons.

Protein partner

Exercise increased a growth factor that in turn dampened a particular pathway that involves a protein partner of ataxin1 called capicua. When capicua levels are decreased in mice carrying mutant ataxin1, several symptoms were improved including motor coordination and memory deficits. In SCA1 mice, certain neurons of the cerebellum called Purkinje cells are usually destroyed, but many of these were spared when capicua was reduced. Additionally, SCA1 mice with reduced levels of capicua were less likely to lose weight and they lived longer – just as the exercised mice did.

"This opens up the possibility for many more studies," said Zoghbi, who is also a Howard Hughes Medical Institute researcher. "Would more rigorous exercise be more helpful or would it hurt them?"

Might translate to humans

"It might translate to humans," said Fryer. "What we don't know yet is what kind of exercise would we recommend? We are not sure what we should tell an ataxia patient at this point but know that with more research we will have answers."

"Having shown that decreasing capicua improves symptoms begs the question if separating mutant ataxin1 and capicua would also suppress symptoms," said Zoghbi. "This work got us to a molecular pathway that might help us subdue the disease. It's like an onion. We are peeling away

the layers to get to the core that will help understand all the details that contribute to this disease."

Dr. Harry Orr, a long-time collaborator and co-discoverer of the SCA1 gene with Zoghbi and director of the Institute of Translational Neuroscience at the University of Minnesota, said, "This is the first time in our collaboration that we found something that will have a direct impact on patients sooner rather than later. This could open additional strategies for treatment. Exercise, however, may not help everyone, particularly those who are far into the disease."

"The path to this finding has been long," said Orr.

It started with finding the families and getting their help in finding the gene. They since developed mouse models that enabled them to study the disease and have looked at several molecular pathways involved.

Turning the corner

"We are starting to turn the corner to go back to the patients," said Orr. "These people have been very courageous and understanding."

"When one is looking at a disease, one cannot look at just one aspect of it," said Zoghbi. "We had to look at many changes in the neurons and mice to reach the conclusion in this paper. It's almost like detective work."

Provided by Baylor College of Medicine