Protein protects against nerve degeneration

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A protein called NMNAT protects against nerve cell degeneration in fruit flies and mice, said Baylor College of Medicine researchers in a report in the *Public Library of Science Biology* that appears online today.

The finding begs the question if a drug might be developed that could stimulate extra protein production and thus neuronal protection – both in injured cells and in those degenerating because of disease, said Dr. Hugo Bellen, the paper's senior author, director of the BCM Program in Developmental Biology and a Howard Hughes Medical Institute investigator. While more work needs to be done to determine whether that would be desirable, Bellen said the finding is an important one because it identifies NMNAT as essential in the life of the body's neurons.

Much of the work described in the paper was done by its first author, Dr. R. Grace Zhai, a postdoctoral fellow in Bellen's laboratory.

The story began two decades ago when researchers in the U.K. discovered a mouse whose injured nerve cells were slow to die. Even when the nerve was cut, it had some function two weeks later while in a normal mouse injured nerves are non-functional within two days, said Bellen.

Five years ago, researchers discovered that the mice had three copies of a gene for a protein that was a fusion of NMNAT and another protein. Bellen and his colleagues sought to determine whether NMNAT was actually protective by studying mutant forms of it in fruit flies or

Drosophila melanogaster, a commonly used model organism. NMNAT exists in a single state in the fruit fly, and there is only one form of it.

When Zhai, Bellen and colleagues bred flies that lack the protein in their visual system, they found that the neurons degenerated very rapidly. However, the degeneration could be slowed by keeping the flies in the dark and preventing their visual neurons from activating.

"In the absence of the NMNAT protein, the photoreceptors in the eye develop normally. They send out axons (tendril extension of the nerve that grow into the brain) and make synapses (the functional connection between a nerve axon and the target cell)," said Bellen.

However, late in the development of the eye, the insects in the pupal stage begin to sense light. As the neurons become active, they degenerate rapidly. Within two weeks after birth, there are almost no neurons left.

"Here is a case where the protein is required for the maintenance of the neuron," said Bellen.

When flies were raised in the dark, the neurons died, but at very slow pace when compared to those exposed to light.

"Activity clearly causes a massive degeneration," he said.

When they exposed flies that made large quantities of NMNAT in the eye to bright sunlight for 30 days, they found that only 20 percent of the neurons died – not the 80 percent that would have been expected.

"This protein can delay the neuronal degeneration process if it is present at a high level," said Bellen.

They also found that NMNAT alone and not the enzyme partner found

in mice and other vertebrates was sufficient to protect the neurons.

Bellen said more work needs to be done to identify the mechanisms at work in the neuronal protection and to determine how to prompt cells to increase productions of the protein.

Source: Baylor College of Medicine