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Protein Protects Against Degeneration of Neurons in Fruit Flies

Researchers have genetically manipulated fruit flies so that the flies produce a human protein that protects against the degeneration of neurons similar to those affected in Parkinson's disease.

The protective protein, called a chaperone, suppresses the toxicity of α -synuclein, a protein associated with Parkinson's disease in humans. Progressive loss of dopaminergic neurons produces the neurological symptoms of Parkinson's disease. Chaperone proteins normally aid in proper folding of proteins and are involved in protecting against cellular stresses.

The findings were reported in the December 21, 2001, issue of *Science* by Howard Hughes Medical Institute investigator [Nancy M. Bonini](#) and colleagues at the University of Pennsylvania School of Medicine.

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In Parkinson's disease and select other neurodegenerative disorders, α -synuclein is a key component of inclusion bodies, known as Lewy bodies, that are characteristic of these diseases. Mutations in α -synuclein have been found in some inherited forms of Parkinson's disease. Working with the fruit fly *Drosophila*, researchers had previously produced similar pathological effects of dopaminergic neuron loss, by engineering α -synuclein over-production in flies.

In previous studies, Bonini and her colleagues had shown that the Hsp70 chaperone protected against neurotoxicity in a *Drosophila* model of a neurodegenerative disorder in which pathogenic human proteins with long

runs of polyglutamine caused the destruction of neurons.

“We had shown that Hsp70 was a very powerful suppressor of polyglutamine toxicity in *Drosophila*, so we theorized that a chaperone that interfered with one neurodegenerative disease might interfere with another,” said Bonini.

In their experiments, the scientists showed that flies engineered to express the gene for human Hsp70 along with α -synuclein showed survival of dopaminergic neurons that normally degenerated upon expression of α -synuclein alone.

“We observed that the inclusion bodies were still present in the neurons,” said Bonini. “But the toxicity of α -synuclein was greatly diminished. This told us that the presence of the Hsp70 was reducing the toxicity of the α -synuclein, despite the continued presence of inclusions.”

The researchers showed that by experimentally interfering with a *Drosophila* counterpart of human Hsp70, they enhanced the toxicity of α -synuclein, suggesting a critical role for chaperones in the dopaminergic neurons. Moreover, loss of chaperone activity caused some loss of dopaminergic neurons in the flies in the absence of α -synuclein. This loss of neurons was similar to the damage caused by α -synuclein alone.

The neuroprotective effect of Hsp70 might stem from the chaperone’s ability to correct an abnormal and toxic conformation of α -synuclein and render it non-toxic. Alternatively, α -synuclein’s toxicity might arise from its ability to bind to Hsp70 and prevent it from doing its normal job. Augmenting levels of Hsp70, as the scientists did in their experiments, might correct that deficit and overcome the toxic effect of loss of chaperone function.

In addition to their studies in flies, the scientists explored whether Hsp70 might be found in Lewy body inclusions in the brain tissue of humans who had Parkinson’s disease. “When we examined brain tissue from Parkinson’s patients, as well as patients with other diseases associated with abnormal α -synuclein aggregation, we could see staining for Hsp70 and for another chaperone, Hsp40,” said Bonini. “This finding makes us hopeful that the protective effect of chaperones we found in flies might also be applicable to humans.”

Bonini said she hopes that her findings will encourage more research on the role of chaperones in mammalian models of disease. “If Hsp70’s role of protecting against α -synuclein toxicity is confirmed in mammals, an important step would be to pursue drugs that upregulate the stress response that produces these chaperones, and determine whether they will protect neurons,” she said.