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# TORquing Toxins

Extra doses of movement-disorder protein guard neurons against poisons

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**SAN FRANCISCO, CALIFORNIA**--A protein that distorts body movements when it malfunctions protects nerves in its normal form, according to work presented here 14 December at the American Society for Cell Biology annual meeting. In high doses, the protein helps worm neurons resist oxidative damage, the study reveals. The results suggest a role for the molecule in protecting against Parkinson's disease (PD).

Patients with the rare disease early-onset torsion dystonia lose control of their muscles, which causes them to twist involuntarily. The illness, often misdiagnosed as PD, results from mutations in the gene that encodes the torsin A protein. Torsin A's function isn't clear, but previous studies suggest that it helps block protein clumping, a hallmark of many neurodegenerative diseases, perhaps at sites of trouble. Torsin A accumulates in Lewy bodies, protein aggregates that pepper the brains of PD patients, and gloms onto α synuclein, another component of those structures; furthermore, it appears prominently in dopamine-producing neurons, the cells that die in PD. In the new work, neurological disease researcher Guy Caldwell and colleagues at the University of Alabama, Tuscaloosa, tested whether normal torsin A protects neurons from damage.

The team turned to the nematode *Caenorhabditis elegans*, which has eight dopamine-manufacturing neurons. Bathing the squigglers in a molecule related to dopamine spurs cells to pump out lethal reactive oxygen species. The researchers engineered worms to produce abnormally large amounts of torsin A or the worm version of the protein in the dopaminergic neurons. Two hours after toxin treatment, normal worms had lost all of their dopaminergic neurons. But even after 3 days, worms with extra torsin protein retained, on average, 60% to 70% of theirs.

Next, the team engineered worms to generate forms of torsin A that are linked to dystonia. After poison treatment, animals with torsin A mutations lost about twice as many neurons as did creatures that cranked out extra amounts of the normal version, but they preserved more neurons than controls, suggesting that even mutated torsin A offers some protection. The results mesh with the fact that only some people who carry defective torsin A develop torsion dystonia, says Caldwell. Torsin A mutations might place people on the brink of disease, and as-yet-unidentified environmental factors might push some of them over the edge.

How torsin A's biochemical activity prevents cell death isn't clear, but oxidative damage can unfold proteins, says cell biologist He-Jin Lee of The Parkinson's Institute in Sunnyvale, California. Torsin protein "somehow reverses that effect," he says. The result might illuminate ways to protect neurons in PD, because the brain is

riddled with oxidative stress in that disease, says PD researcher Anumantha Kanthasamy of Iowa State University in Ames. A key question in PD research, he says, is what makes dopaminergic neurons particularly vulnerable; the new work suggests alterations in torsin protein as a possible answer. Kanthasamy says he's intrigued by the data, but he cautions that "it's a long way from worms to humans." Extending the results could help reveal whether supplementing with torsin A will provide a new twist in keeping mammalian brains straightened out.

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Comment on Article

## References

**1.** S. Cao, C. C. Gelwix, K. A. Caldwell, G. A. Caldwell, Neuroprotective role for TOR-2 against ROS in dopaminergic neurons of *C. elegans*. American Society for Cell Biology 43rd Annual Meeting, 13-17 December 2003, San Francisco, California. [Meeting Web Site]

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