

# Overexcited neurons not good for cell health

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Neurotransmitters have consequences. They initiate events that are critical to a healthy life, giving us the ability to move, to talk, to breathe, to think. But that's if the neurotransmitters are getting it right and sending proper signals downstream to muscle cells, neurons or other cells.

Now a Northwestern University study reports that a mutation in a transcription factor that controls a neurotransmitter in the nematode *C. elegans* causes an imbalance in neuronal signaling that results in protein damage in target cells. Similar results and consequences on protein folding were found to occur upon exposure to the common toxins nicotine and lindane (a pesticide).

Whether due to genetic mutation or exposure to small molecules, the neurons become overexcited and fire incorrect signals too rapidly, resulting in proteins in target muscle cells becoming stressed, misfolding and becoming non-functional.

"To find that small molecules reproduce our genetic observations -- that both environment and genetics cause a molecular defect in the ability of proteins to function in muscle cells -- was not expected," said Richard I. Morimoto, Bill and Gayle Cook Professor of Biochemistry, Molecular Biology and Cell Biology in Northwestern's Weinberg College of Arts and Sciences, who led the research team.

This study provides some of the strongest evidence that nerve cell activity can directly affect the protein folding process in another cell.

(Muscle cells in the case of this study.) Many different diseases and conditions, such as many neurodegenerative diseases, certain cancers, muscular dystrophy and the aging process, cause loss of muscle cell function. How that happens is not well understood.

“We may have discovered an unexpected basis for a number of human diseases,” said Morimoto. “Particularly interesting is the link with the environment. We’ve shown that pesticides, which are widespread and have been linked to an increase in Parkinson’s disease and other neurodegenerative diseases among farmers, have profound effects on nerve communication -- even more than we expected.”

“Neuronal Signaling Modulates Protein Homeostasis in *Caenorhabditis Elegans* Post-synaptic Muscle Cells” is published by the journal *Genes & Development*. In addition to Morimoto, the study’s co-investigators include lead author Susana M. Garcia, a former graduate student of Morimoto’s and now a postdoctoral fellow at Harvard University; M. Olivia Casanueva, a postdoctoral fellow, and M. Catarina Silva, a visiting predoctoral student, both at Northwestern; and Margarida D. Amaral, University of Lisbon, Portugal.

Morimoto and his team studied presynaptic neurons and postsynaptic muscle cells in *C. elegans*, a transparent roundworm whose biochemical environment is similar to that of human beings and whose genome, or complete genetic sequence, is known.

Specifically, the researchers looked at what happened to polyglutamine proteins in muscle cells that were at the tipping point: the proteins were at risk of soon aggregating and losing their function. The scientists wanted to see if they could cause the protein, which is associated with Huntington’s disease, to show its toxicity prematurely. (If misfolded or damaged proteins accumulate beyond a certain critical point, they aggregate and disease can result. )

In separate experiments, the researchers induced two genetic mutations in presynaptic neurons, one that caused the reduction of the neurotransmitter GABA, which inhibits neuronal firing, and one that increases the action of a neurotransmitter called acetylcholine, which stimulates neuronal firing. The result of both mutations was overexcited neurons that disrupted the way the neurons sent signals to the muscle cells and caused protein aggregation.

The effects were similar when the researchers introduced both nicotine (a neurostimulant) and lindane (an inhibitor of GABA, causing overstimulated neurons) to neurons with no mutations.

“Neurons integrate information and transfer this information to surrounding cells, influencing protein homeostasis,” said Morimoto, an expert on Huntington’s disease, amyotrophic lateral sclerosis (ALS) and the cellular and molecular response to damaged proteins. “When a neuron’s electrochemistry is imbalanced every cell downstream is imbalanced. We’ve revealed that it’s an integrated communications network that determines protein folding.”

While Morimoto and his team focused only on postsynaptic muscle cells in this study, they plan to look at other cells and how neuronal signaling affects their function.

Source: Northwestern University

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