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Blocking metabolic protein improves movement in animals with amyotrophic lateral sclerosis

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Turning off a protein that helps cells balance energy increases animal mobility and reduces the death of nerve cells that control movement in animal models of amyotrophic lateral sclerosis (ALS), according to a study in the January 18 issue of *The Journal of Neuroscience*. The findings may one day guide new directions for the treatment of the progressive neurodegenerative disorder, for which there is currently no cure.

ALS is characterized by the breakdown of brain and spinal cord nerve cells that control muscles, eventually leading to weakness and death. In many neurodegenerative diseases, including ALS, nerve cells have difficulty maintaining a sufficient supply of energy — a factor that may contribute to nerve cell dysfunction and death. Recent studies show some people with ALS experience metabolic defects, such as using too much energy while at rest.

In the current study, Robert Kalb, MD, of the Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine, and colleagues examined spinal cord cells from mice that produce a mutant protein present in familial forms of ALS. The cells had abnormally high activity of an enzyme that helps balance a cell's energy production and usage — called AMP-activated protein kinase (AMPK) — compared with cells from normal mice. By reducing AMPK activity in the cells that produce the mutant protein, the researchers found they

could reduce motor cell death.

"We show that AMPK is activated in models of neurodegenerative diseases, and blocking or eliminating this enzyme promotes the survival of nerve cells," said Kalb, senior author of the study. "These observations suggest that responses of nerve cells to energy deficits, although well-intentioned, may in fact contribute to neurodegenerative disorders."

To test the effects of blocking AMPK activity on behavior, Kalb's team bred the microscopic roundworm *Caenorhabditis elegans* (*C. elegans*) to make the mutant ALS protein. While the mutant roundworms initially displayed difficulties moving, when the researchers reduced AMPK activity, their mobility improved.

"Since AMPK and metabolic diseases, like diabetes and obesity, have been studied for decades, this study opens new possibilities for ALS therapy," said Jean-Philippe Loeffler, PhD, an ALS expert from the University of Strasbourg. "Numerous drugs exist to manipulate this enzyme, and the next step in this research will be to demonstrate that drugs targeting AMPK are able to increase the lifespan of animal models of ALS."

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