What doesn't kill the brain makes it stronger: Possible new strategy for treating neurologic disorders

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Johns Hopkins scientists say that a newly discovered "survival protein" protects the brain against the effects of stroke in rodent brain tissue by interfering with a particular kind of cell death that's also implicated in complications from diabetes and heart attack.

Reporting in the May 22 advance online edition of Nature Medicine, the Johns Hopkins team says it exploited the fact that when brain tissue is subjected to a stressful but not lethal insult a defense response occurs that protects cells from subsequent insult. The scientists dissected this preconditioning pathway to identify the most critical molecular players, of which a newly identified protein protector – called Iduna -- is one.

Named for a mythological Norwegian goddess who guards a tree full of golden apples used to restore health to sick and injured gods, the Iduna protein increased three- to four-fold in preconditioned mouse brain tissue, according to the scientists.

"Apparently, what doesn't kill you makes you stronger," says Valina Dawson, Ph.D., professor of neurology and neuroscience in the Johns Hopkins Institute of Cell Engineering. "This protective response was broad in its defense of neurons and glia and blood vessels – the entire brain. It's not just a delay of death, but real protection that lasts for about 72 hours."

The team noted that Iduna works by interrupting a cascade of molecular events that result in a common and widespread type of brain cell death called parthanatos often found in cases of stroke, Parkinson's Disease, diabetes and heart attack. By binding with a molecule known as PAR polymer, Iduna prevents the movement of cell-death-inducing factor (AIF) into a cell's nucleus.

In some of the experiments, Dawson and her team exposed mouse brain cells to short bursts of a toxic chemical, and then screened these "preconditioned" cells for genes that turned on as a result of the insult. Focusing on Iduna, the researchers turned up the gene's activity in the cells during exposure to the toxic chemical that induced preconditioning. Cells deficient in Iduna did not survive, but those with more Iduna did.

In another series of experiments in live mice, the team injected a toxic chemical into the brains of a control group of normal mice and also into a group that had been genetically engineered to produce three to four times the normal amount of Iduna – as if they had been preconditioned. The engineered mice with more Iduna were much less susceptible to brain cell death: They had more functional tissue and markedly reduced stroke damage in their brains. In addition, the Iduna mice were less impaired in their ability to move around in their cages.

"Identifying protective molecules such as Iduna might someday lead to drugs that trigger the brain survival mechanism when people have a stroke or Parkinson's disease," says Ted Dawson, M.D., Ph.D., Leonard and Madlyn Abramson Professor in Neurodegenerative Diseases and scientific director of the Johns Hopkins Institute for Cell Engineering.

In research published April 5 in *Science Signaling*, the Dawsons' laboratories previously revealed the mechanism that underpins AIF's pivotal role in parthanatos.

By studying the 3-D structure of AIF, the team first identified the molecular pocket that looked like a potential PAR binding site. They then swapped that region out for a different one to see if it indeed took up PAR. Using HeLa cells in addition to mouse nerve and skin cells, the scientists noted that the AIF with the swapped region did not bind PAR and was not able to move into the nucleus.

The team genetically manipulated neurons so that they didn't make any AIF, then in some cells added wild-type AIF, and in others added an AIF that did not bind PAR. When those cells were stressed using the "stroke in a dish" technique, the cells with normal AIF died while those with the AIF that could not bind PAR did not, revealing that PAR binding to AIF is required for parthanatos.

"These findings suggest that identifying chemicals that block PAR binding to AIF could be very protective," says Ted Dawson. "On the other hand, identifying chemicals that mimic the effect of PAR polymer could be novel therapeutic agents that would kill cancers by causing cell death."

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