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Future therapies for stroke may block cell death

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A new therapy to re-activate silenced genes in patients who suffer from neurodegenerative diseases or stroke is being developed by researchers at the University of Illinois at Chicago and Cornell University.

During and after a stroke, certain cellular events take place that lead to the death of brain cells. Compounds that inhibit a group of enzymes called histone deacetylases can modulate gene expression, and in some cases produce cellular proteins that are actually neuroprotective -- they are able to block cell death.

"For the first time, we show which one of the 11 histone deacetylase enzymes might be the best target to achieve cellular neuroprotection," said the study's lead investigator, Alan Kozikowski, professor of medicinal chemistry and pharmacognosy and director of the drug discovery program at UIC. "This work gives us a good direction to follow in testing histone deacetylase inhibitors in animal models for diseases such as Parkinson's and Huntington's disease, and even stroke."

Stroke can cause permanent neurological damage or even death if not promptly diagnosed and treated. It is the third-leading cause of death and the leading cause of adult disability in the United States.

A great deal of research has gone into developing histone deacetylase inhibitors as novel therapeutics, but the majority of the work has been directed toward cancer, Kozikowski said -- in which case, paradoxically, the compounds are employed to stimulate the death of rapidly

multiplying cells. The molecule known as SAHA recently received approval by the Food and Drug Administration for use in cancer therapy and is the first of the histone deacetylase inhibitors to be marketed.

"The use of histone deacetylase inhibitors in medicine would thus appear to hold tremendous promise," Kozikowski said. But to be clinically useful, he said, drugs must be designed that are able to discriminate between various forms of histone deacetylase.

Kozikowski said the new findings, performed in collaboration with Dr. Brett Langley at the Burke-Cornell Medical Research Institute in White Plains, N.Y., are significant, and that "other exciting results are on the horizon." Researchers at the Mayo Clinic have found that other histone deacetylase inhibitors they have designed show promise for pancreatic cancer, while yet another, in work performed at the Walter Reed Army Institute of Research, may be effective against malaria.

"This is a new area of drug discovery for the 22nd century," Kozikowski said.

Source: University of Illinois at Chicago

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