MedicalXpress

'Gifted' natural vitamin E tocotrienol protects brain against stroke in three ways

July 5 2011

A natural form of vitamin E called alpha-tocotrienol can trigger production of a protein in the brain that clears toxins from nerve cells, preventing those cells from dying after a stroke, new research shows.

This process is one of three mechanisms identified so far that this form of vitamin E uses to protect brain cells after a stroke, meaning that this natural substance might be more potent than drugs targeting single mechanisms for preventing stroke damage, according to Ohio State University scientists who have studied the nutrient for more than a decade.

These researchers previously reported that the tocotrienol form of vitamin E protects the brain after a stroke by blocking an enzyme from releasing toxic fatty acids and inhibiting activity of a gene that can lead to neuron death.

Vitamin E occurs naturally in eight different forms, and all of this work is focused on the tocotrienol form, also known as TCT. The commonly known form of vitamin E belongs to a variety called tocopherols. TCT is not abundant in the American diet but is available as a nutritional supplement. It is a common component of a typical Southeast Asian diet.

In this new study, the researchers first clarified the role of a protein called MRP1, or multidrug resistance-associated protein 1. This protein clears away a compound that can cause toxicity and cell death when it builds up in neurons as a result of the trauma of blocked blood flow

associated with a stroke.

They then determined that TCT taken orally influences production of this protein by elevating the activity of genes that make MRP1. This appears to occur at the microRNA level; a microRNA is a small segment of RNA that influences a gene's protein-building function.

This is one of the first studies to provide evidence that a safe nutrient – a vitamin – can alter microRNA biology to produce a favorable disease outcome," said Chandan Sen, professor and vice chair for research in Ohio State's Department of Surgery and senior author of the study. "Here, a natural nutritional product is simultaneously acting on multiple targets to help prevent stroke-induced brain damage. That is a gifted molecule."

The research appears online and is scheduled for later print publication in the journal Stroke.

Over the past decade, Sen has led numerous studies on how the TCT form of vitamin E protects the brain against stroke damage in animal and cell models, and intends to eventually pursue tests of its potential to both prevent and treat strokes in humans. Approximately 795,000 Americans suffer new or recurrent strokes each year, and stroke is the third-leading cause of death in the United States, according to the American Stroke Association.

These latest research findings in mice follow a recent Food and Drug Administration certification of TCT as "Generally Recognized as Safe." The scientists conclude in the paper that even before clinical trials can take place, "TCT may be considered as a preventive nutritional countermeasure for people at high risk for stroke."

To determine the role of MRP1 in protecting brain cells, the researchers

compared the effects of an induced stroke in two groups of mice: normal mice and animals that were genetically modified to be deficient in the MRP1 protein.

Both groups of mice showed comparably decreased blood flow in the area of the stroke, but the mice deficient in MRP1 had a larger volume of tissue death than did normal mice.

The mice with the protein deficiency also had a 1.6-fold higher level of a toxin that is cleared by MRP1. This toxin is called GSSG, or glutathione disulfide, and these researchers have previously shown that a failure to clear this toxin appears to trigger neuron death in the brain after stroke.

"The protein has the effect of dredging out the toxin," said Sen, who is also a deputy director of Ohio State's Davis Heart and Lung Research Institute. "A significant finding in this work is the recognition that MRP1 is a protective factor against stroke. Thanks to tocotrienol, we were able to identify that path."

The presence of GSSG is linked to an excessive amount of glutamate that is released in the brain after a stroke. Glutamate is a neurotransmitter that, in tiny amounts, has important roles in learning and memory. Too much of it triggers a sequence of reactions that lead to the death of brain cells – the most damaging effects of a stroke.

This experiment showed for the first time that the loss of MRP1 function impairs the clearance of GSSG, and that MRP1 cells were recruited to the site of the stroke in normal mice, indicating this protein has a protective role in the brain after a stroke.

The researchers searched databases containing genomic data for a microRNA that appeared to have potential to influence production of MRP1. MicroRNAs bind to messenger RNA, which contains the actual

set of instructions for building proteins. When that connection is made, however, the microRNA inhibits the building of protein from messenger RNA. So an inverse relationship exists between a microRNA and a protein it controls.

The researchers saw this very relationship in the cell study in which they manipulated the candidate microRNA levels and observed the effects of changing those levels on the presence of the MRP1 protein.

Finally, the researchers compared mice that were treated with TCT supplements or corn oil as a control for 13 weeks before a stroke was induced. The amount of damaged brain tissue was smaller in the mice that received TCT supplementation than in the mice receiving corn oil. In addition, TCT supplementation was associated with a lower level of the candidate microRNA in the damaged brain tissue, as well as an increase in the abundance of MRP1 cells at the stroke site.

"Essentially what we are showing with mechanistic explanation is that tocotrienol protects neural cells. It is anti-neurodegenerative," Sen said. "This form of vitamin E helped us identify three major checkpoints in stroke-related neurodegeneration that were not known before we began testing tocotrienols against neurodegeneration"

Provided by The Ohio State University