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New treatments prevent brain injury hours after stroke in rats

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Two novel treatments -- a basic compound found in every cell in the body and an extract of green tea -- may prevent brain damage caused from stroke, according to two studies in rats led by a researcher at the San Francisco VA Medical Center.

Both treatments were administered through the nose, rather than intravenously, the conventional method for delivering drugs to the brain.

In one study, rats' brains were subjected to ischemia -- severely reduced blood flow – for two hours in a model of stroke. Researchers then administered nicotinamide adenine dinucleotide, or NAD+, immediately after "reperfusion," or resumption of blood flow. Reperfusion is the time when stroke damage actually occurs because brain cells are suddenly exposed to highly reactive and unstable oxygen molecules, which are toxic.

The researchers found that NAD+ reduced brain cell death from reperfusion by 70 to 86 percent compared with rats not given the treatment, according to lead author Weihei Ying, PhD, a research scientist at SFVAMC and an assistant adjunct professor of neurology at the University of California, San Francisco.

The study appears in the January 1, 2007 issue of *Frontiers in Bioscience*.

NAD+ plays a number of essential roles in cell metabolism. One role is supporting the activity of the DNA repair enzyme PARP-1, which

normally repairs cell damage from brain infection. In response to reperfusion following ischemia or brain trauma, PARP-1 is overactivated. As a result, it quickly depletes all available NAD+, in a sense its "fuel," and is unable to repair cell damage, leading to brain cell death.

In previous studies, SFVAMC researchers including Ying provided the first evidence that administration of NAD+ can completely prevent PARP-1-induced cell death in cell culture. The current study is the first to investigate NAD+ administration as a potential treatment for brain injury in animal models, and the first to demonstrate its effectiveness in an animal model, he says.

"Basically, we replenish the NAD+," Ying explains. "The protective effect is profound."

Administration of NAD+ also significantly reduced motor impairments commonly observed in rats after stroke, ranging from involuntary limb bending to inability to walk, says Ying.

A second study led by Ying investigated whether administration of the green tea extract gallotannin, or GT, can protect against post-ischemic brain damage. In previous cell culture studies by Ying and other researchers, GT had been shown to inhibit the action of PARG, an enzyme closely related to PARP-1, and in doing so decrease cell death under ischemia-like conditions. Ying's study indicates that it does the same in rats, reducing brain cell death significantly when administered intranasally up to three hours after reperfusion.

The results of the study were reported at the 2006 annual meeting of the American Society for Neurosciences.

In the same study, Ying and his team also discovered that intranasal GT

completely blocked a secondary post-ischemic effect associated with PARP-1 activation: the movement of the protein known as apoptosis inducing factor (AIF) from where it resides in a dormant state in the mitochondrion — the cell's power plant — into the nucleus, where it becomes active and causes the cell to die.

Significantly, GT provided no protection at all against either PARG or AIF when administered intravenously (IV). Ying designed the study in such a way that a comparison could be made of the efficacy of intranasal and IV drug delivery — the first known study to make such a comparison using an animal model of stroke.

"This finding suggests that the intranasal method could be more advantageous than IV for delivering a drug for treating central nervous system diseases," Ying says. "It may get much more of the drug past the blood-brain barrier."

Ying characterizes both compounds as "promising," but speculates that NAD+ has the greater potential as an agent for preventing brain cell death for several reasons.

"Our experimental results have suggested that NAD+ can produce greater protective effects than GT against ischemia," he notes. "Plus, NAD+ is a fundamental molecule for cell metabolism, so it is known to have relatively low toxicity." In addition, he says, NAD+ loss occurs after PARP-1 activation, meaning that NAD+ might be used later after injury than GT. Ying is currently investigating this question.

Finally, says Ying, recent studies have suggested that NAD+ plays an important role in basic biological processes such as calcium metabolism and aging. He speculates that it might become "a novel class of drug" for a variety of brain diseases and conditions including Parkinson's disease, Alzheimer's disease, traumatic brain injury, and hypoglycemic brain

injury.

Ying says that because both compounds provide significant protection hours after the onset of ischemia, both studies have important potential implications for treatment of ischemic brain injury among humans. In current medical practice, treatment during the first 60 minutes after injury — the so-called "golden hour" — is considered crucial if the patient is to survive with minimal damage.

Source: University of California - San Francisco