Modified tPA could be effective stroke treatment without bleeding risk

July 17 2012

Even when its clot-dissolving powers are removed, the stroke drug tPA can still protect brain cells from the loss of oxygen and glucose induced by a stroke, researchers have discovered.

The finding suggests that a modified version of tPA could provide benefits to patients who have experienced a stroke, without increasing the risk of bleeding.

The results will be published in the Journal of Neuroscience.

"We may have been giving the right medication, for the wrong reason," says senior author Manuel Yepes, MD, associate professor of neurology at Emory University School of Medicine. "tPA is more than a clot-busting drug, it functions naturally as a neuroprotectant,"

The co-first authors of the paper are postdoctoral fellows Fang Wu and Jialing Wu from the Department of Neurology, and Andrew Nicholson from the Department of Radiology and Imaging Sciences.

tPA was introduced as a treatment for acute stroke in the 1990s. Doctors have debated its effectiveness and safety ever since, because it can increase the likelihood of deadly hemorrhage. Many people experiencing a stroke do not receive tPA because of time constraints or other contraindications.

"tPA is supposed to be administered within the first 3-4.5 hours of the

onset of the stroke," Yepes says. "Otherwise there is no beneficial effect and instead there is an increase in the risk of hemorrhagic transformation."

Long before tPA ever became a drug, tPA was a protein produced by several tissues in the body, including brain cells. One of its functions is to convert the inactive protein plasminogen into the enzyme plasmin, which breaks down clots. Yepes' team has been studying tPA's additional functions beyond acting on plasminogen.

Exposing cultured neurons from the cerebral cortex to tPA protects the neurons from dying after being deprived of oxygen and glucose, the researchers found. tPA appears to induce a set of proteins that helps cells deal with the lack of oxygen and glucose that come from an interruption of blood flow.

This result contradicts previous reports about tPA's effects in the nervous system, some of which concluded that it can act as a neurotoxin.

"The discrepancy could be a matter of experimental design or dose," Yepes says. "Our results do suggest that the dose of tPA that is needed for a neuroprotective effect is significantly lower that the dose that we give to destroy the clot in our stroke patients."

A mutated form of tPA that could not activate plasminogen still had the protective effect on neurons in culture. Yepes' team also studied the effects of the mutated form of tPA in living animals. In mice, the researchers blocked a vessel supplying blood to the brain for one hour, simulating a stroke. Treatment with both regular and modified tPA could reduce the size of the damaged area of the brain.

The possibility that tPA may be working as a neuroprotectant also may explain why, clinically, tPA's benefits are sometimes not observed until

several weeks after treatment as it has been demonstrated in large clinical studies, Yepes says.

"If it was just a matter of the clot, getting rid of the clot should make the patient better quickly," he says. "It's been difficult to explain why you should have to wait three months to see a benefit."

"One of the main implications of our finding is that a form of tPA that does not act on plasminogen could still provide benefits, without the risks of inducing a bleeding in the brain," Yepes says. "The risk of bleeding creates a lot of anxiety, and it has resulted in the regrettable fact that only a small number of stroke patients currently benefit from treatment with tPA."

Yepes says a next step would be to try a "protease-inactive" version of tPA in a pilot clinical trial.

More information: F. Wu et al. Tissue-type plasminogen activator regulates the neuronal uptake of glucose in the ischemic brain. *J. Neurosci* (2012).

Provided by Emory University