tPA: Clot buster and brain protector

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(Medical Xpress)—Ever since its introduction in the 1990s, the "clot-busting" drug tPA has been considered a "double-edged sword" for people experiencing a stroke. It can help restore blood flow to the brain, but it also can increase the likelihood of deadly hemorrhage. In fact, many people experiencing a stroke do not receive tPA because the window for giving the drug is limited to the first few hours after a stroke's onset.

But Emory neurologist Manuel Yepes may have found a way to open that window. Even when its clot-dissolving powers are removed, tPA can

still protect brain cells in animals from the loss of oxygen and glucose induced by a stroke, Yepes' team reported in the *Journal of Neuroscience* (July 2012).

"We may have been giving the right medication, for the wrong reason," Yepes says. "tPA is more than a clot-busting drug. It functions naturally as a neuroprotectant."

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

"This would be a major breakthrough in the care of patients with stroke, if it could be developed," says Michael Frankel, director of the Marcus Stroke and Neuroscience Center at Grady Memorial Hospital.

tPA is a protein produced by the body and has several functions. One is to activate the enzyme plasmin, which breaks down clots. But Yepes' team has discovered that the protein has additional functions. For example, in cultured neurons, it appears to protect neurons in the brain, turning on a set of genes that help cells deal with a lack of oxygen and glucose. This result contradicts previous reports that the protein acts as a neurotoxin in the nervous system.

Tweaking tPA so that it is unable to activate plasmin—while keeping intact the rest of its functions—allowed the researchers to preserve its protective effect on neurons in culture. This modified tPA also reduced the size of the damaged area of the brain after simulated stroke in mice, with an effect comparable in strength to regular tPA. The next step is to test the modified version of tPA in a pilot clinical trial.

The possibility that tPA may be working as a neuroprotectant may explain why, in large clinical studies, tPA's benefits sometimes go

unobserved until several weeks after treatment, 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."

Provided by Emory University

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