Brain may use clot-busting drug naturally as protection against stroke

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New research on the properties of the clot-busting stroke drug tPA (tissue-type plasminogen activator) suggests that tPA can act as a neuroprotectant and may form the keystone of an adaptive response to a reduction in blood flow.

Scientists from Emory University School of Medicine have shown that certain parts of the brains of mice lacking the gene for tPA are more vulnerable to stroke. In addition, tPA can protect neurons in the same part of the brain from the stress of hypoxia (low oxygen).

The results are published online this week in the Journal of Clinical Investigation.

tPA was introduced as a treatment for acute stroke in the 1990s. Physicians have debated its safety and effectiveness ever since then, because it can increase the likelihood of hemorrhage. Previous research has shown that in some situations, tPA can be seen as a neurotoxin. In addition to dissolving clots, tPA can increase the permeability of the blood-brain barrier, and it can cross from the blood vessels into the brain tissue, generating inflammation.

"tPA is not only a drug, it is a natural protein produced in response to hypoxia," says senior author Manuel Yepes, MD, associate professor of neurology at Emory University School of Medicine. "If you look at the parts of brain where the gene for tPA is turned on the most, one of these is the hippocampus. It is well known that the hippocampus is especially

vulnerable to hypoxia compared with other regions of the brain. We believe there is a reason for this overlap."

The hippocampus is a structure in the middle of the brain thought to be responsible for memory formation. In mice lacking the gene for tPA, neurons in the hippocampus are more vulnerable to dying after a short simulated stroke lasting 20 minutes, Yepes and his colleagues found. In the laboratory, pre-treatment with tPA protects hippocampal neurons in culture from hypoxia. In contrast, tPA has the opposite effect on neurons from the cortex.

tPA's protective properties suggest that it may be playing a role in a process called "ischemic preconditioning," where a less-than-lethal stroke can protect the brain against a later repeat, Yepes says. tPA's effects on the blood-brain barrier can be seen as a way to get more blood to a deprived part of the brain.

In most people who experience a stroke, atherosclerosis has gradually restricted blood flow over a long time period, provoking attempts by the brain to work around the obstacle.

"Many individuals who have a transient ischemic attack, which is a non-lethal mini-stroke, go on to have a more serious and debilitating stroke," Yepes says. "This means we should be thinking about tPA less as a way of treating ischemic stroke but more as a way to prevent it."

One way to use tPA preventively could be to prolong the effects of tPA produced naturally in the brain, a strategy Yepes and his colleagues are investigating now.

They are also probing which molecules in neurons are necessary for the protective effects of tPA. tPA appears to be acting on a class of neurotransmitter receptors known as NMDA receptors, they show in the

paper.

More information: Tissue-type plasminogen activator is a neuroprotectant in the murine hippocampus. R. Echeverry, J. Wu, W.B. Haile, J. Guzman and M. Yepes. J. Clin. Invest. (2010)

Provided by Emory University