

# **Stress response in the brain relies on a blood-thinning protein**

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A stressed-out mouse tends to be a bit timid, tentative, even fearful. For that matter, so does a stressed-out human. Our ability to learn from frightening situations is part of what helps us avoid them in the future. When that learning process goes awry, it can lead to depression and a decreased ability to recognize dangerous situations. Now, research by Rockefeller scientists has pinned down a protein in the hippocampus — a part of the brain that controls memory, learning and fear — that's essential for maintaining this stress response.

The protein tPA (tissue plasminogen activator) is best known for its ability to dissolve blood clots. But more and more studies are showing that it also plays a role in neural plasticity in the brain. Sidney Strickland, head of the Laboratory of Neurobiology and Genetics, and postdoc Erin Norris have taken the research a step further to see whether tPA has anything to do with how stress affects memory, learning ability and anxiety.

Prior research from the Strickland lab had shown that mice lacking tPA also seem to lack fear, a behavior largely dictated by a part of the brain called the amygdala. To determine whether tPA also affects behavior controlled by the hippocampus, Norris and Strickland compared normal mice to tPA-deficient ones. Then they divided the mice up further: Half of each group they left alone, and the rest they exposed to six hours of painless restraint stress.

Once the groups were complete, the researchers placed each mouse —

wild-type, stressed wild-type, tPA-deficient and stressed tPA-deficient — into a small chamber, where the rodents were exposed to a sound paired with a small electric shock. The next day they returned the mice to the chamber, but this time left them alone.

All of the non-stressed as well as the stressed wild-type mice appeared to have learned from experience, showing their fear of the chamber in the form of freezing behavior. In comparison, the mice lacking tPA had significantly reduced freezing responses. “So they were either less fearful of their situation, or they just didn’t remember — they didn’t learn from their training,” Norris says. “We could say that if you don’t have tPA and you are in a stressful situation, you don’t have synaptic plasticity changes in the hippocampus.” The wild-type mice were capable of learning because tPA could induce changes in their brains’ neural synapses.

Norris and Strickland believe that the underlying mechanism for this has to do with a receptor that normally resides at the cell membrane but changes its location during stress. They found that, in mice lacking tPA, the receptor stayed anchored at the membrane even during stress. And without the receptor’s change in position, there could be no stress response. Norris has since begun investigating whether tPA could also be an important factor in depression, since stress has been shown to lead to this disorder in humans.

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