

# Abnormal emotional behavior of mice overexpressing the antiprotease neuroserpin mice is corrected by co-expression of a tissue-type plasminogen activator transgene

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Increasing evidence suggests that the balance between extracellular proteases, such as tissue-type plasminogen activator (tPA), and antiproteases, such as neuroserpin, is critical for neuronal function and pathology. We have found previously that transgenic mice with neuronal overexpression of tPA under the control of the promoter Thy1.2 (ThytPA) have massively elevated brain tPA activity and improved learning. Mice overexpressing the antiprotease neuroserpin under the control of the same promoter (ThyNs) show decreased brain tPA activity. Recent analysis of their explorative behavior revealed an anxiety-like phenotype. To address the question whether these phenotypes are due to a disturbed balance between tPA and neuroserpin, we generated bi-transgenic mice, by crossing the ThytPA and ThyNs lines. Zymographic analysis shows that tPA activity in bi-transgenic brains is restored to near wild-type level, although activity remains slightly elevated in some regions, such as CA1 or deep layer of the neocortex. The behavioral phenotype of bi-transgenic mice was compared with littermates bearing only one or none of the transgenes in a battery of tests. When confronted to a novel object, both ThytPA and ThyNs mice showed increased avoidance behaviors, while bi-transgenic mice behaved as wild-type littermates. Thus, normal behavior could be restored if the balance between tPA and its inhibitor was reestablished by over expressing both as a transgene. However, this was not the case when we assessed episodic memory in a water-maze task. As expected, ThytPA mice showed improved performance. By contrast, the ThyNs transgene had no effect on performance in this task. It also failed to diminish the effect of ThytPA transgene in bi-transgenic mice. This suggests that spatial learning is modulated by actions of tPA that are independent of neuroserpin. Taken together, our results provide the first evidence that dysregulation of the balance between proteases and antiproteases in the brain might disturb emotional behavior.

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