

Reduced exploratory behavior in mice with altered expression of the extracellular protease inhibitor neuroserpin

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Neuroserpin (Ns), a member of the serpin family of serine protease inhibitors, is expressed in the central nervous system and is an inhibitor of tissue type plasminogen activator (tPA) and plasmin. Available evidence suggests that the balance between antiproteases and their target proteases in the extracellular space may be critical for neuronal function and pathology. Transgenic mice which overexpress neuroserpin in neurons (Thy/cNs) have decreased brain tPA proteolytic activity and show a reduced infarct size following focal ischemia. Mice genetically made deficient in neuroserpin (NsKO) have recently been generated. Western-blot and immunoprecipitation confirm that homozygous NsKO mice lack Ns protein completely, whereas heterozygous mice express a reduced amount. Interestingly, zymographic analysis of NsKO brain did not reveal increased tPA activity, suggesting that other inhibitors contribute to the regulation of tPA and may compensate for the defect. We analyzed NsKO and Thy/cNs mice in a preliminary behavioral screen. Both mutants are healthy and show normal spontaneous behaviour. Although available evidence suggests that the extracellular proteolysis may be critical for learning and memory, both NsKO and Thy/cNs mice perform normally in a water-maze task assessing spatial reference memory. However, homozygous NsKO mice exhibited reduced exploratory activity, in particular they were reluctant to investigate the open zones of an elevated maze, as well as a novel object introduced into a familiar arena. A milder form of this phenotype was observed also in heterozygous mice. Thy/cNs mice showed normal activity in most of these tests but displayed a neophobic reaction towards the novel object. These results implicate Ns in the regulation of emotional behaviour through a mechanism that are at least in part independent of tPA activity and shed new light on the regulation of extracellular proteolysis in the brain.

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