

Altered expression of the extracellular protease inhibitor neuroserpin interferes with exploratory behavior and reaction to novelty

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Available evidence suggests that the balance between antiproteases and their target proteases in the extracellular space may be critical for neuronal function and pathology. Neuroserpin, 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. Mice genetically made deficient in neuroserpin (NsKO) have been generated. Homozygous NsKO mice lack neuroserpin 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. These mice, together with transgenic mice which overexpress neuroserpin in neurons under the control of Thy1.2. promoter (Thy/cNs) have been subjected to analysis of activity in their home cages and to a battery of behavioral tests. Both NsKO and Thy/cNs mutants show normal levels and circadian patterns of home cage activity. However, homozygous NsKO mice exhibited reduced exploratory activity in novel environments, 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 neuroserpin in the regulation of emotional behaviour through a mechanism that is at least in part independent of tPA activity and they shed new light on the role of extracellular proteolysis in the brain.

Supported by Swiss National Foundation, BIO4CT980297/BBW98.0125, The Roche Research Foundation, Société Suisse de la Recherche Médicale, Hartmann-Müller Foundation and NCCR Neural Plasticity and Repair

Keywords: learning, emotional behavior, extracellular proteolysis