The function of the DCLK gene in the stressed hippocampus

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Aberrant concentrations of glucocorticoids, as is the case during periods of chronic stress, are having devastating effects on the hippocampus, a brain area involved in learning and memory processes. As the two glucocorticoid receptors, the glucocorticoid receptor and the mineralocorticoid receptor, act as transcription factors, glucocorticoid-responsive genes likely mediate these devastating effects on the hippocampus.
Using large scale screening methods, such as Sage and Gene-chips, we have recently identified several glucocorticoid-responsive genes in the hippocampus. A novel, putative glucocorticoid-responsive gene, the doublecortin-like kinase (DCLK) gene, encodes numerous transcripts by means of alternative splicing. Interestingly, one of these transcripts, CARP (calcium/calmodulin dependent protein kinase related peptide), is up-regulated in the hippocampus in reaction to epileptic drugs and is also responsive to cocaine. Also, it was found to be specifically induced in apoptotic granule cells in the hippocampus of adrenalectomized rats. Moreover, another product of this gene, DCLK-short, has clear amino acid homology with members of the calcium/calmodulin dependent protein kinase-family. In addition, it was found to be expressed predominantly in the adult limbic system, and given the role for CaM kinases in general, may be important in processes involving the structural plasticity of the hippocampal formation.
These data strongly suggest an important role for the DCLK gene in stress-related hippocampal plasticity and neurodegeneration. However, its role *in vivo* remains largely unclear. Therefore, the aim of this project is to generate and characterize transgenic mice over-expressing CARP and DCLK-short.
Three transgenic C57/BL6 mouse lines were established: 1) two lines over-expressing a construct encoding the 55 amino acid serine-rich peptide CARP (lines CARP-77 and CARP-89) and 2) one line over-expressing a FLAG-tagged, constitutively active form of DCLK-short (line ΔC-94). We will present evidence showing that all three lines express the desired constructs specifically in limbic brain areas, including the hippocampal formation. In addition, preliminary results on adrenalectomy-induced morphological alterations in the hippocampus of CARP-77 mice, will be shown.

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