

Matrix metalloproteinase-9 (MMP-9) in brain function and dysfunction

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Understanding of the role immediate early genes/inducible transcription factors in the brain requires identification of their genomic targets. The most advanced example for Fos-Jun/AP-1 control of gene expression in the adult brain has been provided for TIMP-1. Jaworski *et al.* (1999) combined a variety of approaches to show that gene encoding TIMP-1 may be an AP-1 target in the rodent hippocampus in response to seizures.

TIMP stands for tissue inhibitor of matrix metalloproteinases. TIMP-1 appears to be the TIMP family member that is specifically directed towards the extracellular matrix (ECM) protease, MMP-9 (matrix metalloproteinase-9). Hence, we have investigated whether MMP-9 may also be responsive to neuronal activity in the hippocampus *in vivo*. We have found indeed that MMP-9 is upregulated in the dentate gyrus (DG) neurons of the hippocampus in response to kainate-evoked seizures. This upregulation was observed at the level of mRNA abundance and its apparent translocation towards the activated dendrites. Furthermore, enzymatic activity of the MMP-9 was markedly increased throughout the dentate gyrus and dendrites of the granule neurons. It is of note that such selective, limited to the dentate gyrus, response to kainate is rare and of great interest, since the DG is in our hands the only part of the hippocampus that is spared of neurodegeneration and, furthermore, undergoes plastic changes. We have also proposed that MMP-9 may be directly involved in breaking down beta-dystroglycan at the synapse, and may play a role in a retrograde synaptic signaling. Recently, we have found further support for synaptic localization of the MMP-9 as well as functional evidence for MMP-9 to play a role in neuronal plasticity, including learning and memory. In another set of studies MMP-9 has been implicated in excitotoxic neuronal death (Rivera *et al.*, 2002). In conclusion the aforementioned results and considerations raise an intriguing possibility that TIMP-1/MMP-9 extracellular proteolytic system may act as an AP-1 target in neuronal plasticity and apoptotic cell loss. Finally, it is of note the fact that the system acts extracellularly makes what makes it particularly amenable for therapeutic manipulation.

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