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CENTRAL-NERVOUS-SYSTEM INJURY INDUCES EXPRESSION OF NEUTRAL ENDOPEPTIDASE-24.11 (NEP-ENKEPHALINASE) IN REACTIVE ASTROCYTES - IMPORTANCE FOR PEDIATRIC GLIOMAS

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Authors

BACK, SA
LIU, A
FALLON, JH
et al.

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CENTRAL NERVOUS SYSTEM INJURY INDUCES EXPRESSION OF NEUTRAL ENDOPEPTIDASE-24.11 (NEP; "ENKEPHALINASE") IN REACTIVE ASTROCYTES: IMPORTANCE FOR PEDIATRIC GLIOMAS.

S. A. Back*, A. Liu*, J.H. Fallon*, F. L. Meyskens Jr.**, and S. Loughlin*. Depts. of Pediatrics, Anatomy and Neurobiology and the Clinical Cancer Center, University of California, Irvine, CA

The enzyme NEP is identical to the common acute lymphocytic leukemia antigen (CALLA), a tumor marker associated with improved prognosis in children diagnosed with acute lymphocytic leukemia. NEP is expressed in human glioma cell lines and rat mixed glial tumors, suggesting a role in pediatric gliomas. In the present study, NEP expression in astrocytes was examined histochemically in the forebrain of rats 3-28 days after the neurotoxin N-methyl-D-aspartate (NMDA) was stereotaxically injected into the caudate putamen (Back and Gorenstein, J. Neurosci. 9:4439-4455, 1989) or a traumatic injury was induced by stereotaxically advancing a 1 µl Hamilton syringe into the cerebral cortex or caudate. Tissue sections were processed for immunocytochemical localization of the astrocyte marker glial fibrillary acidic protein (GFAP) or transforming growth factor-alpha (TGFα). In normal forebrain, NEP localized to occasional GFAP-labeled protoplasmic astrocytes in layer 1 of the neocortex. At 3 to 28 days after NMDA injection, a marked reactive astrocytosis surrounded the site of injury. Many of these reactive astrocytes contained GFAP and NEP, as demonstrated using a double-labeling fluorescence technique. The specificity of the NEP localization was verified using the selective NEP inhibitors, JHF-26 or phosphoramidon, which abolished all astrocyte staining at concentrations as low as 10 nM. Numerous TGFα–immunoreactive astrocytes were also observed at the site of NMDA injection, many of which contained both NEP and TGFα. Colocalization of GFAP and TGFα confirmed that the population of cells expressing TGFα were exclusively astrocytes. Parallel studies, after traumatic injury, similary demonstrated that numerous reactive astrocytes at the injury site coexpressed NEP and TGFα.

These studies provide the first evidence that astrocytes can express NEP. NEP expression correlates with both the proliferative state of CNS astrocytes and the expression of TGFα. While, resting astrocytes rarely express NEP, NEP activity is markedly increased in TGF-α-positive reactive astrocytes. Recently, TGFα was shown to be highly associated with human malignant gliomas in one series of 20 patients. Reactive astrocytes, thus, behave like malignant gliomas cells in that they also coexpress NEP and TGFα. We hypothesize that enhanced NEP expression occurs in reactive astrocytes as part of a mobilization of the immune system in the CNS, and may occur in response to an immune mediator such as the cytokine interleukin-1, an *in vitro* substrate of NEP and a known mediator of astroglial and glioma cell proliferation. This reactive astrocyte model represents a useful system to study the mechanisms which regulate NEP expression in proliferating glial cells, and may yield new insights into the functional importance of NEP in pediatric gliomas. S.A.B. is a Bank of America-Giannini Foundation fellow.