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BRAIN RESEARCH

Research Report

Upregulation of cathepsin S in the aging and pathological nervous system of mice

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ABSTRACT

Cathepsins have long been regarded enzymes that are primarily involved in general protein turnover within lysosomes. However, more recently, their differential cell and tissue distributions suggest that at least some of them participate in specific cellular processes. Cathepsin S (CATS) is mainly expressed in cells of mononuclear phagocytotic origin and plays a major role in the MHC-II-mediated antigen presentation. Although a central role for CATS in brain function has also been suggested, its localization and regulation in the central nervous system are still poorly understood. In the present study we investigated the regional and cellular expression of CATS in normal, aging and pathological mouse brain. Our studies show that CATS is expressed throughout the adult mouse brain, in particular in microglial cells. In aged mice, CATS protein expression increases in these cells. In addition, it became apparent that in old mice a larger number of neuronal cells stained positive for this protease. At the subcellular level, CATS immunostaining accumulated in granules, indicating a lysosomal localization. In a transgenic mouse model of amyotrophic lateral sclerosis expressing mutant superoxide dismutase 1 (SOD1), CATS transcript and protein levels were significantly upregulated in spinal cord and lower brain regions displaying neuronal degeneration. The majority of strongly immunopositive cells in these regions exhibited microglial morphology. These results suggest that CATS participates in inflammatory processes accompanying aging and pathologies of the CNS.

1. Introduction

Cathepsins are lysosomal proteases involved in physiological protein degradation (Kirschke and Barrett, 1987). According to their catalytic mechanism, they are further defined as cysteine, aspartic or serine proteases. With eleven human members (cathepsin B, C, F, H, K, L, O, S, V, W and X) and eight additional members in the mouse (cathepsin 1, 2, 3, 6, J, M, Q and R) the cysteine proteases represent the major group of these enzymes (Turk et al., 2000; Deussing et al., 2002). The

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Abbreviations: ALS, amyotrophic lateral sclerosis; BSt, brainstem; CATB, cathepsin B; CATD, cathepsin D; CATE, cathepsin E; CATL, cathepsin L; CATS, cathepsin S; CATX, cathepsin X; Cor, cortex (cerebral); Cer, cerebellum; GFAP, glial fibrillary acidic protein; Hipp, hippocampus; LM, littermate; MF, mature from of CATS; PF, proform of CATS; PPF, preproform of CATS; SC, spinal cord; SOD1, superoxide dismutase 1; TG, transgenic

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lysosomal cysteine cathepsins belong to the papain superfamily (clan CA, family C1) of cysteine proteases (Barrett et al., 1998). They are synthesized as inactive preproenzymes. The prepeptide is removed during the passage to the endoplasmic reticulum and the procathepsin undergoes proteolytic processing to the mature enzyme in the lysosomal compartment.

Besides their physiological role in cellular protein metabolism some cathepsins are involved in specific cellular processes like antigen processing and bone remodelling, represented by a tissue- and cell-specific expression pattern (Chapman et al., 1997; Riese et al., 1998; Nakagawa et al., 1999). Cathepsin S (CATS) belongs to the cathepsins with a distinct substrate specificity. As such it degrades the invariant

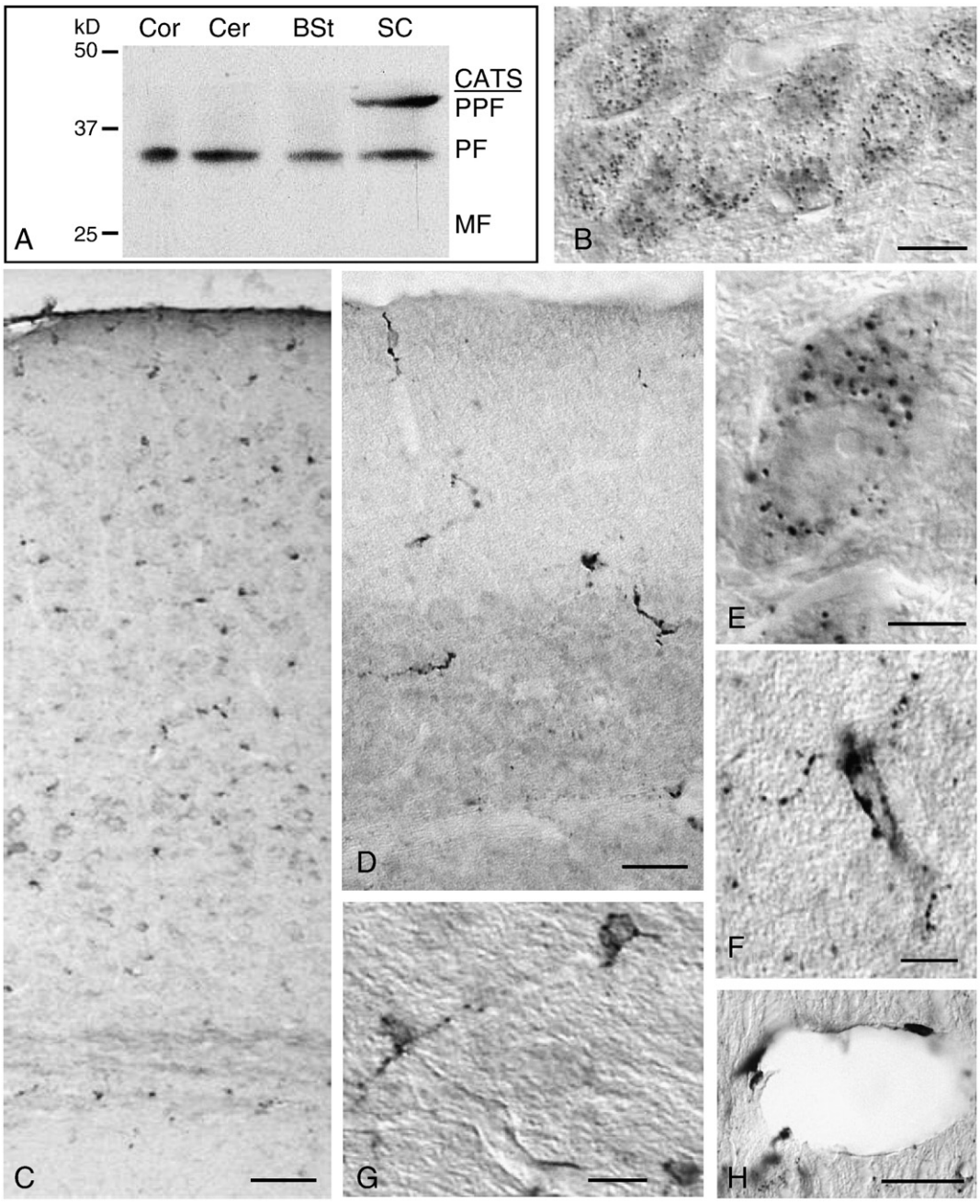

Fig. 1 – CATS in the adult mouse brain. (A) Western blot analysis of the relative abundance of CATS protein in the cerebral cortex (Cor), the cerebellum (Cer), the brainstem (BSt) and spinal cord (SC) of a 4-week-old C57BL/6 mice. Signals of the proform (PF) were detected in all regions analyzed, whereas the preproform (PPF) could only be detected in spinal cord tissue. Expression of the mature form (MF) was not found in any of the analyzed regions. Exposure times: PPF/PF band = 5 min, MF band = 30 min, tubulin band = 2 min. (B–H) Light micrographs of CATS-immunoreactive cells in the hippocampus (B), the cortex (C, F, H), the cerebellum (D, G), and the brainstem (E). Granular immunodeposits are localized in the pyramidal neurons of the hippocampus (B), single large neurons in the brainstem (E), small glia-like cells (F, G), and cells around blood vessels (H). Scale bars: 50 μm (C, D, F), 20 μm (B, G), and 10 μm (E, H).