DEFINITION OF A ROLE FOR MATRIX METALLOPROTEINASES (MMPS) IN NEURONAL APOPTOSIS INDUCED BY HIV-1 GP120 IN RAT

Rossella Russo[1], M. Tiziana Corasaniti[2] and Giacinto Bagetta[1]

[1]Department of Pharmacobiology, University of Calabria, 87036 Arcavacata di Rende (CS) Italy
[2]Department of Pharmacobiological Sciences, University of Catanzaro Magna Graecia, 88100 Catanzaro, Italy

HIV-associated dementia (HAD) is a frequent complication of HIV-1 infection, characterized by cognitive and motor dysfunctions. The human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein, gp120, has been proposed as the major aetiologic agent of the neuronal loss reported, post-mortem, in the brain cortex of AIDS patients.
Experimental evidences demonstrate that gp120 causes excitotoxic neuronal degeneration and death of several types of neurons *in vitro* and *in vivo*. Transgenic mice expressing gp120 in the brain develop neuropathological changes recapitulating those described in the brain of patients affected by HAD. Using transmission electron microscopy in conjunction with immunogold labeling of neuronal epitopes and TUNEL staining techniques we have reported that subchronic intracerebroventricular (i.c.v.) injection of recombinant gp120 in the adult rat causes DNA fragmentation and ultrastructural changes typical of neuronal apoptosis in the brain neocortex. The observed neuronal damage induced by gp120 is preceded by microglial activation and early enhancement of the expression of the pro-inflammatory cytokine IL-1beta triggered by activation of the CXCR4 chemokine receptor. In fact, SDF-1α, the natural ligand of CXCR4, minimizes IL-1beta elevation and prevents neuronal death induced by the viral protein. More recent experiments have yielded original data to implicate metalloproteinases (MMPs)-9 and MMP-2 in the cleavage and activation of IL-1beta triggered by gp120 in the brain neocortex of rat. In fact, administration of the HIV-1 coat protein gp120 (100 ng, i.c.v.) enhanced the expression of pro-MMP-9, active MMP-9 and MMP-2 as early as 1 hour after the exposure to the viral protein. Pharmacological manipulation of MMPs activity, using the specific, broad spectrum MMPs inhibitor GM6001 (10 ng/rat, given i.c.v. 1 hour before gp120), minimized the increase in IL-1beta immunoreactivity and prevented neuronal apoptosis caused by gp120. These findings point to a novel role for MMPs in the processing and activation of the pro-inflammatory cytokine, IL-1beta, during neuroinflammation.

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