

Protective effect of glutathione in HIV-1 lytic peptide 1-induced cell death in human neuronal cells.

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To elucidate the pathogenic mechanisms involved in neurodegeneration in AIDS patients with cognitive deficits, we have examined the toxic effect of the lentivirus lytic peptide 1 (LLP-1) corresponding to the carboxyl terminus of HIV-1 transmembrane glycoprotein gp41 on human neuronal and glial cell lines. LLP-1 induced a significant lactate dehydrogenase (LDH, a marker of cell death) release from these cells in a concentration- and time-dependent manner, while the noncytolytic LLP-1 analog 2 had little effect. Application of LLP-1 to SH-SY5Y, a well-characterized human neuronal cell line, caused the decline of intracellular glutathione (GSH) content that appeared to occur before a significant LDH release. Furthermore, LLP-1 elicited a significant loss of mitochondrial function as measured by mitochondrial transmembrane potential (MTP). Among the reducing agents and antioxidants tested, GSH and a GSH prodrug N-acetylcysteine (NAC) provided protection against LLP-1-induced neuronal cell death, evidently by restoring the intracellular GSH levels and blocking the disruption of mitochondrial integrity. Thus, gp41-derived LLP-1 may be a potential neurotoxic agent capable of causing the intracellular GSH depletion and disturbing the mitochondrial function, possibly contributing to the neurodegenerative cascade as seen in HIV-1-associated dementia. Our data indicate that restoring both GSH concentration and mitochondrial function may hold promise as possible therapeutic strategies for slowing disease progression of dementia in AIDS patients.

