

The RNA-binding protein HuD promotes spinal GAP43 overexpression in antiretroviral-induced neuropathy

M.D. Sanna, A. Quattrone, T. Mello, C. Ghelardini, N. Galeotti

A B S T R A C T

Nucleoside reverse transcriptase inhibitors (NRTIs) are known to produce painful neuropathies and to enhance states of pain hypersensitivity produced by HIV-1 infection in patients with AIDS leading to discontinuation of antiretroviral therapy, thus limiting viral suppression strategies. The mechanisms by which NRTIs contribute to the development of neuropathic pain are not known. In the current study, we tested the hypothesis that HuD, an RNA binding protein known to be an essential promoter of neuronal differentiation and survival, might be involved in the response to NRTI-induced neuropathy. Antiretroviral neuropathy was induced by a single intraperitoneal administration of 2',3'-dideoxycytidine (ddC) in mice. HuD was physiologically expressed in the cytoplasm of the soma and in axons of neurons within DRG and spinal cord and was considerably overexpressed following ddC treatment. ddC up-regulated spinal GAP43 protein, a marker of neuroregeneration, and this increase was counteracted by HuD silencing. GAP43 and HuD colocalize in DRG and spinal dorsal horn (SDH) axons and administration of an anti-GAP43 antibody aggravated the ddC-induced axonal damage. The administration of a protein kinase C (PKC) inhibitor or the PKC γ silencing prevented both HuD and GAP43 increased expression. Conversely, treatment with the PKC activator PDBu potentiated HuD and GAP43 overexpression, demonstrating the presence of a spinal PKC-dependent HuD-GAP43 pathway activated by ddC. These results indicated that HuD recruitment and GAP43 protein increase are mechanistically linked events involved in the response to antiretroviral-induced neurodegenerative processes.
