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HIV-1 uses a neuroimmune receptor, VPAC1, to facilitate its integration

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It has previously been reported that gp120 of the HIV-1 envelope interacts with VPAC1 to provide a facilitation signal for HIV-1 infection. VPAC1 is one of three, seven transmembrane-spanning G protein-coupled receptors belonging to the secretin family of neuroendocrine receptors. VPAC receptors also function in immune-mediated mechanisms. Blocking the VPAC1 signal transduction pathway by specific signal-blocking antibody or using strategies to knock-down or over-express VPAC1 confirmed the facilitation effect of VPAC1 on HIV-1 infection. Initial results that examined 2-LTR circular DNA suggested that the VPAC1 signal initiated by HIV-1 gp120 activation acts on the formation of the HIV-1 pre-integration complex and/or its transport into the nucleus prior to integration of the HIV-1 provirus. To examine this hypothesis, we used Chinese Hamster Ovary (CHO) cells transfected to express VPAC1. CHO cells do not express human CD4 or chemokine co-receptors; thus, these cells are not infectable with HIV-1. CHO cells expressing VPAC1, however, were infected using amphotropic VSV-G pseudoenvelope-typed HIV-1 having a reporter luciferase gene. This approach was able to deposit HIV-1 cDNA into the CHO cell cytoplasm with minimal luciferase activity indicating a lack of integration of the HIV-1 cDNA. Using secretin to specifically stimulate VPAC1, we were able to show an increase in luciferase activity indicating that signaling through VPAC1 was facilitating the integration of the viral cDNA. This increased integration of the HIV-1 cDNA was more prominent when using whole, intact HIV-1 virions to stimulate the CHO cells through VPAC1. These results argue that stimulation of VPAC1 by natural ligand and/or HIV-1 itself can provide a cellular signal to facilitate integration of viral cDNA into the host genome. Strategies aimed at blocking the signaling pathway of VPAC1 may have benefit for the prevention of HIV-1 integration and latency, and could lead to future therapies for the treatment of HIV/AIDS.

Keywords: Human immunodeficiency virus, Neuroimmune receptor, VPAC1, HIV integration