HIV-1 Glycoprotein 120 Enhancement of N-Methyl-D-Aspartate NMDA Receptor-Mediated Excitatory Postsynaptic Currents: Implications for HIV-1-Associated Neural Injury

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Abstract: Objective Human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein 120 (gp120) plays an important role in HIV-1-associated neuropathology. Multiple pathways have been proposed for gp120-induced neurotoxicity, amongst is the activation of N-Methyl-D-Aspartate receptors (NMDARs). It has been shown that gp120 causes neuronal injury and gp120 transgenic mice exhibit neurological similarity to humans infected with HIV-1, all of which can be blocked or attenuated by NMDAR antagonists. Several lines of evidence indicate the subtype and location of activated NMDARs are key determinants of the nature of NMDAR physiology. The present study is to examine the subtype and the location of NMDARs affected by gp120. Methods “blind” whole-cell patch recordings were used to study gp120 on subtype NMDAR-mediated EPSCs in the CA1 region of rat hippocampal slices. Results Our results showed bath application of gp120 increased both NR2A- and NR2B-mediated EPSCs possibly via a presynaptic mechanism, with much stronger effect on NR2B-mediated EPSCs. In contrast, gp120 failed on enhancing AMPA receptor-mediated EPSCs. Ca2+ imaging studies revealed that gp120 potentiated glutamate-induced increase of intracellular Ca2+ concentration in rat hippocampal neuronal cultures which were blocked by a NMDAR antagonist, but not by an AMPA receptor antagonist, indicating gp120 induce Ca2+ influx through NMDARs. Further investigation demonstrated that gp120 increased the EPSCs mediated by extrasynaptic
NR2BRs. **Conclusion** Taken together, these results demonstrate that gp120 interacts with both NR2A and NR2B subtypes of NMDARs with a predominant action on the extrasynaptic NR2B, which may implicate a role for NR2B in HIV-1-associated neuropathogenesis.

**Keywords:** HIV; Synaptic transmission; CA1; Glutamate receptors; Neurodegeneration