# IL-1 β AND NMDA RECEPTOR: A DANGEROUS LIASON IN NEUROAIDS

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Interleukin-1 beta (IL-1β) is a proinflammatory cytokine implicated in pathological conditions involving NMDA receptor (NMDAR) activation, including AIDS dementia complex (HAD).
No information is available on the molecular mechanisms recruited by native IL-1β produced in this type of condition. Using a sandwich coculture of primary hippocampal neurons and glia, we investigated whether native IL-1β released by HIV-gp120 activated glia (i) affects NMDAR functions, (ii) and the relevance on neuronal spine density and survival, two specific traits of HAD. Increased phosphorylation of NR2B Tyr-1472 was observed after 24h exposure of neurons to 600 pM gp120. This effect occurred only when neurons were treated in the presence of glial cells and was abolished by IL-1 receptor antagonist (IL-1ra; 1 μg/ml). Gp120-induced phosphorylation of NR2B resulted in a sustained elevation of intracellular $Ca^{2+}$ in neurons and in a significant increase of NR2B binding to PSD-95. Increased intracellular $Ca^{2+}$ was prevented by 10 μM ifenprodil, a channel blocker which binds only to NR2B, by IL-1ra and by Ca-pYEEIE, a src family SH2 inhibitor peptide. These last two inhibitors, prevented also NR2B binding to PSD-95. Finally, gp120 reduced by 35% of the total PSD-95 positive spine density after 48h treatment and induced by 30% of the neuronal death. Again, both of these effects were blocked by Ca-pYEEIE.
All together, our data shows that HIV-gp120 releasing IL1β from glia increases tyrosine phosphorylation of NMDA receptors. Thus, tyrosine phosphorylation may contribute to the sensitization of the receptor increasing its function and synaptic localization. Both of these effects are relevant for synaptic simplification and neurodegeneration.