Loss of Sirt3 induced by HIV gp120 with morphine in neuropathic pain, is mediated by H3K27me3 in the spinal cord

Xun Zhu, Hyun Yi, Jun Gu, Daigo Ikegami, Kentaro Hayashi, Shue Liu, Roy C. Levitt, and Shuanglin Hao

Department of Anesthesiology, University of Miami Miller School of Medicine, Miami, FL33136

Many of people living with HIV are drug abusers. Evidence shows that drug abuse exacerbates HIV-associated painful neuropathology. Therefore, it is important to elucidate the molecular mechanisms of neuropathic pain induced by HIV with chronic morphine. In the present study, we examined the role of anti-oxidative Sirt3 loss induced by HIV envelope protein gp120 with morphine in neuropathic pain. Repeated intrathecal injection of HIV gp120 with morphine induced neuropathic pain (gp120/M). HIVgp120/M down-regulated the expression of Sirt3 in the spinal dorsal horn. It also up-regulated the expression of transcription factor cMyc and epigenetic writer EZH2 and H3K27me3 in the spinal dorsal horn. Intrathecal recombinant Sirt3, antisense oligonucleotide against cMyc, or GSK126 (an EZH2 inhibitor) reduced mechanical allodynia and thermal hyperalgesia in the gp120/M model. Knockdown of cMyc reduced spinal EZH2 expression the gp120/M rats. Chromatin immunoprecipitation (ChIP)-PCR assay showed that the enrichment of cMyc binding to ezh2 gene promoter region was increased, and that the enrichment of H3K27me3 to sirt3 gene promoter region was increased in the gp120/M rats. In cultured B35 neurons, luciferase report assay demonstrated that cMyc mediated ezh2 gene transcription at ezh2 gene promoter region, and that H3K27me3 silenced sirt3 gene transcription at its gene promoter region. These results demonstrated that spinal Sirt3 loss in the gp120/M-related neuropathic pain state was mediated by cMyc and EZH2/H3K27me3 in an epigenetic manner.