Title: Epigenetic modification of MCU in the spinal cord dorsal horn in chronic morphine tolerance and HIV-related neuropathic pain state.

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Morphine remains one of the most frequently prescribed drugs for the treatment of moderate to severe pain. However, the long-term use of this excellent pain reliever in clinic is limited by side-effects that include analgesic tolerance. Increase in dosage results in respiratory depression, and the potential for drug abuse. Unfortunately, the exact mechanism of opioids resulting in the neuropathological changes in chronic morphine tolerance (MT), is not yet fully understood. Recent evidence show that mitochondrial calcium uniporter (MCU) plays an important role in glutamate-induced neuronal toxicity and in synaptic plasticity underlying chronic pain. Here, we determined the epigenetic modification of MCU in chronic morphine tolerance. Intrathecal chronic morphine induced antinociceptive tolerance using the mechanical threshold and thermal latency testing. Intrathecal MT increased spinal protein expression of MCU and phospho-CREB (pCREB). Intrathecal injection of MCU inhibitor Ru360 or intrathecal knockdown CREB expression with CREB antisense ODN reduced morphine tolerance. ChIP-PCR assay for epigenetic modification showed CREB enrichment on the MCU promoter region in MT rats was higher than that in control group rats. Similarly, in HIV neuropathic pain model, we found that HIV coat protein gp120 induced neuropathic pain, in which spinal MCU and pCREB were involved. Spinal MCU was expressed in the spinal dorsal horn neurons. HIV gp120 increased CREB enrichment on the MCU promoter region compared to sham group using ChIP-PCR assay. HIV gp120 also increased mRNA of MCU. The results will provide important insights into the pathogenesis of both opioid tolerance and HIV neuropathic pain in epigenetic modification. Supported by NIH NS066792 and DA34749.

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