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Translation Regulation in Development of Opioid Tolerance and Hyperalgesia

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Several studies demonstrated that opioid exposure alters gene expression profiles underlying the acute and chronic neuronal plasticity. These changes in gene expression contribute to the opioid-induced analgesic effect, as well as the development of addiction, tolerance, dependence, and hyperalgesia. Eukaryotic elongation factor 2 kinase, eEF2K, is a non-conventional CaMK III. It is activated downstream of AMPK and PKA signaling as well as by Ca²⁺-dependent calmodulin binding. The eEF2K phosphorylates eEF2 on Thr56, leading to inhibition of elongation step of protein synthesis and, thus, a suppression of general protein synthesis. However, translation of several specific mRNAs is upregulated by phosphorylated eEF2. Among them, the mRNA of protein involved in the control of synaptic plasticity, such as BDNF. In our experiments, we observed increased phosphorylation of eEF2 in various brain areas in rats and mice chronically treated with opioids. Moreover, it coincided with translational upregulation of BDNF. To investigate the eEF2K role in development of opioid-induced tolerance and hyperalgesia, wild type (WT) and eEF2K KO mice were chronically treated with morphine for 30 days. Both male and female eEF2 KO mice demonstrated lack of development of signs of opioid tolerance or hyperalgesia. Lower level of the morphine-induced BDNF expression in the KO mouse brains may explain the lack of tolerance or hyperalgesia development after chronic morphine administration in KO mice.