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Epigenetic regulation of opioid dependence by microRNAs

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MicroRNA (miRNA) has been recognized as a crucial regulator participating in a wide range of neuronal functions. We previously reported a repressive role of let-7 family miRNAs on the expression of μ opioid receptor (MOR), which contributed to the development of opioid tolerance at the post-transcriptionally level. The aim of this study was to test the hypothesis that miRNA-mediated cellular adaptations are critical for the development of dependence in opioid addiction. We identified the expression of a specific cluster of miRNAs were significantly increased in SH-SY5Y cells that were treated with morphine (1 uM, for 48 h). LNA-modified antisense oligonucleotides (LNA-anti-miRs) targeting these miRNAs not only inhibited endogenous expression of miRNAs in SH-SY5Y cells, but also abolished morphine-induced cAMP overshoot phenomena, a cellular biomarker for opioid dependence. In agreement with the *in vitro* findings, miRNA levels were elevated after chronic treatment with morphine in mice.

Real-time PCR analysis further demonstrated a temporal correlation between miRNA up-regulation and the development of opioid dependence (one 75 mg morphine pellet/mouse, s.c.). Meanwhile, treatment with LNA-anti-miRs decreased the supraspinal level of miRNAs and attenuated naloxone-induced withdrawal in mice dependent on morphine. Morphine conditioned place preference (CPP) was also blocked by knocking down the specific miRNAs cluster.

Moreover, Ca2+ /calmodulin-dependent protein kinase II (CaMKII) was discovered as an essential regulator for the biogenesis of the miRNAs cluster in response to opioids. Taken together, these data suggest miRNA plays an integral role in the development of opioid addiction.