Name: Lingyong Li Email: lingyongli@uabmc.edu

Tiam1 Signaling in Morphine-Induced Behavioral and Structural Plasticity

Qisheng Wang, Jenna Anderson, Changqun Yao, and Lingyong Li

University of Alabama at Birmingham

Genome-wide association studies (GWAS) found that the expression of Tiam1 in several critical addiction-related brain areas was significantly associated with the phenotypes for opioid use disorder, but how Tiam1 functions in opioid behaviors is unclear. Rho GTPase family members, such as Rac1, are the key regulators of the actin cytoskeleton remodeling and play essential roles in controlling synapse development and plasticity. Tiam1 is one of the Rac1 regulatory proteins that promotes excitatory synaptogenesis and remodeling by modulating actin cytoskeletal dynamics. Notably, Tiam1 is activated by NMDARs and TrkB receptors and mediates their effects on actin and spine remodeling. In the NAc and VTA, activated NMDARs and TrkB receptors are critically involved in opioid action, which places Tiam1 signaling in a good position as the downstream event of these receptors in modulating structural and behavioral plasticity in response to opioid exposure. To study Tiam1 functions in opioid use disorder, we generated Tiam1 global KO mice and cKO mice in the C57 strain. We found that global Tiam1 deletion and Tiam1 deletion from NAc neurons decrease morphine-induced locomotor sensitization, while Tiam1 deletion from VTA neurons enhances morphine-induced locomotor sensitization. Locomotor sensitization is thought to reflect biochemical adaptations that contribute to drug addiction and relapse. Further studies showed that Tiam1 signaling in NAc MSNs and VTA DA neurons plays an opposite role in modulating structural and behavioral plasticity in response to morphine exposure. Our research identifies Tiam1-Rac1 signaling within the NAc and VTA as the underlying event that differently modulates morphine reward behavior.