

Submitter Name: Yan Jouroukhin  
Submitted email: [yanjouro@buffalo.edu](mailto:yanjouro@buffalo.edu)

## **Role of astrocyte mu opioid receptors in morphine withdrawal**

Kate Murlanova<sup>1</sup>, Yun Guan<sup>2</sup>, Mikhail V. Pletnikov<sup>1</sup>, and Yan Jouroukhin<sup>1</sup>

<sup>1</sup>Department of Physiology and Biophysics, University at Buffalo; <sup>2</sup>Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University.

Astrocytes express mu opioid receptor (MOR) and change their morphology and/or physiology following chronic exposures to opiates. However, contribution of astrocytes to the brain mechanisms of opioid addiction, withdrawal or relapse remains poorly understood. We evaluated whether astrocyte MORs are involved in mediating the behavioral effects of morphine, including morphine withdrawal, by selectively deleting in astrocytes the *Oprm1* gene that encodes for MOR. To generate mice with conditional deletion of *Oprm1* (*Oprm1* cKO), *Aldh1l1-CreERT2* BAC transgenic mice were crossed with *Oprm1<sup>fl/fl</sup>*, and conditional recombination in astrocytes was induced with intraperitoneal injection of tamoxifen at the age of one month. This approach initiates deletion of the *Oprm1* gene in astrocytes throughout the brain. No changes in motor activity, anxiety or spatial memory were noted in *Oprm1* cKO mice, nor did *Oprm1* deletion alter acute analgesic effects of morphine or morphine-produced conditioned place preference. In contrast, compared to respective control mice, both saline- and morphine-treated *Oprm1* cKO mice exhibited significantly increased naloxone-precipitated conditioned place aversion. Our study for the first time indicates that astrocyte MOR are involved in the mechanisms of aversion produced by naloxone-precipitated withdrawal in naïve and morphine-treated mice. These findings suggest that astrocytes could provide new potential targets for treatment of aversion produced by opioid withdrawal to prevent relapse in people with opioid dependence.