Name: Kateryna Murlanova Email: kmurlano@buffalo.edu
PI Name: Mikhail Pletnikov PI email: mvpletni@buffalo.edu

Loss of astrocytic mu opioid receptors exacerbates aversion associated with morphine withdrawal in mice: a role for mitochondrial respiration

Kateryna Murlanova[1], Yan Jouroukhin[1], Ksenia Novototskaya-Vlasova[1], Shovgi Huseynov[1], Olga Pletnikova[2], Michael J. Morales[1], David M. Dietz[3], Mikhail V. Pletnikov[1]

[1]Department of Physiology and Biophysics, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY 14203, USA
[2]Department of Pathology and Anatomical Sciences, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY 14203, USA
[3]Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY 14203, USA

Astrocytes express mu opioid receptors, but the function of these receptors remains poorly understood. We evaluated the effects of astrocyte-restricted knockdown of mu opioid receptors on reward- and aversion-associated behaviors in mice chronically exposed to morphine.
Specifically, the *Oprm1* gene encoding mu opioid receptor 1 was selectively deleted from brain astrocytes in *Oprm1* conditional knockdown (cKD) mice. These mice did not exhibit changes in locomotor activity, anxiety, or novel object recognition or in their responses to the acute analgesic effects of morphine. *Oprm1* cKD mice displayed increased locomotor activity in response to acute morphine administration but unaltered locomotor sensitization. *Oprm1* cKD mice showed normal morphine-induced conditional place preference but exhibited stronger conditioned place aversion (CPA) associated with naloxone-precipitated morphine withdrawal. Notably, elevated CPA lasted up to 6 weeks in mutant mice. Astrocytes isolated from the brains of *Oprm1* cKD mice had unchanged levels of glycolysis but elevated oxidative phosporylation. The basal augmentation of oxidative phosphorylation in *Oprm1* cKD mice was further exacerbated by naloxone-precipitated withdrawal from morphine and, similarly to that for conditioned place aversion, was still present 6 weeks later. Our findings suggest that mu opioid receptors in astrocytes are linked to oxidative phosphorylation and contribute to long-term changes associated with opioid withdrawal.