The inhibition of MAG Lipase reduces opioid reward via VTA CB1 receptors without altering analgesia

Arlene Martínez-Rivera[1], Robert N. Fetcho[2,3], Lizzie Birmingham[4], Jin Xu[5], Ruirong Yang[6], Pan Ying-Xian[5], Lisa A. Briand[4], Francis S. Lee[2,6], and Anjali M. Rajadhyaksha[1,2]

1.Division of Pediatric Neurology, Department of Pediatrics, Weill Cornell Medicine, New York, NY USA. 2. Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY, USA. 3. Weill Cornell/Rockefeller/Sloan Kettering Tri-Institutional MD-PhD Program, New York, NY, USA. 4. Department of Psychology, Temple University, United States: Neuroscience Program, Temple University, PA USA. 5. Department of Anesthesiology, Rutgers New Jersey Medical School, Newark, NJ USA. 6. Department of Psychiatry, Weill Cornell Medicine, New York, NY USA.

The interaction between the opioid and endocannabinoid systems suggests that targeting the endocannabinoid system (eCB) could be a viable approach to develop new pharmacological treatments in conjunction with opioid-based therapies. The eCB signaling is controlled by two main enzymes: monoacylglycerol lipase (MAGL), responsible for regulating 2-Arachidonoylglycerol (2-AG), and fatty acid amide hydrolase (FAAH), which regulates anandamide (AEA). Using conditioned place preference and self-administration experiments conducted with both male and female mice (C57BL/6 mice, 8-12 weeks old), we demonstrate that systemic inhibition of MAGL that enhances 2-AG levels, significantly reduces the rewarding effects of opioids (morphine and oxycodone), without altering their analgesic effects. Conversely, pharmacological inhibition of FAAH has minimal impact on opioid reward or analgesia. To identify the brain site of action, animals received JZL184 directly into the Ventral Tegmental Area (VTA) and as with systemic treatment, intra-VTA JZL184 attenuated morphine reward without altering analgesia. The observed effects are mediated by CB1 receptors (CB1Rs), as systemic inhibition of CB1Rs using the inverse agonist AM251 (dose dependently), counteracted the JZL184-induced blunting of morphine reward. By using fiber photometry with calcium and dopamine (DA) fluorescent sensors, we found that JZL184 reduces the activity and DA neurotransmission related to opioid reward in the nucleus accumbens (NAc), a brain region associated with reward processing. These findings indicate that enhancing 2-AG counteracts the rewarding properties of opioids and presents a potential additional therapeutic strategy for opioid-related analgesic treatments. All experiments include a sample size of 8 or more animals, and differences among treated groups were established after performing the corresponding statistical analyses with p-values equal to or below 0.05.