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YOU ARE INVITED TO ATTEND THE

DEFENSE OF THE DOCTORAL

DISSERTATION

"Investigating the Role of Gβγ-Mediated Inhibition of the TRPM3 Ion Channel in Opioid-Induced Pruritus and Analgesia"

by

Nawoo Kim

M.D./Ph.D. Program

B.S. 2015, Emory University, Atlanta, GA

Thesis Advisor:

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https://rutgers.zoom.us/j/96872044912?pwd=TFZtSk5aZHhKRTNUVEZ6aEI5dTk0dz09

Meeting ID: 968 7204 4912
Password: 245016

Wednesday, March 29, 2023
11:00 A.M.
MSB H-Level Conference Room (H-609), Zoom

Abstract

Opioid-induced itch (pruritus) is a frequent and severe side effect of neuraxial opioid therapy. Current treatments for opioid-induced pruritus include antihistamines or opioid antagonists, which are either ineffective or can reverse the desired analgesia respectively, complicating the treatment process further. The heat- and pain-sensing Transient Receptor Potential Melastatin 3 (TRPM3) channel is found in the nervous system and is robustly inhibited by the activation of opioid receptors. This inhibition is mediated by direct binding of Gβγ subunits to the TRPM3 protein, on a specific 10-amino acid peptide encoded by exon 17. To better understand the physiological significance of this inhibition, we used CRISPR to create a mouse in which there is no Gβγ inhibition site in TRPM3 (TRPM3$^{\Delta Ex17}$) by deleting exon 17. Ca^{2+} signals in the dorsal root ganglion (DRG) neurons of these mice induced by the TRPM3 agonist PregS were not inhibited by DAMGO, a μ-opioid receptor agonist, indicating that Gβγ inhibition is absent. Findings showed that the itching caused by intrathecal injection of morphine was significantly reduced in the TRPM3$^{\Delta Ex17}$ mice, and co-injecting pregnenolone sulfate (PregS), a TRPM3 agonist, alleviated morphine-induced itch. Additionally, intrathecal injection of primidone, a TRPM3 antagonist, was sufficient to cause itch in wild type mice. Peripheral opioid-induced itch from intradermal injection of DAMGO was significantly less as well in the TRPM3$^{\Delta Ex17}$ mice. Despite the absence of TRPM3 inhibition by opioid receptor activation, the analgesic effects of systemic or intrathecal morphine were largely maintained. TRPM3$^{\Delta Ex17}$ mice did not exhibit any deficits in locomotion, memory, and anxiety. These findings suggest that activating TRPM3 may provide a potential therapeutic approach to counter opioid-induced itching while maintaining the pain-relieving benefits of opioids.