UMD Department of Chemistry & Biochemistry
Spring 2022 Seminar Series
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3:30 p.m. ~ Chem 200

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KATP Channel Prodrugs Reduce Hypersensitivity in Mouse Models of Chronic Pain

Opioids are commonly used for the treatment of chronic pain, but long-term opioid use can lead to tolerance. As the analgesic effect of opioids is attenuated over time, this leads to dosage escalation to accomplish the same level of analgesia, which can potentially lead to substance dependence. While opioids are incredibly effective therapeutics for chronic pain, it is necessary to find therapeutics that will pharmacologically reduce the need for opioid analgesics and alleviate opioid tolerance development and symptoms of withdrawal to help fight the opioid epidemic in the United States.

The goal of this project is to develop therapeutics for chronic pain treatment to combat the overuse of opioids. The body produces similar physiological changes in its response to chronic pain and opioid therapy, including the loss of activity of potassium channels in the nervous system. Previous studies show ATP-sensitive potassium (KATP) channel agonists can counteract the decreased antinociceptive effects seen with long term use of opioids. Many agonists of KATP channels are not soluble in physiologically relevant vehicles, needing adaptation for clinical use. Novel KATP channel targeting prodrugs, CKLP1, CF3-CKLP1 and CKLP2, were developed as they are cleaved by endogenous alkaline phosphatase enzymes present in the nervous system. Analgesic capabilities of intrathecally injected prodrugs were tested in a rodent model of chronic neuropathic and inflammatory pain. The reduction of opioid tolerance and opioid-induced hypersensitivity in mice treated chronically with morphine was also evaluated. Future studies will determine how prodrug pharmacokinetics affect analgesic efficacy in our mouse models. The studies may aid in the further development of KATP channel prodrugs for use in treatments of chronic pain, opioid tolerance, and withdrawal.