Targeting HCN1 channels for the treatment of neuropathic pain

July 31

Tuesday, 12:30 pm

Weekly Colloquium

Billings Building
Rosedale Conference Room

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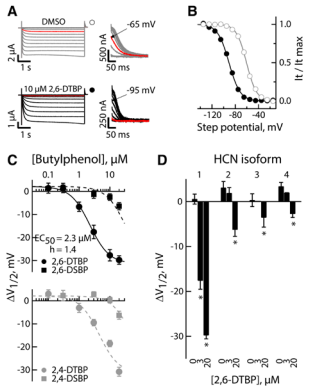
Abstract

Chronic pain impairs an individual's quality of life, is widely prevalent, and has significant economic cost. In the US alone, at least 116 million adults suffer from chronic pain; associated costs exceed $500 billion/yr. Neuropathic pain (chronic pain arising from aberrant activity in the CNS or PNS) accounts for 18% of patients with chronic pain. Opioid analgesics are routinely prescribed for the treatment of chronic pain but there are substantial risks involved with such therapy, including physical dependence, addiction, and, increasingly, fatal poisoning. Moreover, neuropathic pain is often refractory to this, as well as other, treatments. Thus, there is a critical need for new, safe, effective, non-opioid anti-hyperalgesics. Neuronal hyperexcitability and spontaneous activity characterize neuropathic pain, properties associated with activity of hyperpolarization-activated, cyclic nucleotide-regulated (HCN1-4) channels, the source of the pacemaker current, Ih. HCN1 channel expression and the Ih current in HCN1/2-rich sensory neurons increase following their injury. Peripheral administration of pan-isoform HCN pore blockers (ZD7288 or ivabradine) in animal neuropathic pain models reverse spontaneous discharges in injured nerve fibers and are anti-hyperalgesic with respect to late-phase inflammatory pain, nerve injury-induced mechanical allodynia, and chemotherapy-induced mechanical and thermal hyperalgesia. These, and other, findings support the conviction that HCN1 is an important anti-hyperalgesic target for treating neuropathic pain. Using in vitro, in silico, and in vivo approaches, our lab is actively pursuing the development of novel, non-opiate, antihyperalgesics targeting HCN1 for the treatment of neuropathic pain.



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Aromolaran KA, Goldstein PA. Ion channels and neuronal hyperexcitability in chemotherapy-induced peripheral neuropathy; cause and effect? Mol Pain. 2017 Jan-Dec;13:1744806917714693. doi: 10.1177/1744806917714693.

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