Peptidomimetic Modulator of CaV2.2 N-type Calcium Channel for Treatment of Chronic Pain

Effective and non-addictive chronic pain therapeutics with minimal side effects.

Technology

The Khanna Lab, formerly at NYU, along with colleagues from the University of Pittsburgh, have developed a potential first-in-class peptidomimetic small molecule, termed CBD3063, that modulates transmembrane $Ca_V2.2$ calcium channel function to block neuropathic and inflammatory pain without causing negative side effects. $Ca_V2.2$ calcium channels supply the calcium necessary for nociception neurotransmission. The Khanna team has previously demonstrated that collapsin response mediator protein 2 (CRMP2) regulates $Ca_V2.2$ function, and CRMP2 overexpression enhances neurotransmission and pain. CBD3630 selectively targets the intracellular interaction between $Ca_V2.2$ and CRMP2 (Figure 1), uncoupling $Ca_V2.2$ from CRMP2 thereby antagonizing $Ca_V2.2$-mediated calcium influx, inhibiting neurotransmission, and mitigating chronic pain. In published proof-of-concept studies (*Gomez et al. PNAS 2023*), the Khanna team demonstrated that CBD3063, administered through four different routes (intraperitoneal, intrathecal, intraplantar, and intranasal), reversed nociceptive behaviors in four distinct pain models across two different murine species of different sexes, without altering sensory, sedative, depressive, and cognitive behaviors. Additionally, CBD3063 inhibited spinal neuronal activity and neurotransmission of pain signals in mouse spinal cord slices, reducing the release of the excitatory pronociceptive neurotransmitter calcitonin gene-related peptide (CGRP) by ~63%. The research team evaluated the potential antinociceptive properties of CBD3063 in mice against the first-line neuropathic pain analgesic, Gabapentin (GBP), using the spared nerve injury (SNI) model of neuropathic pain. CBD3063 (10 mg/kg) was comparable to the antinociceptive strength of GBP (30 mg/kg) in alleviating neuropathic pain and reduced the SNI-induced increase in glutamatergic neuron activity. In summary, these findings highlight CBD3630 as a promising therapeutic candidate for the effective management of neuropathic and inflammatory pain without adverse side effects, offering a significant advantage over existing treatments.

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Category

Life Sciences/Biochemicals & Small Molecules

Doug Brawley

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Olivia Zelony

Authors

Rajesh Khanna, PhD

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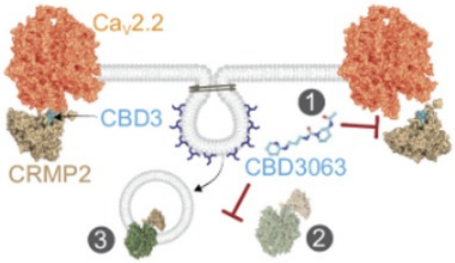

Figure 1. Schematic illustrating the mechanisms of action for the analgesic peptidomimetic CBD3063, whereas shown in (1) CBD3063 disrupts $Ca_V2.2$–CRMP2 binding, (2) prevents CRMP2-mediated surface trafficking of $Ca_V2.2$ channels to the plasma membrane and (3) blocks $Ca_V2.2$ endocytosis.

POC Study

https://pubmed.ncbi.nlm.nih.gov/37972067/

Background

Chronic pain, defined as pain lasting for longer than three months, is a serious public health issue that results in substantial healthcare costs, diminished quality of life, and lost productivity. In the United States alone, 20.9% of adults (51.6 million people) report experiencing chronic pain, with 6.9% (17.1 million people) suffering from high-impact chronic pain that significantly interferes with daily activities. Furthermore, chronic pain has been linked with depression, Alzheimer's disease and other dementias, higher suicide risk, and substance abuse. Transmembrane $Ca_V2.2$ (N-type) voltage-gated calcium channels represent promising new targets for pain management and have already been genetically and pharmacologically validated in the literature. However, commercially available non-opioid drugs that target $Ca_V2.2$ for chronic neuropathic pain, such as Ziconotide, Gabapentin, and Pregabalin, are associated with a myriad of serious side effects, including overdose-related death, limited efficacy, and a narrow therapeutic window. Given the lack of safe and effective therapeutic options, coupled with the high patient population, there is a critical unmet need for new pain medications with minimal side effects.

Applications

Pain management, including chronic inflammatory and neuropathic pain, such as orofacial pain.

Advantages

- **Minimal systemic side effects:** No alteration of sensory, sedative, affective, or cognitive behaviors observed in vivo.
- **$Ca_V2.2$ selectivity:** CBD3063 decreases N-type currents, but has no effect on other DRG-expressed voltage-gated ion channels nor CRMP2 phosphorylation.
- **Fast-acting:** CBD3063 reaches peak concentration within 15 minutes.
- **Retention of protective response to acute pain:** CBD3063 does not impair somatosensation in uninjured mice, thereby preserving the functional role of pain unlike Gabapentin.
- **Targeted treatment for orofacial pain:** CBD3063 via intranasal delivery effectively reduces trigeminal neuropathic allodynia and acute nociception.

Intellectual Property

NYU has filed a co-owned, pending U.S. non-provisional patent application (with the Univ. of Pittsburgh) covering the composition of CDB3063 for the treatment of pain, and the computational method of identifying other compounds for CaV2.2 modulation.

References

1. Gomez, Kimberly et al. , https://pubmed.ncbi.nlm.nih.gov/37972067/