Opinion

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Compound that Resets Genetic Switch to Reduce Chronic Pain is found in Cancer Drug "Junkyard" Screen

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Introduction

Chronic pain associated with nerve injury or metastatic cancer is a medical need that has yet to be satisfied. Researchers from Duke University Medical Center and the University of California, Irvine, have combed through a "junkyard of cancer medications" to find kenpaullone (KP), a chemical that could be repurposed as a strong pain reliever. Kenpaullone appears to work by increasing the expression of an ion transporter gene involved in maintaining inhibitory GABA-ergic neurotransmission, according to studies, with tests in rodent models of nerve injury and bone cancer confirming that the drug effectively reduced pathologic pain-like behaviour.

"New medications and other therapy for chronic pain need to be safe," stated study leader Wolfgang Liedtke, PhD, who has practised pain medicine at Duke University Medical Center for the past 17 years and directed the former Liedtke-Lab to unravel basic pain mechanisms. "It's critical that they're non-addictive and non-sedative, as well as effective against nerve injury and cancer pain, and that they have a short time to official clearance." Because chronic pain, like many chronic diseases, is caused by genetic switches being reprogrammed in a negative way, a disease-modifying treatment for chronic pain should reset the genetic switches rather than just mask the pain, as opioid and aspirin/Tylenol-type medicines do. "-aminobutyric acid (GABA) works predominantly as an inhibitory neurotransmitter in the mature vertebrate central nervous system (CNS), and this signalling molecule is crucial for normal CNS functioning," the authors said. It could also be a good place to start looking for novel ways to treat pain that are both effective and safe. "GABA-ergic transmission is disrupted in chronic pain, generating circuit dysfunction and altering inhibitory neuronal networks," the researchers concluded. "We could address the unmet medical need of chronic pain with safer and more effective alternatives to opioids if therapeutic techniques for restoring physiologic GABA-ergic transmission were developed [1,2]".

Low chloride content in neurons is required for inhibitory GABA-ergic neurotransmission, which is maintained by KCC2, a neuroprotective ion transporter that effectively expels chloride from neurons. Pain signals are muted when inhibitory neurotransmission is powerful and strong in pain pathways. However, in chronic pathologic pain, KCC2 expression is reduced in specific neurons, and KCC2 vanishes from the neurons that make up the principal pain gate in the dorsal spinal cord in almost all forms of chronic pain investigated in experimental animals and human spinal cord models.

"KCC2 expression in the principal sensory gate in spinal cord dorsal horn (SCDH) neurons is diminished in persistent pathologic pain," the investigators stated. "Because it corrupts inhibitory neurotransmission, this essential pathophysiological mechanism contributes to an imbalance of excitation/inhibition by causing inhibitory circuit failure... We reasoned that boosting Kcc2/KCC2 gene expression would “re-normalize inhibitory transmission for chronic pain relief.”

To find prospective Kcc2 gene expression-enhancing candidates, the researchers used cultured mouse primary cortical neurons to screen 1,057 chemicals from two National Cancer Institute libraries. Cancer medications were of special interest to the researchers since many of them alter gene epigenetic regulation. Such epigenetic effects can reset maladaptive genetic switches in non-dividing brain cells, in addition to blocking quickly dividing cancer cells from growing. "As a result, we performed an unbiased screen of cell growth-regulating chemicals," the researchers explained. "We looked at these substances because we thought a lot of them worked by interfering with epigenetic and transcriptional machinery to stop cells from dividing." Because mature neurons do not divide, these chemicals are promising candidates for using epigenetic mechanisms to increase Kcc2/KCC2 gene expression, decreasing intraneuronal chloride levels and restoring normal GABAergic inhibitory functioning” [3,4].

Liedtke's team examined the chemicals in neurons obtained from genetically altered mice to discover prospective candidate anti-pain medicines from this initial pool. These cells have a knock-in

alteration that allows them to function as a reporter gene system. Compounds that increase the expression of the Kcc2 gene cause these cells to produce a detectable bioluminescent signal.

Their search yielded 137 chemicals that improved Kcc2 expression. Following this, iterative retesting identified four extremely interesting possibilities, with kenpaullone being chosen for future investigation since it has a solid record of neuroprotection in numerous experimental paradigms.

Kenpaullone was found to be beneficial against pain induced by nerve constriction injury and pain generated by cancer cell seeding in the femur in rats. The pain reduction was significant, long-lasting, and gradual, which is consistent with the drug's effect on gene regulation. "KP restored Kcc2 expression and GABA-evoked chloride reversal potential in the spinal cord dorsal horn in a nerve-injury pain paradigm," the authors said. "At this point, we knew we had accomplished the basic condition of our screen of shelved cancer medicines, which was to identify Kcc2 gene expression-enhancers and show that they are analgesics in valid preclinical pain models," Liedtke said.

The researchers then investigated if kenpaullone impacts pain processing in the spinal cord and, if so, whether treatment with the drug could lessen nerve injury-induced chloride increase in pain-relaying neurons. Both sets of trials provided promising results, prompting the researchers to investigate how exactly kenpaullone boosts Kcc2 gene expression. They uncovered the underlying signalling mechanism through which kenpaullone inhibits GSK3-beta, an enzyme that attaches phosphate tags to proteins and has a significant function-switching impact; phosphate tags have a potent function-switching effect. Liedtke's team discovered a novel function for -cat in relation to Kcc2 expression and pain signal transmission. They demonstrated that non-phosphorylated delta-CAT is carried into the nucleus of the cell, where it binds directly to the promoter region of the Kcc2 gene, turning on the production of a switched-off Kcc2 gene. Liedtke and colleagues designed a gene-therapeutic strategy in which they loaded an AAV9 viral vector with phosphorylation-resistant -cat to investigate the relevance of this pathway for pain. They injected AAV9 into the CSF fluid of mice to infect spinal cord dorsal horn neurons with phosphorylation-resistant delta-CAT. Surprisingly, they discovered that the analgesic effects of this experimental gene therapy were similar to those of kenpaullone. "We found that spinal transgenesis of -cat(S276A) was enough to restore neuropathic pain and correct reduced Kcc2 mRNA expression in the SCDH," they wrote. "KP analgesia was imitated by transient spinal overexpression of delta-catenin."

The findings suggest that kenpaullone and similar kinase-inhibitory compounds, as well as -cat gene therapy, have the potential to become new tools in the toolbox for chronic refractory pain, such as nerve injury pain and cancer bone pain, as well as other chronic pain types (trigeminal pain) associated with low Kcc2 expression. This strategy could also be useful for other neurologic and psychiatric illnesses in which this mechanism appears to play a role [5].

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