Drug derived from cannabis shows promising pain-halting effects in mice

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For patients with chronic pain, ineffective treatments, lowered work productivity, and other factors often coalesce, fueling feelings of hopelessness and anxiety and setting the stage for even bigger problems,

including substance use disorders. In 2017 alone, some 18 million Americans misused prescription pain relievers over the course of the previous year. In many of these instances, patients suffering from chronic pain became addicted to prescription opioids.

In addition to being highly addictive, many studies suggest that prescription opioids do not effectively control pain over the long term, and hence researchers have been exploring various alternatives, including cannabidiol (CBD). CBD is a non-psychoactive substance derived from the Cannabis plant.

Studies have shown that while CBD reduces pain sensation in animals, its ability to do so in humans is limited by low bioavailability, the extent to which the drug successfully reaches its site of action. Now, new work by scientists at the Lewis Katz School of Medicine at Temple University suggests this obstacle may be overcome by a novel CBD analog known as KLS-13019.

"In a mouse model of chemotherapy-induced peripheral neuropathy (CIPN), we've been able to show for the first time that KLS-13019 works as well as, if not better than, CBD in preventing the development of neuropathy and reversing pain sensitivity after pain has been established," said Sara Jane Ward, Ph.D., Assistant Professor of Pharmacology at the Katz School of Medicine and senior investigator on the new study. The findings were published online April 6 in the *British Journal of Pharmacology*.

KLS-13019, developed by the Pennsylvania-based bio-pharmaceutical and phyto-medical company Neuropathix, Inc., is among the most promising neuroprotective CBD analogs currently under investigation. In previous work in cell models, it was found to be more potent than CBD, and studies in animals suggested it had improved bioavailability.

Encouraged by those initial studies, Dr. Ward and colleagues set out to better understand the pain-relieving capabilities of KLS-13019, relative to CBD, in animals with CIPN. CIPN is a common side effect of certain cancer treatments that damage peripheral nerves, which carry sensory information to the arms, legs, and brain. The severe pain, or peripheral neuropathy, caused by CIPN manifests in different ways in human patients but frequently involves tingling or burning sensations and numbness, weakness, or discomfort in the limbs.

In a series of experiments designed to gauge animals' pain responses, the researchers found that pain sensitivity was greatly reduced in animals with CIPN that were treated with KLS-13019 or CBD. KLS-13019 further reversed sensitivity to painful stimuli in animals in which peripheral neuropathy was already established, an effect that was not observed in CBD-treated animals.

Earlier studies have also hinted at the possibility that CBD is able to reduce opioid craving in patients with opioid use disorder.

"Many patients who use opioids for pain management enter a cycle of reinforcement, where each use of opioids triggers reward pathways and perceived pain relief, leading to addiction," Dr. Ward explained.

While Dr. Ward and colleagues did not find evidence supporting a role for CBD in reducing opioid craving, they did observe significantly reduced opioid-seeking behavior in KLS-13019-treated animals.

"This tells us that KLS-13019 has benefits beyond its ability to alleviate pain," Dr. Ward said.

The researchers suspect that while likely sharing a mechanism with CBD for pain relief, KLS-13019 may have an additional mechanism of action, one that breaks up the pathways reinforcing opioid use.

In future work, Dr. Ward and her team plan to explore the mechanisms by which KLS-13019 exerts its effects, particularly those underlying the drug's ability to disrupt opioid-seeking behavior. They also plan to test the ability of KLS-13019 to alleviate other types of pain, beyond CIPN.

More information: Jeffery D. Foss et al, Behavioral and pharmacological effects of cannabidiol (CBD) and the CBD analogue KLS-13019 in mouse models of pain and reinforcement, *British Journal of Pharmacology* (2021). DOI: 10.1111/bph.15486

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