An alternative to medical marijuana for pain?

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Medical marijuana is proliferating across the country due to the ability of cannabis ingestion to treat important clinical problems such as chronic pain. However, negative side effects and the development of tolerance limit the widespread therapeutic use of ?9-tetrahydrocannabinol (?9-THC), the major psychoactive ingredient in cannabis.

THC's side effects are produced via its actions at cannabinoid CB1 receptors in the brain. Thus, scientists theorized that an agent with similar mechanistic actions, but that activate CB2 receptors instead, may eliminate the unwanted side effects while maintaining an equivalent level of efficacy.

Dr. Andrea Hohmann and her colleagues at Indiana University tested this strategy and found that, unlike ?9-THC, repeated dosing with the cannabinoid CB2 agonist AM1710 suppresses chemotherapy-induced pain in mice without producing tolerance, physical withdrawal, motor dysfunction, or hypothermia. Moreover, the therapeutic effects of AM1710 were preserved in mice lacking CB1 receptors but absent in mice lacking CB2 receptors.

Their findings are reported in the current issue of *Biological Psychiatry*.

"Our study is important because it demonstrates beyond doubt that activation of cannabinoid CB2 receptors suppresses neuropathic pain without producing signs of physical dependence (i.e., a withdrawal syndrome) or other unwanted side effects associated with activation of CB1 receptors in the brain," said Hohmann.

Their studies used animals that were treated with a chemotherapeutic agent (paclitaxel) to produce pain. When animals were given AM1710, a CB2 agonist, its pain-suppressive effects were fully preserved and its therapeutic effects were maintained even after repeated dosing.

Alternatively, and as expected, when animals were given ?9-THC, they developed complete tolerance to the pain-suppressing effects of THC and with repeated dosing, THC was no longer effective in suppressing neuropathic pain.

When the THC-treated animals were challenged with a drug that blocks CB1 receptors in the brain, the animals showed a prominent withdrawal syndrome, indicating signs of physical dependence following removal of THC. Strikingly, this was not the case with the CB2 agonist; blocking either CB1 or CB2 receptors produced no signs of withdrawal in animals treated chronically with the CB2 agonist.

Hohmann added, "We think our data suggests that CB2 receptors are an important target for suppressing chronic pain without unwanted side effects (e.g. psychoactivity, addiction)."

"It is important to know whether the benefits of cannabis ingestion for pain could be attributed in large part to the stimulation of CB2 receptors," commented Dr. John Krystal, Editor of *Biological Psychiatry*. "CB2 agonists, in theory, would present less risk regarding addiction and intoxication than the ingestion of cannabis or THC."

More work will be necessary before CB2 receptor agonists could be prescribed for use in humans, but for now, these data support the therapeutic potential of CB2 agonists for managing pain without the adverse effects associated with cannabis.

More information: "Chronic Cannabinoid Receptor 2 Activation Reverses Paclitaxel Neuropathy Without Tolerance or Cannabinoid Receptor 1–Dependent Withdrawal" by Liting Deng, Josée Guindon, Benjamin L. Cornett, Alexandros Makriyannis, Ken Mackie, Andrea G. Hohmann (DOI: 10.1016/j.biopsych.2014.04.009). The article appears in *Biological Psychiatry*, Volume 77, Issue

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