Delta opioid receptor identified as promising therapeutic target for inflammatory pain relief

15 June 2020

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Delta opioid receptors have a built-in mechanism for pain relief and can be precisely targeted with drug-delivering nanoparticles—making them a promising target for treating chronic inflammatory pain with fewer side effects, according to a new study from an international team of researchers. The study, published in *Proceedings of the National Academy of Sciences (PNAS)*, was conducted using cells from humans and mice with inflammatory bowel disease, which can cause chronic pain.

Opioid receptors—which are primarily located throughout the central nervous system and gut—relieve pain when they are activated by opioids, both those naturally produced by the body and those taken as medications. While there are several types of opioid receptors, the majority of opioid medications like oxycodone and morphine act on the mu opioid receptor. Opioid medications have significant side effects mediated by the mu opioid receptor, including constipation and difficulty breathing. These drugs are addictive and their effectiveness diminishes over time, so people require higher doses to manage their pain, leading to increased side effects and risk of overdose.

In this study, the researchers focused on a different opioid receptor: the delta opioid receptor, which also inhibits pain when activated but offers a promising target for treating pain with fewer side effects. Using biopsies from the colons of people and mice with ulcerative colitis, an inflammatory bowel disease, the researchers discovered that the delta opioid receptor provides a built-in mechanism to relieve inflammatory pain. The inflammatory cells from the colon release their own opioids, which activate the delta opioid receptor and block the activity of neurons in the gut that transmit painful signals.

Importantly, the researchers also learned that the delta opioid receptor signals from a compartment within the cell called an endosome—not just at the surface of cells, as previously thought. In the endosome, receptors signal for prolonged periods, which means delta opioid receptors can inhibit pain for longer stretches. This sustained decrease in excitability (a measurement of pain) was found when the delta opioid receptors were activated in the inflammatory cells studied.

"We've shown that the delta opioid receptor has a built-in mechanism of pain control and inhibits pain by signaling within an endosome. With this new knowledge, we thought the receptor would be a promising target for the treatment of chronic inflammatory pain," said senior author Nigel Bunnett, Ph.D., professor and chair of the Department of Molecular Pathobiology at New York University (NYU) College of Dentistry.

To target the delta opioid receptor, the researchers encapsulated a painkiller called DADLE, which binds to the delta opioid receptor, inside

nanoparticles—microscopic vehicles used to deliver drugs to cells. They then coated the nanoparticles with the same painkiller, which steered the nanoparticles specifically to nerve cells that control pain and away from other cell types, avoiding side effects.

"Incorporating drugs into nanoparticles can enhance the stability and delivery of drugs, improving their effectiveness and often requiring smaller doses—and smaller, more targeted doses lower the risk of drugs causing unwanted side effects," said Bunnett.

After binding to the receptors of nerve cells, the nanoparticles entered the cells to reach the endosome and then slowly released the painkiller to activate the delta opioid receptor. This resulted in a long-lasting activation of the delta opioid receptor, suggesting a sustained ability to inhibit inflammatory pain.

"Our findings demonstrate that not only are delta opioid receptors in endosomes a built-in mechanism for pain control, but also a viable therapeutic target for relief from chronic inflammatory pain," said Bunnett.

A previous study by Bunnett and colleagues used nanoparticles to deliver a drug that blocked a different type of receptor to relieve pain, while the *PNAS* study focuses on delivering a drug to activate the delta opioid receptor. The researchers hypothesize that effective pain control will involve blocking and activating multiple pain-transmitting pathways at the same time, which may lead to encapsulating a combination of drugs inside nanoparticles.

More information: Nestor N. Jimenez-Vargas el al., "Endosomal signaling of delta opioid receptors is an endogenous mechanism and therapeutic target for relief from inflammatory pain," *PNAS* (2020). www.pnas.org/cgi/doi/10.1073/pnas.2000500117

Provided by New York University