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Opioid receptors outside the brain targeted in rats; new direction for painkillers

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Opioid abuse is a growing public health crisis, affecting up to 36 million people worldwide. Many of these individuals first get hooked on prescription painkillers that target mu opioid receptors in the brain. A study in rats published August 25 in *Cell Reports* suggests that a different approach that targets delta opioid receptors on sensory neurons in peripheral tissues might avoid the side effects and high abuse potential of currently available pain relievers.

"People living with chronic pain have few innovative analgesic options available to them outside of systemic opioids. Prolonged use of these opioids can result in respiratory depression, tolerance, addiction, and overdose," says senior study author Nathaniel Jeske of the University of Texas Health Science Center at San Antonio. "Being able to increase the responsiveness of peripheral opioid receptor systems could lead to a reduction in systemic opioid administration, thereby reducing the incidence of side effects."

Most clinical opioids currently available target mu opioid receptors, including those located in the brain, and therefore have a high potential for abuse. By contrast, drugs targeting delta opioid receptors in the peripheral nervous system rather than the brain and spinal cord produce fewer side effects in animals and have a much lower abuse potential. However, delta opioid receptors in peripheral tissues only become activated in the presence of inflammation. Because it has not been clear how to overcome this need for an inflammation trigger, the development of peripherally restricted drugs targeting delta opioid receptors has been

limited.

In the new study, Jeske and first author Allison Doyle Brackley of the University of Texas Health Science Center at San Antonio set out to address this problem. They found that a protein called GRK2 binds to and prevents delta opioid receptors on rat sensory neurons from responding normally to opioids, but when these peripheral neurons were exposed to a natural inflammatory molecule called bradykinin, GRK2 moved away from the delta opioid receptors, setting off a biochemical reaction that restored the functioning of these receptors. Moreover, rats with reduced GRK2 levels in peripheral sensory neurons regained sensitivity to the pain-relieving effects of a drug that activates delta opioid receptors without the need for an inflammatory trigger.

The findings expand the known function of GRK2 to include a role in inhibiting the function of delta opioid receptors in peripheral sensory neurons. Moving forward, the researchers will attempt to replicate the findings using human tissues. "By shedding light on how inflammation activates delta opioid receptors, this research could potentially lead to the development of safer, more effective opioids for the treatment of pain," Jeske says.

More information: Cell Reports, Brackley et al.: "GRK2 Constitutively Governs Peripheral Delta Opioid Receptor Activity" www.cell.com/cell-reports/full … 2211-1247(16)31030-0 , DOI: 10.1016/j.celrep.2016.07.084

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