Genetic anti-opioid system: A protein that could make opioid use safer in the future

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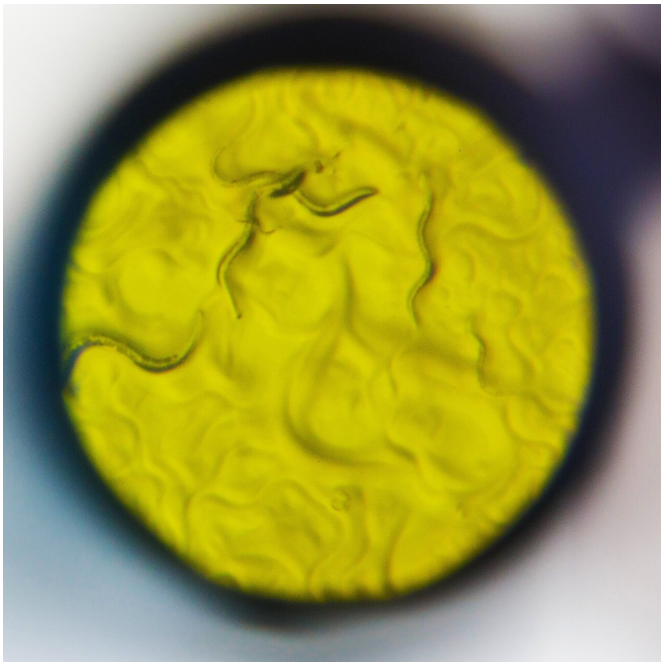

The nematode worm *C. elegans* is commonly used by neuroscientists to understand the nervous system. Scientists at Scripps Research in Florida used it in a new way to discover fresh insights about how cells regulate opioid signaling. Credit: Scott Wiseman for Scripps Research

A team of researchers from the Scripps Research Institute and the University of Kansas has found a protein that could one day be manipulated to make it safer for pain sufferers to use opioids. In their paper published in the journal *Science*, the group describes their study of intentional mutations in nematodes and what they learned.

Opioids are a class of drugs that comprise one of the best-known ways to reduce pain—but they are also highly addictive. Unfortunately, scientists have been unable to find an alternative to opioids, so some have begun to look for ways to make existing drugs less addictive. In this new effort, the researchers looked at ways to genetically alter nematodes to reduce addiction to opioids.

The work involved creating over 900 kinds of mutations in the genes of nematodes and then testing each to see if it resulted in any changes in sensitivity to opioids. They report that they found one mutation in a gene called FRPR-13 that appeared to lessen symptoms. The team next found the mammalian analog to FRPR-13—a gene that codes for the production of a protein called GPR139, which they found produces an inhibitory effect on mu-opioid receptor (MOR) signaling. The researchers then turned their attention to how the gene and the protein work in mice. One of their tests involved genetically altering the mice to prevent GPR139 coding, which in turn prevented the proteins from being produced. They found that doing so tended to enhance the ability of an opiate (morphine) to inhibit neurons from firing—levels of MOR were reduced. The net result was that pain was reduced. But testing showed something else—disabling GPR139 production resulted in fewer withdrawal symptoms in addicted mice.

The researchers suggest the reduction of withdrawal symptoms was likely due to changes in the rate of neurons firing in the locus coeruleus—a part of the brain that prior research has shown is involved in handling withdrawal signaling. They conclude by suggesting that GPR139 could someday play a significant role in reducing withdrawal symptoms in human patients—making opioids safer to proscribe.

More information: Dandan Wang et al. Genetic behavioral screen identifies an orphan anti-opioid system, *Science* (2019). DOI: 10.1126/science.aau2078

Press release