Researchers identify source of opioids' side effects

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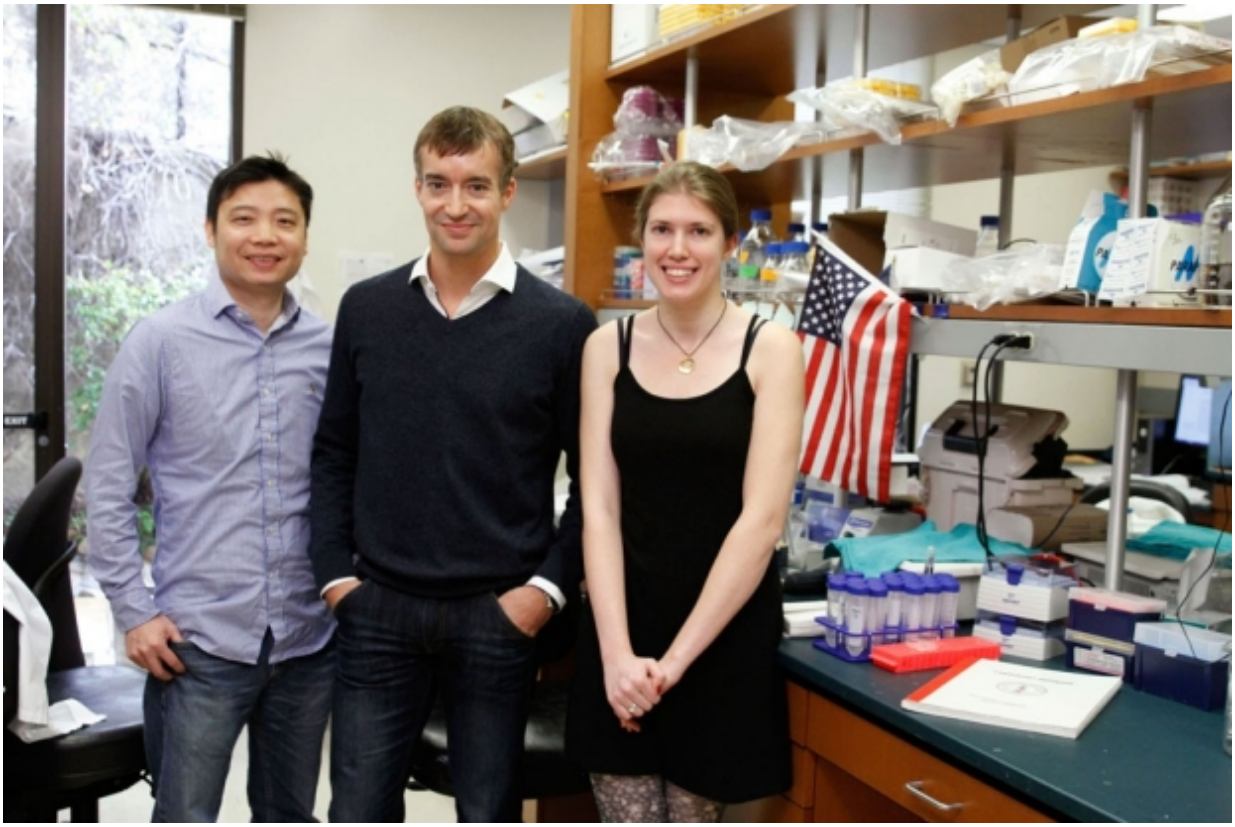

Dong Wang, Gregory Scherrer and Elizabeth Sypek are co-authors of a study that found that two side effects of opioids — growing tolerance to the drugs and increased sensitivity to pain — may be specifically caused by the drugs' effect on peripheral pain neurons in the body, not those in the spinal cord or brain. Credit: Paul Sakuma

A commercially available drug may help drastically reduce two side effects of opioid painkillers—a growing tolerance and a paradoxical increased sensitivity to pain—without affecting the drugs' ability to reduce pain, according to a study by researchers at the Stanford University School of Medicine.

These two side effects often mean patients require higher doses of opioids to maintain pain relief, increasing the risk of addiction and respiratory failure. Opioid overdoses were responsible for more than 20,000 deaths in 2015, according to the American Society of Addiction Medicine, and are now the leading cause of accidental death in the United States.

"In some patients, you don't have much margin between how much painkiller you can give and their ability to breathe normally, or the occurrence of other significant side effects," said Gregory Scherrer, PhD, assistant professor of anesthesiology, perioperative and pain medicine and of neurosurgery. "Our goal was to understand how opioids cause their side effects, to find ways to separate these detrimental side effects from pain relief properties and to make these painkillers safer."

Scherrer is the senior author of the study, published online Jan. 16 in *Nature Medicine*. The lead authors are postdoctoral scholars Gregory Corder, PhD, and Dong Wang, PhD; anesthesiology instructor Vivianne Tawfik, MD, PhD; and graduate student Elizabeth Sypek.

Working in mouse models, Scherrer and his colleagues found that tolerance and increased sensitivity to pain may be specifically caused by opioids' effect on peripheral pain neurons in the body, not those in the spinal cord or brain. They also established that contrary to the prevailing view in the field, microglia—non-neuronal cells found in the spinal cord and brain—are not initiating opioids' side effects because they lack the gene that forms the receptors necessary to cause them.

By using a drug that blocks only the effects of opioids on the periphery, they were able to eliminate the two dangerous properties without affecting the pain-relieving effects.

"We demonstrate that these two side effects can be drastically reduced with co-administration of an already used compound, methylnaltrexone bromide, currently used to combat constipation, which is another unwanted side effect of opioids, while still maintaining pain relief," Scherrer said. Methylnaltrexone bromide is approved by the Food and Drug Administration for the treatment of opioid-induced constipation.

Clinical trials needed

Clinical trials are now needed to test whether the findings hold true in humans, with the goal of reducing the number of deaths from overdoses while improving the function of prescription painkillers, Scherrer said. Growing concern about an epidemic of opioid-painkiller abuse has drawn the attention of physicians, patients and public health authorities. According to the Centers for Disease Control and Prevention, about 100 Americans die each day from drug overdoses, and more than half of those deaths involve opioid pain relievers.

From a clinical standpoint, these pain relievers not only present safety risks, but they often prove a disappointment in how well they work to control pain, said co-author David Clark, MD, PhD, a Stanford professor of anesthesiology, perioperative and pain medicine who treats patients at the Palo Alto Veterans Affairs Health Care System.

"They don't in general provide substantial pain relief for a long period of time," said Clark. The prevalence of chronic pain in veterans is unusually high, he said. In addition to the chronic pain from such illnesses as cancer and diabetes, many veterans also face lifelong pain from battle wounds, such as traumatic brain injuries, shrapnel injuries

and injuries to limbs.

"Once patients start on opioids, the drugs may work for weeks or months, but then it's common to see the pain relief dissipate, and these patients face the decision of whether or not to increase the dose," Clark said. "With increasing doses comes the increasing risk of adverse events."

"If you're coming back from the battlefield in your 20s, what does your future look like if you are taking these drugs over the next 50 or so years of life?" he added.

Scherrer's lab investigates how neural circuits generate a sensation of pain and distinguish it from other sensory experiences, such as an itch. Credit: Paul Sakuma

Knocking out morphine receptors

At a molecular level, opioids work by attaching to specific protein-binding sites on neurons throughout the body. These sites are called mu

opioid receptors. The binding of morphine and similar painkillers, including oxycodone, fentanyl and hydrocodone, obstruct the neurons' pain signals so that they don't reach brain regions for pain perception. However, mu opioid receptors are present on many types of neurons in the nerves, spinal cord and brain. Which of these populations of receptors is specifically responsible for side effects has been unclear, preventing the development of therapeutic strategies to separate side effects from pain relief.

Based upon previous research that indicated peripheral pain neurons, known as nociceptors, may be responsible for certain unwanted side effects from opioids, the researchers hypothesized that if they could block mu opioid receptors on peripheral pain neurons specifically, they could eliminate the bad effects while keeping the good effects of the drugs.

To test their hypothesis, the researchers injected morphine into both normal mice and a group of mice in which the mu opioid receptors had been knocked out.

"What we did was to remove morphine receptors from only one type of neuron—the pain neurons in the periphery—to test the function of the mu opioid receptors in the periphery. We wanted to determine precisely what morphine is doing on the periphery," Scherrer said. "Then we did a number of pain tests in the mice to measure the efficacy of morphine."

Researchers found that the acute pain relief from the drugs remained the same, but that when injected chronically it actually lasted much longer in the mice lacking the mu opioid receptor compared with the normal mice. The researchers concluded that the action of morphine on nociceptors was causing the growing tolerance to the drug in the normal mice.

They also concluded that the pain-relieving properties generated by

opioids must occur primarily in the brain because the drugs worked without acting on the nociceptors in the altered mice.

Existing drug

Next, researchers showed that by using the opioid receptor antagonist drug methylnaltrexone bromide, which block mu opioid receptors in the periphery, they were able to prevent the tolerance and increased sensitivity to pain caused by opioid use while keeping the pain relief.

"The trick was to use a compound that blocks pain receptors only in the periphery," Scherrer said. "Methylnaltrexone bromide is an already known compound that doesn't cross the blood brain barrier and stays on the periphery."

Results showed that with co-administration of methylnaltrexone bromide and morphine to mice, no significant difference in pain relief occurred, but the two side effects—tolerance and increased pain sensitivity—were almost completely lost, the study said.

There's an urgent need to test the findings of this mouse study in human trials, Scherrer said.

"This is the same drug which is used for reducing the side of effect of constipation caused by opioid painkillers," Scherrer said, adding that the drug works by blocking neurons in the gut to stop constipation, a totally different process. "It's a safe drug. There is great potential for translating this to the clinic."

The future ramifications for possibly reducing the opioid dose needed to maintain pain relief go beyond the clinic, Clark said.

"The issues of drug abuse and exposure which can lead to heroin abuse

are huge problems," Clark said. "By limiting the dosages of the drugs given to the patient, we also reduce the amount of these drugs leaking out into the community."

The team's work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

More information: Gregory Corder et al. Loss of μ opioid receptor signaling in nociceptors, but not microglia, abrogates morphine tolerance without disrupting analgesia, *Nature Medicine* (2017). DOI: 10.1038/nm.4262

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