Researchers identify potential pathway to make opioids safer, more effective

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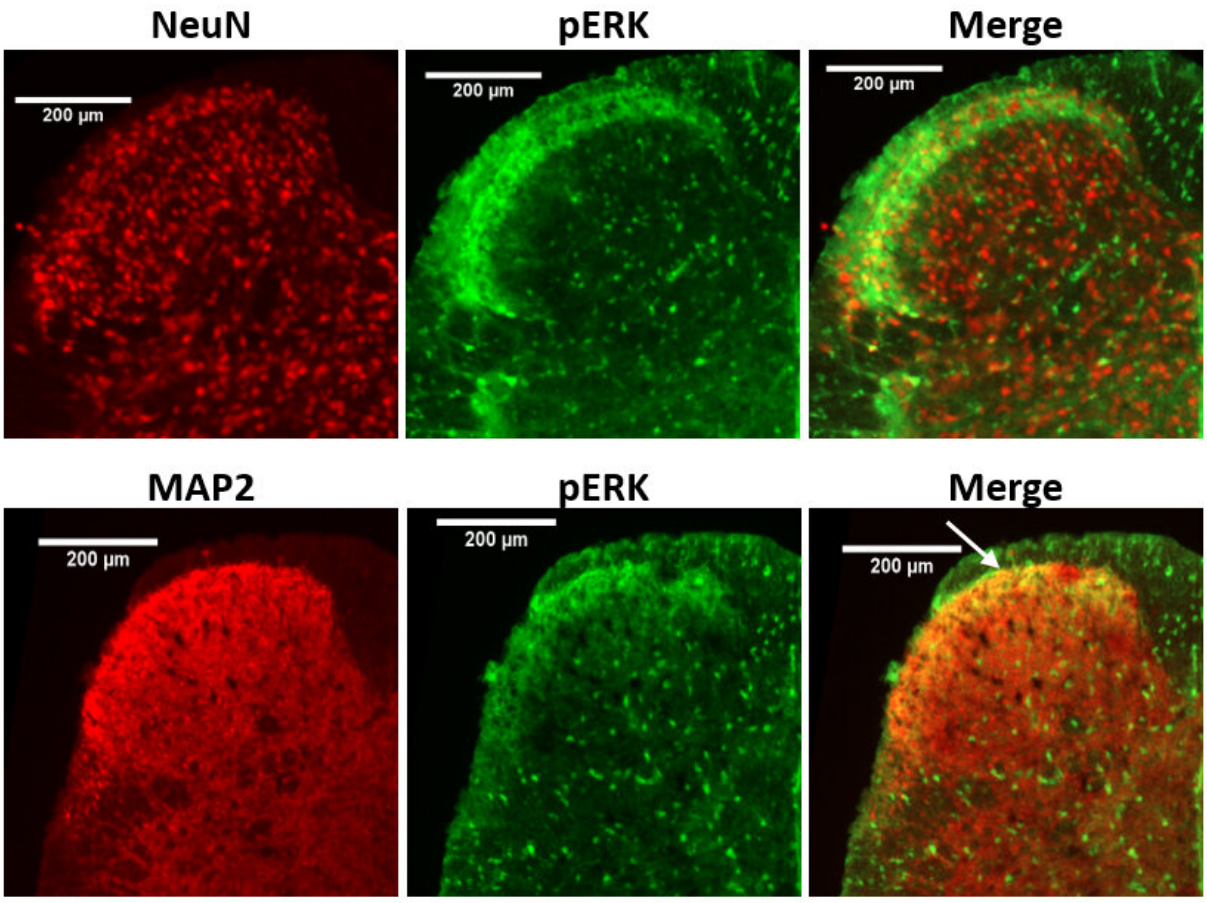


Stained neurons from mice showing pERK (green) and the neuronal markers NeuN and MAP2 (red). Credit: D.I. Duron et al., Science Signaling (2020)

Opioids are one of the most effective treatments for chronic pain, in

spite of the fact that their worst side effects have created a national health care crisis.

A potential solution to the high-risk use of opioids was discovered recently by University of Arizona Health Sciences researchers, who found that inhibiting a key protein in signaling pathways in the spinal cord enhances the efficacy and presumably decreases the side effects of opioid therapy.

John Streicher, Ph.D., an assistant professor in the College of Medicine—Tucson Department of Pharmacology, and graduating doctoral student David Duron, Ph.D., focused their research on one specific protein—heat shock protein 90 (Hsp90) - and its role in receptor activation and pain relief.

"There are pathways that produce pain relief in the spinal cord," said Dr. Streicher, who is the paper's senior author. "It seems like heat shock protein 90 is inhibiting one of those pathways in the spinal cord and preventing it from being activated. When we give this inhibitor in the spinal cord, it unblocks that pathway, which provides another route to greater pain relief."

The findings suggest that Hsp90 inhibitors could give doctors the opportunity to implement a dose-reduction strategy for patients. Less opioid drug could be prescribed, but patients would get the same levels of pain relief while experiencing lower side effects.

When an opioid such as morphine enters the body, it binds to a protein target called the μ-opioid receptor (MOR) and launches a series of effects known as a signaling cascade. As signaling molecules work their way downstream, some cause positive effects, such as pain relief. Others result in negative side effects, such as: respiratory depression, which can cause death; reward, which can lead to addiction; and tolerance, which

can increase the quantity of drug needed to provide the same amount of pain relief.

"Our overall research program is looking at the signaling links between receptor activation and pain relief downstream, and one of the proteins in the middle that we've been studying for a number of years is called heat shock protein 90," Dr. Streicher said. "Heat shock protein 90 does a lot of things, but one of the things it does is regulate how that receptor talks to the downstream changes in your brain, like pain relief."

In an earlier study, Dr. Streicher and his team examined the role of Hsp90 in MOR signal transduction—the cell's conversion of a signal into a response—in the brain in mice. When Hsp90 was inhibited, morphine's antinociceptive properties were blocked—it lost its ability to reduce the sensation of pain.

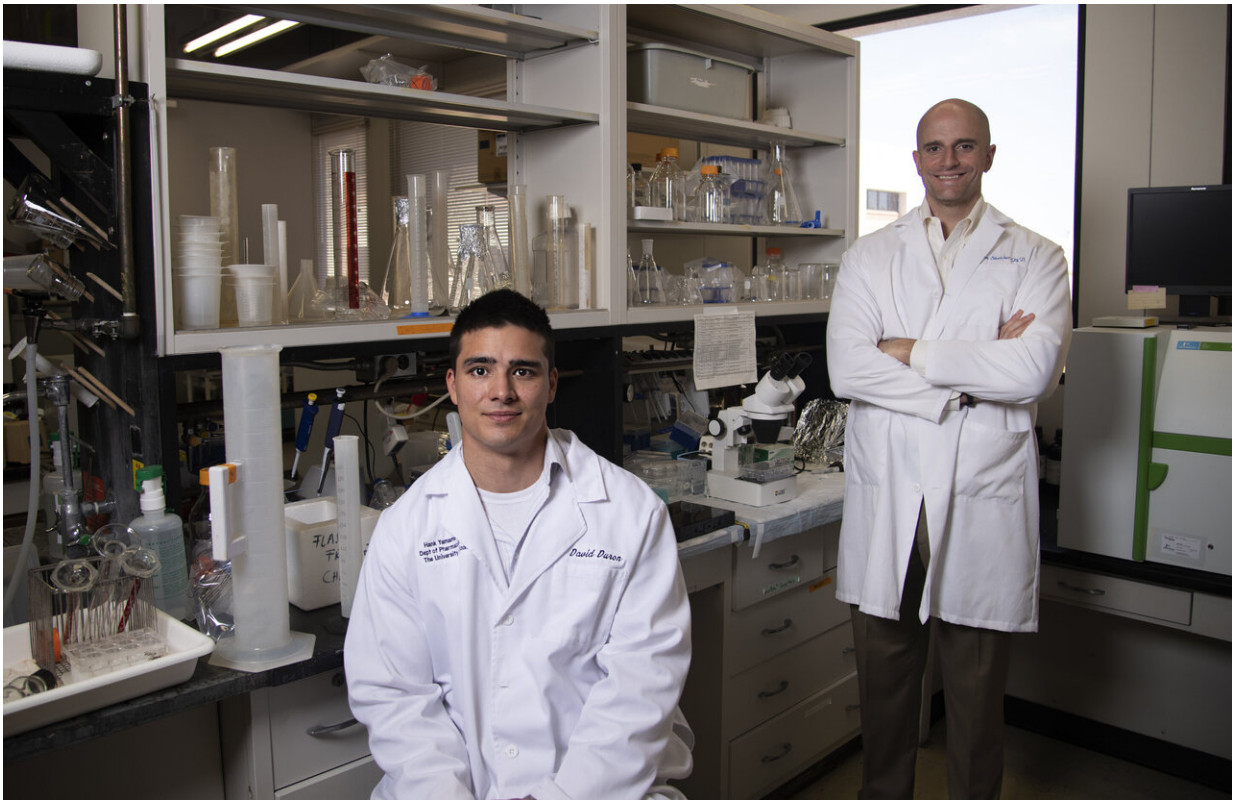
Drs. Duron and Streicher decided to see if Hsp90 functioned similarly in the spinal cord. To their surprise, it did not.

"Initially, we somewhat expected that it would be similar to the brain, at least at the signaling level," said Dr. Duron, who is first author on the paper. "We found that it actually has an opposite effect, which was very surprising."

When Hsp90 was inhibited in the spinal cord, morphine's pain-relieving effects were amplified.

"When we found these effects in the spinal cord, my 'a-ha moment' was realizing that this could potentially be something that could have an application in the clinic," said Dr. Duron, who is hoping to begin law school this fall and pursue a career in intellectual property and drug-discovery law.

The prospects for developing a clinical Hsp90-inhibitor drug are promising, as several cancer researchers are also studying Hsp90 inhibitors and demonstrating strong proof-of-concept in the lab. Still, approval by the U.S. Food and Drug Administration is likely years away.



From left: Graduating doctoral student David Duron, PhD, and his faculty mentor John Streicher, PhD, an assistant professor in the College of Medicine - Tucson Department of Pharmacology, found that inhibiting a key protein in signaling pathways in the spinal cord enhances the efficacy and presumably decreases the side effects of opioid therapy. Credit: University of Arizona Health Sciences/Noelle Haro-Gomez

In his lab, Dr. Streicher is continuing his work into how Hsp90 works in

the spinal cord to amplify the antinociceptive effects of opioids, including studying a previously unknown signaling circuit in the spinal cord that was discovered during this study. Working with the College of Medicine—Tucson's Quantitative Proteomics Laboratory, Dr. Streicher and his team have identified more than 200 proteins that may provide additional insight on how MOR signaling is organized in the spinal cord.

"The opioid crisis stems from a lot of factors, but one of the primary factors is that we have a real chronic pain problem in the U.S." Dr. Streicher said. "There are over 100 million people with some sort of chronic pain. For especially those people with moderate to severe pain, opioids are often the only efficacious options they have. So we have a lot of people in pain, a lot of those people are still going to need to take opioids. Finding new ways to treat people's pain without them getting addicted to some sort of pain-relieving drug is by far one of the most effective ways we have to fight the opioid crisis."

This research will appear in the May 5 issue of the journal *Science Signaling*.

More information: "Inhibition of Hsp90 in the spinal cord enhances the antinociceptive effects of morphine by activating an ERK-RSK pathway," *Science Signaling* (2020). stke.sciencemag.org/lookup/doi …26/scisignal.aaz1854

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