Proof-of-principle study shows protein isoform inhibitors may hold the key to making opioids safer

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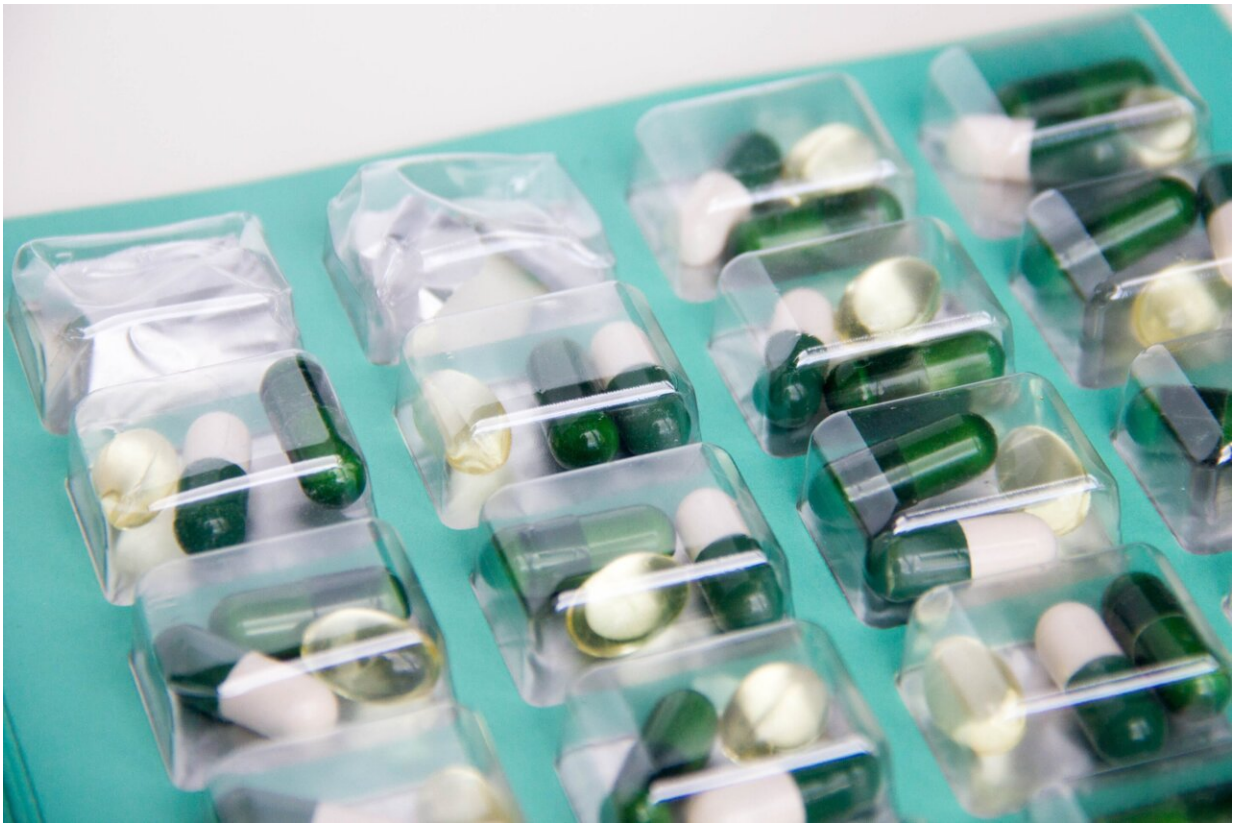

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Researchers at the University of Arizona Health Sciences identified a new way to make opioids safer, increasing the pain-relieving properties

of opioids while decreasing unwanted side effects through the spinal inhibition of a Heat shock protein 90 isoform.

Opioids are the gold standard of chronic pain treatment, but they come with a host of negative side effects including constipation, addiction potential and respiratory depression that can lead to death. This study, published in Scientific Reports, offers a potential new way to treat acute and chronic pain by reducing the amount of opioid needed for pain relief while also lowering its addiction potential.

"We have been investigating the role of Heat shock protein 90 in regulating opioid signaling in the spinal cord for some time," said John Streicher, Ph.D., member of the Comprehensive Center for Pain & Addiction at UArizona Health Sciences and a professor in the College of Medicine—Tucson's Department of Pharmacology.

"This study provides proof of principle that Hsp90 isoform inhibitors are effective at improving opioid pain relief and reducing side effects. This is the critical link that makes our work translationally relevant, giving us a clear path forward to develop a new drug that could benefit millions of people who live with chronic pain."

Heat shock protein 90 is a chaperone protein that helps other proteins function, including those that promote tumor growth. It has been studied primarily in the context of cancer. Streicher is leading in a long-term effort to investigate its role in opioid receptor activation and pain relief.

Streicher's prior research showed that Heat shock protein 90 acted upon opioid receptors in the brain differently than in the spinal cord. Inhibiting Hsp90 in the brain blocked the analgesic properties of morphine, meaning the opioid lost its ability to reduce the sensation of pain. But inhibiting Hsp90 in the spinal cord amplified the pain-relieving effects of morphine.

Building on that research, the team tested nonselective Hsp90 inhibitors in mouse models and saw a twofold-to-fourfold increase in the potency of pain relief provided by morphine. At the same time, tolerance was reduced and established tolerance was reversed. Tolerance is a condition where the body gets used to a medication so that more medication or a different medication is needed to achieve the same response.

Early cancer-focused studies, however, found that nonselective Hsp90 inhibitors can cause serious side effects, including macular degeneration. Streicher's solution was to target individual isoforms of Hsp90, of which there are four.

"Isoforms are different versions of the same thing, like trim packages on a car," Streicher said. "They are all slightly different and have similar roles, but not identical roles. So these four Hsp90 isoforms are four proteins that we can target individually."

By using selective inhibitors to target each isoform, they were able to identify and isolate the isoforms that are active in the spinal cord from Hsp90-alpha, the one that is active in the brain. Recent reports have linked Hsp90-alpha with the serious side effect of retinal degeneration.

"We took isoform-selected inhibitors that we got from our collaborator, Brian Blagg, Ph.D., at the University of Notre Dame, and gave them to mice systemically via IV injection," Streicher said. "We found that you can give these isoform-selective inhibitors by a translatable route and get the benefits. Pain relief goes up and side effects go down, and presumably we're going to avoid some of those nasty side effects of the nonselective Hsp90 inhibitors."

The findings suggest that selective Hsp90 inhibitors could be used as part of a dose-reduction plan in conjunction with opioid therapy prescribed by a physician for chronic pain. The goal is for doctors to be able to

prescribe lower amounts of opioids that provide patients with the same pain-relieving benefits and fewer negative side effects.

"What I'm envisioning is you'd be given a pill that is a combination therapy of an opioid with one of these isoform inhibitors," Streicher said. "The addition of that Hsp90 inhibitor would make the opioid better—it would increase the effectiveness of the pain relief and decrease the side effects."

Streicher and his team are working to optimize the selective Hsp90 inhibitors to produce a stable drug that can be taken orally.

"Dr. Streicher's research is an excellent example of the innovative, translational science that is needed to transform health care for pain and addiction," said Todd Vanderah, Ph.D., director of the Comprehensive Center for Pain & Addiction, Regents Professor and head of the Department of Pharmacology. "This study is an important step toward developing a novel evidence-based therapy that will provide better treatment options with fewer disruptive side effects, empowering people with chronic pain to thrive."

More information: David I. Duron et al, Inhibiting spinal cord-specific hsp90 isoforms reveals a novel strategy to improve the therapeutic index of opioid treatment, *Scientific Reports* (2024). DOI: 10.1038/s41598-024-65637-6

Provided by University of Arizona

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