Researchers identify osteoarthritis 'pain pathway'

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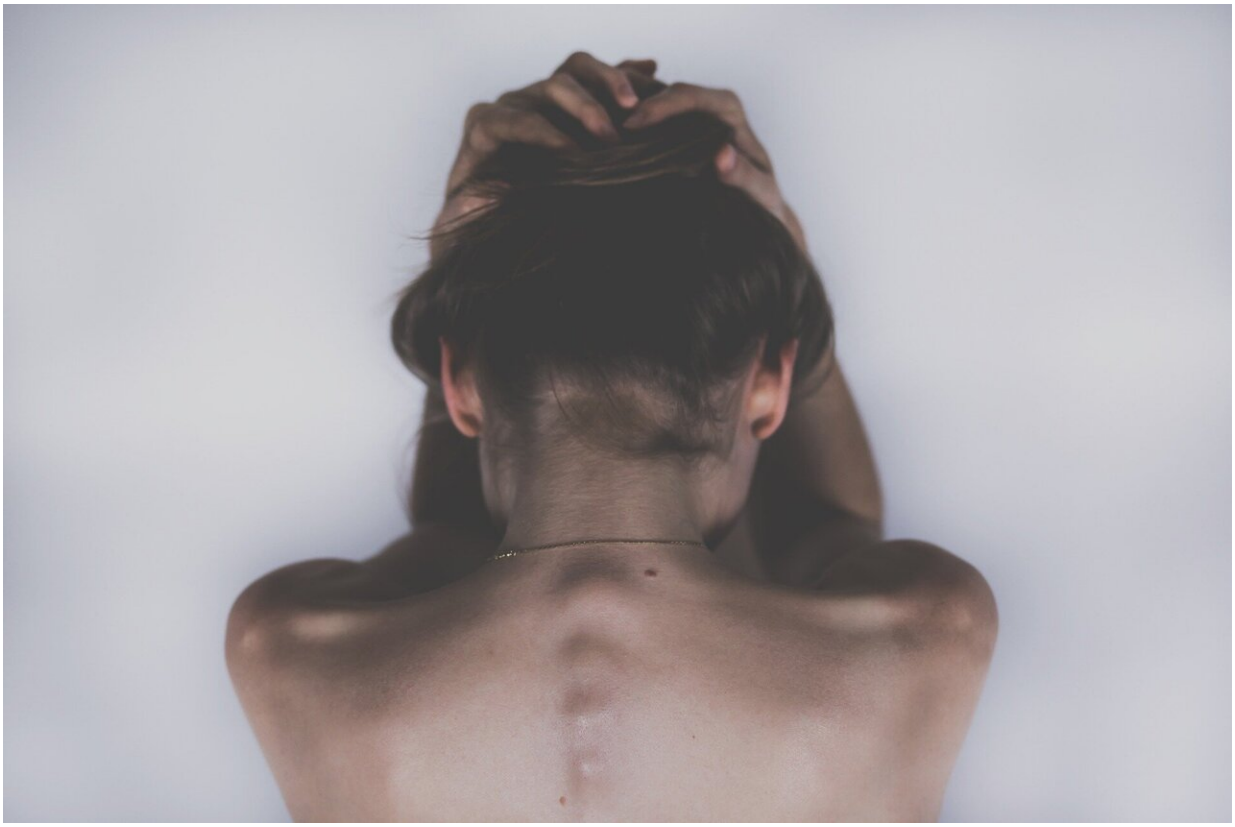

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Researchers from North Carolina State University have discovered that a particular molecular signaling pathway plays an important role in producing osteoarthritis (OA) pain. Using a mouse model of painful

osteoarthritis, they show that blocking this signaling pathway eliminates pain and results in a return to normal limb use. This work is the first to find an association between this pathway and OA pain, and could lead to the development of new, effective pain treatments for human OA sufferers.

Over 32.5 million U.S. adults suffer from painful OA, making it the most common joint disorder in the country. The incidence of OA is increasing, and while it can range in severity, OA can be associated with pain which limits mobility and function.

"There are currently very few effective and safe long-term ways to manage OA pain, which is chronic and often very debilitating," says Duncan Lascelles, professor of translational pain research and management at NC State and co-corresponding author of the research.

Previously, Lascelles, an expert in companion animal pain management, and his colleague, NC State neurobiologist Santosh Mishra, observed increased levels (or upregulation) of the components of this signaling pathway in the joint fluid, blood and sensory nerves of dogs with naturally occurring OA. The components in question—the ligand, or binding molecule artemin, and its receptor GFRα3—were known to pain researchers, but had not been associated with OA pain signaling.

"When you feel pain, that's the result of a molecule at the painful site interacting with a receptor on a sensory nerve, setting off a cascade of events within the nerve that lead to a signal being produced," Lascelles says. "This signal travels along the nerve, and is interpreted as painful by the brain."

"For acute pain, the artemin/GFRα3 system has been known to play a role, particularly in situations like cold hypersensitivity," says Mishra, assistant professor of neuroscience at NC State and co-corresponding

author of the work. "However it had not been associated with pain in a chronic condition like OA. Observing upregulation of a particular molecule doesn't necessarily mean it's relevant in a particular condition, so we decided to explore whether this pathway was functionally involved in pain signaling in OA—that is, explore whether this signaling pathway was actually contributing to OA pain."

In a mouse model of chemically induced OA the researchers found that GFRα3 was upregulated in the sensory nerves—just as it was in dogs with naturally occurring OA—versus a control group of healthy mice. A subset of the OA mice were then treated with monoclonal antibodies designed to bind to GFRα3, preventing artemin from binding to GFRα3 and effectively blocking the pain signaling pathway.

Within two hours post-treatment with the antibodies, limb function had returned to normal levels in the treated mice, indicating that the artemin/GFRα3 pathway most likely plays an important role in OA pain.

"While this is a proof-of-concept study, the findings are encouraging and we hope to continue working to understand this pathway and its involvement in OA pain," Mishra says.

"Although the work here is in a mouse model, it was based on robust observations in dogs with naturally occurring OA pain," Lascelles says. "Because OA in dogs and humans is so similar, we believe our findings are highly relevant to both. Hopefully this work can lead to targeted drug therapies to relieve pain in both canine and human OA patients. While we cannot reverse the joint damage, we can hopefully alleviate suffering caused by pain, decreased mobility and decreased ability to function."

The research appears in *Frontiers in Neuroscience*, and was supported by funding from NC State's Translational Research in Pain Program. Former NC State graduate student Laura Minnema, and current

NC State graduate student, Ankita Gupta, are co-first authors.

More information: Laura Minnema et al, Investigating the Role of Artemin and Its Cognate Receptor, GFRα3, in Osteoarthritis Pain, *Frontiers in Neuroscience* (2022). DOI: 10.3389/fnins.2022.738976