Research suggests chronic pain is different for males and females

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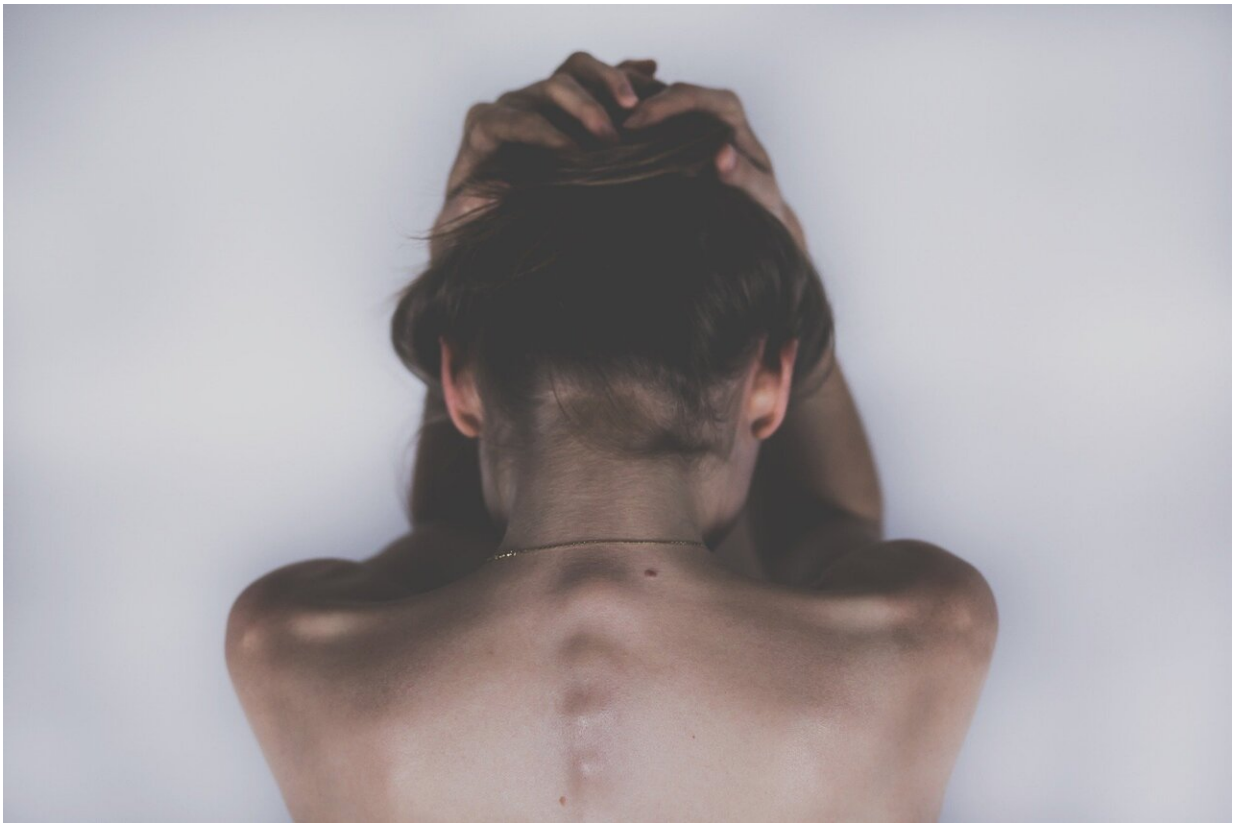

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A University of Alberta research team has uncovered differences in the way male and female mice develop and resolve chronic pain, pointing to potential pathways for future targeted treatments for humans.

In recently published research in *Brain, Behavior, and Immunity*, the team reports on its study of mice with chronic pain resulting from inflammation rather than direct injury. The researchers found that the female mice were more sensitive to the effects of immune cells called macrophages. They also identified an X chromosome-linked receptor that is critical for resolving both acute and chronic inflammation in both sexes.

"We're always interested in understanding the triggers for pain, but in this study, we went up the next step to ask how pain resolves to determine how these immune cells are involved," explains principal investigator Bradley Kerr, professor of anesthesiology and pain medicine in the Faculty of Medicine & Dentistry.

"Our findings indicate that it might come down to the composition of the immune cells themselves that are influencing not only the disease state, but whether or not pain becomes chronic," says Kerr, who is also an adjunct professor with the departments of pharmacology and physiology.

Chronic pain is defined as pain that lasts for three months or longer, or past the point of typical tissue healing, according to Pain Canada. About 20% of Canadians live with chronic pain, affecting more women than men. Autoimmune diseases such as multiple sclerosis that can lead to chronic pain also affect about twice as many women as men.

Kerr notes that it was only in the last decade or so that scientists started using both male and female mouse models in their studies of pain to look for sex differences as a standard research question.

Kerr says his lab is interested in studying the causes of chronic pain in hopes of figuring out ways to treat it, explaining that pain at the beginning of an illness or right after an injury can be protective.

"We're interested in understanding pain that doesn't have a good use anymore. It's not keeping you safe and telling you that you should take a rest and let your broken leg heal," Kerr says. "Having an understanding of where this pain is coming from and how it goes away naturally is really important, and I think we're a step closer."

Kerr's team examined the pain pathways in the mouse models using various methods. Previous work in Kerr's lab with mice that have multiple sclerosis showed that females have two to three times more of the pain receptor Tlr7 than males. In this study, they genetically deleted Tlr7 and found that pain did not resolve properly.

In contrast, the team treated mice that had chronic pain with an antiviral medication used to treat warts that is known to stimulate Tlr7 artificially. They found that the pain resolved three to five days sooner than without treatment. Tlr7 is the receptor within the immune system that activates an antiviral response when it detects a virus in your body, which is why you get that sore and achy feeling when you have a fever.

"We're hoping to inform future therapies and identify things like the Tlr7 receptor that could be potentially very beneficial down the line if we can refine how to activate it in a controlled way," Kerr says.

All of these findings indicate that chronic pain is inextricably linked to the function or dysfunction of the immune system, says Kerr, and future treatments may need to be sex-specific.

"We learned that you've got to stimulate the immune system in just the right way to get that proper resolution of pain," he says. "If the macrophages don't get activated or the pathways don't get engaged properly at the start, that sets up this kind of continuous chronic pain state that doesn't resolve."

Kerr says the next step for the research will be to test the effect of stimulating macrophages and Tlr7 on models that have pain caused by a nerve injury rather than a disease like multiple sclerosis.

More information: Timothy N. Friedman et al, Sex differences in peripheral immune cell activation: Implications for pain and pain resolution, *Brain, Behavior, and Immunity* (2023). DOI: 10.1016/j.bbi.2023.07.029

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