Study shows first evidence of sex differences in how pain can be produced

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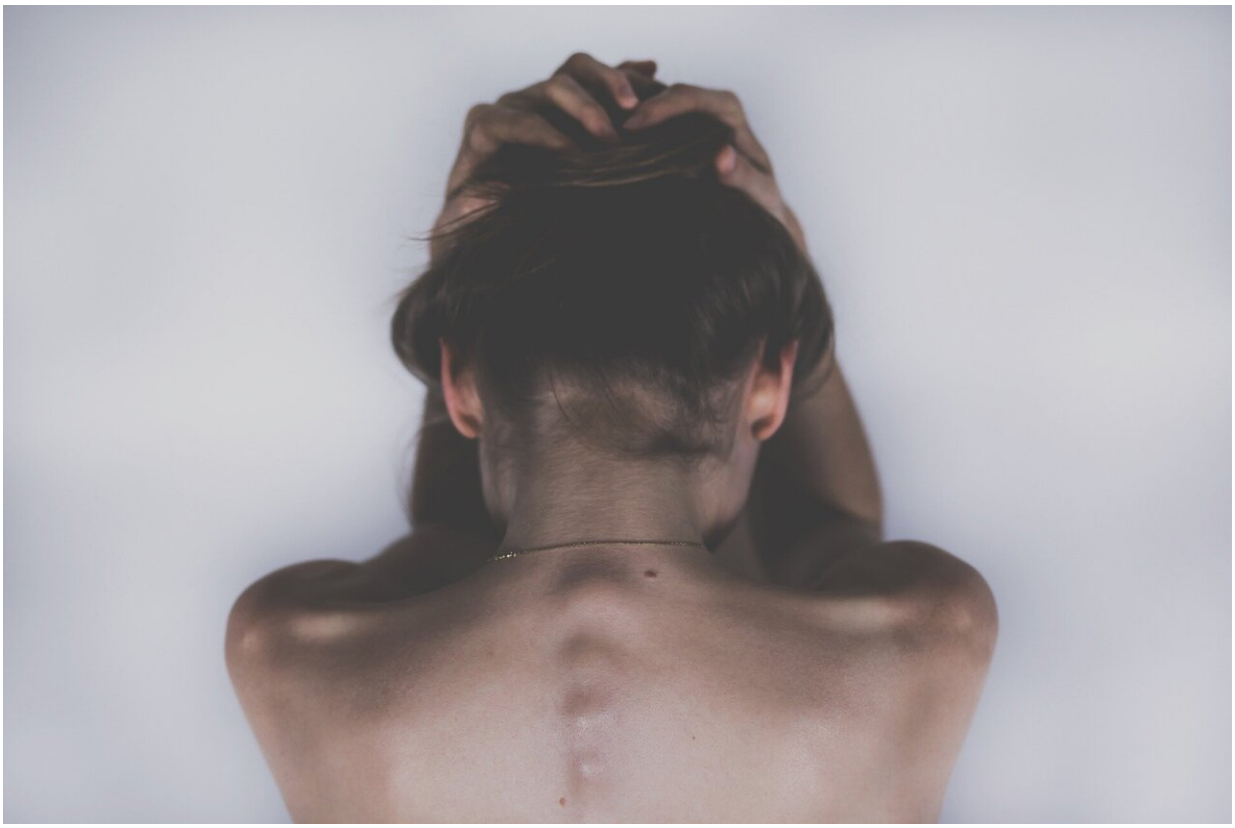

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Research suggests that males and females differ in their experience of pain, but up until now, no one knew why. In a recent study published in *Brain*, University of Arizona Health Sciences researchers became the first to identify functional sex differences in nociceptors, the specialized nerve cells that produce pain.

The findings support the implementation of a precision medicine-based approach that considers patient sex as fundamental to the choice of treatment for managing pain.

"Conceptually, this paper is a big advance in our understanding of how pain may be produced in males and females," said Frank Porreca, Ph.D., research director of the Comprehensive Center for Pain & Addiction at UArizona Health Sciences and professor and associate department head of pharmacology at the UArizona College of Medicine-Tucson. "The outcomes of our study were strikingly consistent and support the remarkable conclusion that nociceptors, the fundamental building blocks of pain, are different in males and females. This provides an opportunity to treat pain specifically and potentially better in men or women, and that's what we're trying to do."

Porreca and the research team focused their study on the excitability of nociceptor cells located near the spinal cord in the dorsal root ganglion. Nociceptors, when activated by damage or injury, send a signal through the spinal cord to the brain that results in the perception of pain. Nociceptors are also adaptable in their response to injury.

For example, touching a hot stove is a high-intensity stimulus, while a shirt collar rubbing a sunburn is low-intensity, yet both produce the perception of pain. In injury settings such as sunburn, pain medications, including nonsteroidal anti-inflammatory drugs such as ibuprofen, work

by normalizing the threshold for nociceptor activation, thereby blocking pain produced by low-intensity stimuli such as the rubbing of a shirt.

Following up on prior research on the relationship between chronic pain and sleep, unexpected sex differences led Porreca to choose two substances—prolactin and orexin B—for this study. Prolactin is a hormone responsible for lactation and breast tissue development; orexin is a neurotransmitter that helps to promote staying awake. However, both prolactin and orexin have many other functions that are only now being revealed.

The research team used tissue samples from male and female mice, nonhuman primates and humans to test the effect of prolactin and orexin B on nociceptor activation thresholds that can allow low-intensity stimuli to produce pain.

"What we found is that in males and females—animals or humans—what changes the thresholds of the nociceptors can be completely different," Porreca said. "When we added the sensitizing substances that lower these thresholds for activation, we found that prolactin only sensitizes female cells and not male cells, and orexin B only sensitizes male cells and not female cells. The startling conclusion from these studies is that there are male nociceptors and female nociceptors, something that has never previously been recognized."

Taking the research one step further, they then blocked prolactin signaling and orexin B signaling and examined the effect on the threshold for activation of the nociceptors. As anticipated, blocking prolactin signaling reduced nociceptor activation in females and had no effect in males, while blocking orexin B signaling was effective in males and not in females.

"Until now, the assumption has been that the driving mechanisms that

produce pain are the same in men and women," Porreca said. "What we found is that the basic, underlying mechanisms that result in the perception of pain are different in male and female mice, in male and female nonhuman primates, and in male and female humans."

The findings suggest a new way to approach treating pain conditions, many of which are female prevalent. Migraine and fibromyalgia, for example, have female-to-male ratios of 3:1 and 8 or 9:1, respectively.

Porreca believes preventing prolactin-induced nociceptor sensitization in females may represent a viable approach for the treatment of female-prevalent pain disorders, while targeting orexin B-induced sensitization might improve the treatment of pain conditions associated with nociceptor activation in males.

Moving forward, Porreca and his team will continue looking for other sexually dimorphic mechanisms of pain while building on this study to seek viable ways to prevent nociceptor sensitization in females and males. He is encouraged by his recent discovery of a prolactin antibody, which could prove useful in females, and the availability of orexin antagonists that are already Food and Drug Administration-approved for the treatment of sleep disorders.

"We are bringing the concept of precision medicine—taking a patient's genetics into account to design a therapy—to the treatment of pain," Porreca said. "The most basic genetic difference is, is the patient male or female? Maybe that should be the first consideration when it comes to treating pain."

More information: Harrison Stratton et al, Nociceptors are functionally male or female: from mouse to monkey to man, *Brain*

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