PAIN

Sex differences in learned conditioned pain sensitivity

A unique paradigm to investigate the intersection between memory, pain, and stress reveals new details about the processes that underlie pain memory. In both mice and men, males seem more susceptible.

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Pain is important. Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"[1]. Although unpleasant, the sensation of pain is a necessary component of the body's defense system and facilitates survival. However, pain loses its biological purpose when it transitions from an acute to chronic state. Following injury or disease, chronic pain can persist even after the body has healed. The idea that the progression from acute to chronic pain is a form of associative learning, termed "pain memory", has emerged among pain researchers[2]. Unfortunately, little is known about the classical conditioning of pain.

A new article by Loren Martin and colleagues[3] describes a novel paradigm to investigate the intersection between memory, pain, and stress, and demonstrates that placing mice or humans in an environment that was previously associated with pain can lead to heightened sensitivity in the absence of a painful stimulus. The animal model that the authors developed has translational value that advances our understanding of conditioned pain sensitivity, and their findings highlight important sexual dimorphisms in the underlying pain memory processes in both mouse and man.

It is routine for pain researchers to conduct conditioning experiments that require repeated pairings of noxious stimuli with context; however, such paradigms do not traditionally measure changes in pain thresholds following contextual learning. The unique experimental design in this study involved assessing thermal pain sensitivity before and after a single application of an acute noxious stimulus in CD-1 outbred mice and humans. Pain sensitivity was tested in either the same context in which the subjects received the noxious stimulus—for the mice, that meant in the same container in the same room (Fig. 1); for humans, in the same room with the same tester—or in a different one (a different container and room for mice or different building and tester for humans). Intriguingly, both male mice and men exhibited hyperalgesia in the *same* context, whereas females did not. This was in spite of the fact that males and females of both species exhibited equivalent pain behavior to the acute noxious stimulus, suggesting differences in pain memory formation between the sexes.

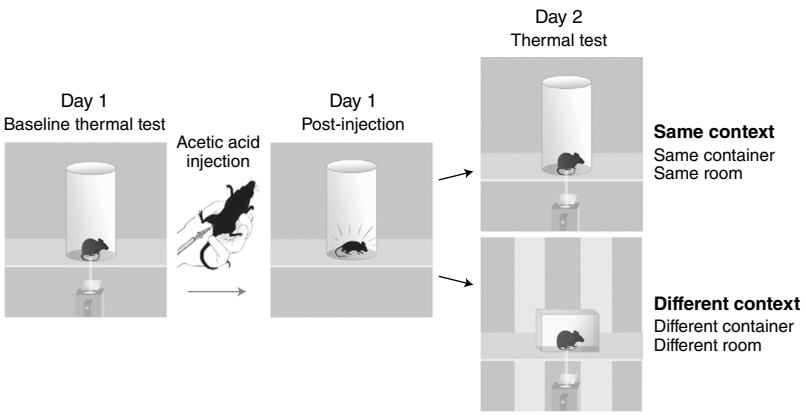

Fig. 1 | Schematic of Martin et al's mouse-conditioning paradigm. They developed a similar paradigm for humans that involved a different tester and building to satisfy the 'different' context criteria. Reprinted with permission from Martin et al (2019). Elsevier.

Females are typically more sensitive to pain in experimental studies and report greater pain in a clinical setting[4]. Therefore, it was surprising to the authors (and readers) to observe a male-specific hypersensitivity. In order to gain mechanistic insight into this unexpected sexual dimorphism, the authors explored the contributions of both sex hormones and stress to pain hypersensitivity. Martin and colleagues repeated the paradigm with gonadectomized mice of both sexes and found this phenomenon to be testosterone-dependent. Castrated male mice did not exhibit conditioned hypersensitivity, and administration of testosterone propanoate to female mice elicited context-dependent hypersensitivity.

The authors hypothesized that the conditioned hypersensitivity they observed in males was stress-induced through activation of the endocrine stress response. To test this, they inhibited corticosterone synthesis and activation of the hypothalamic-pituitary-adrenal (HPA) axis. Pharmacological blockade of the stress response abolished context-dependent hypersensitivity in male mice, but had no effect on pain sensitivity in females. In addition, male mice exhibited increased corticosterone levels when returned to the original context, positively correlating with pain behavior. Notably, these findings were paralleled in human subjects: subjective stress ratings and pain hypersensitivity were correlated only in men, not women. Nevertheless, the authors acknowledged that only self-report measures were included in this study. Future studies should explicitly test physiological measures of stress, such as cortisol levels, blood pressure, and/or heart rate readings in addition to self-report data to establish a stronger relationship between stress and pain in humans.

In a final experiment, Martin and colleagues examined the contribution of atypical protein kinase C (aPKC), an enzyme that has previously been implicated in spinal pain processing and memory[5,6], to male-specific conditioned pain hypersensitivity. They demonstrated that both intrathecal (i.t.) and intracerebroventricular (i.c.v.) administration of zeta inhibitory peptide (ZIP), an inhibitor of aPKC, reversed same-context conditioned hypersensitivity in male mice and had no effect on females. The authors propose two possible mechanisms underlying this behavior: ZIP administration i.c.v. suggests a reduction in the ability to recall pain memory through inhibiting aPKC, whereas i.t. administration may involve aPKC sensitization of spinal pain circuitry.

The findings in this study suggest that males may be more susceptible to learning cues in a pain context and/or have an intrinsic predisposition to forming stress-induced pain memories. The authors present compelling evidence that this difference is due to circulating levels of testosterone. Given that testosterone levels are known to vary between male cage mates[7], measuring and correlating testosterone levels with conditioned pain hypersensitivity of the individual could provide greater insight into the role of testosterone in pain hypersensitivity.

It is interesting to consider that females may not be as efficient in acquiring pain memories, raising the question of whether pain plays a role in impairing learning and memory processes in females. Though, as with any sexually dimorphic behavior, it is important to acknowledge the potential difference in the outward expression of pain and reflexive behavior between males and females. It is possible that sexual dimorphisms in context-dependent hypersensitivity are a consequence of differences in the observable response to acute noxious stimuli or pain thresholds. Nonetheless, this study establishes important sex differences in conditioned pain hypersensitivity and contributes to the fundamental understanding of the neurobiological mechanisms involved in pain memory. These findings provide a solid foundation for examining learning and memory mechanisms as potential therapeutic targets in treating males suffering from chronic pain. ❐

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