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Why we should study osteoarthritis pain in experimental models in both sexes

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Females and males show clear differences in their susceptibility to many diseases, notably autoimmune diseases and malignancies, but also certain infectious diseases [1]. In addition to sex differences in disease susceptibility, there is abundant epidemiological and experimental evidence that sex is a major determinant of pain. Women are markedly overrepresented in chronic pain states, including several painful musculoskeletal conditions such as low back pain, fibromyalgia, and myofascial pain [2-4]. While there are many factors that may contribute to the observed sex differences in pain susceptibility, including sociocultural, psychological, and biological factors such as genetic or hormonal modulators (for a review, see [5]), recent years have seen the emergence of an interesting paradigm that involves sexual dimorphism in neuroimmune interactions that contribute to pain in experimental animals [3].

In the past decade, neuroimmune crosstalk has emerged as a key process in establishing and maintaining chronic pain, and this at different levels of the pain neuraxis [6]. In the periphery, neurons and immune cells (macrophages, T cells, mast cells) can talk to each other in the innervated tissues - for example, the synovium in an OA joint may be infiltrated by immune cells that release inflammatory mediators that can sensitize nociceptors. Neuroimmune crosstalk also occurs in dorsal root ganglia (DRG) where the cell bodies of the nociceptors reside. It has been shown that in chronic pain states, including in experimental OA, the DRGs get infiltrated with macrophages, resulting in pain-promoting feedback loops between macrophages and sensory neurons (for a recent review on the role of neuroimmune interactions in OA pain, please see [7]). Neuroimmune interactions also occur in the central nervous system (CNS). Specifically, interactions between neurons and microglia (the resident macrophages of the CNS) and other immune cells occur in the spinal cord. Microglial activation in the dorsal horn has been documented in many pain models, including models of rheumatoid arthritis (RA) and OA, where they are thought to contribute to increased neuronal excitability and synaptic efficacy, and hence to central sensitization [6]. Finally, neuroimmune interactions may also occur in the brain, where the role of microglia has been extensively studied in neurodegenerative disorders, but also in chronic pain syndromes such as fibromyalgia [6].

These observations have sparked great interest in targeting microglia with modulators such as minocycline to treat pain [8]. However, as is the case for the majority of studies in laboratory animals, studies pointing toward a role for microglial activation in chronic pain have largely been conducted in male animals [9]. Remarkably, in recent years it has emerged that the contribution of microglia to establishing pain in mice is sex dependent.

Experimental nerve injury results in mechanical allodynia and microglial activation in both female and male mice, but inhibitors of microglial activation block allodynia only in males and not in females. By contrast, female mice use adaptive immune cells in the spinal cord to establish pain [10], but this is highly dependent on the hormonal context in that female mice still use microglia to establish pain when testosterone levels are elevated [10].

In addition to these microglia findings, there have been reports on sexual dimorphism in the role of spinal Toll-like receptor 4 (TLR4) in pain, where it has been reported that intrathecal administration of the TLR4 ligand, lipopolysaccharide (LPS), causes much more robust mechanical allodynia in males than in female mice [11]. Furthermore, *Tlr4* deficiency or treatment with the TLR4 inhibitor, TAK-242, attenuated allodynia induced by intrathecal administration of LPS in male mice, but not in female mice [12].

If translatable to humans, these divergent pathways mediating chronic pain in the two sexes may have clear implications for drug development and drug testing. Sex-dependent findings in mouse models of inflammatory and neuropathic pain reflect the growing body of literature indicating that sex as a variable has a tremendous influence on innate and adaptive immune responses, where females generally mount a more robust immune response than males. Several biological factors can contribute to this sexual dimorphism, including genetic, hormonal, and environmental influences on the immune system (for a comprehensive and fascinating review, please see [1]). Clearly, in view of the increasing evidence for a role for innate immune pathways and TLR signaling in chronic pain in general, as well as in the pathogenesis of osteoarthritis (OA) [13] and OA pain [7], it is highly likely that pathways mediating OA pain may differ between the sexes.

In humans, female sex is a major risk factor for OA, particularly after menopause [14], for reasons that are incompletely understood. Women have a greater risk for developing knee OA than men, and women with knee OA experience more pain than men regardless of radiographic severity [15]. These sex differences in OA pain reflect the greater incidence of musculoskeletal pain in females compared to males in general. In spite of this female preponderance, experimental OA is predominantly modelled in male animals [16]. In fact, experimental knee OA induced by destabilization of the medial meniscus (DMM) is currently the most widely used mouse model of OA, but female mice are less susceptible to OA after this surgery unless they have been ovarectomized [17]. Pain behaviors and pain pathways in this model have been studied for several years by different laboratories, including our own, but only in male mice [18].

Clearly, going forward it will be important to compare the development of pain-related behaviors in experimental OA in males and females side by side. This is precisely what the study by Temp *et al.* in the current issue of *Osteoarthritis and Cartilage* aimed to do [19]. The authors used the medial meniscotibial transection (MMT) in C57BL/6 mice. As in other OA models, MMT surgery caused more severe cartilage damage in male mice than in female mice, while osteophyte development was similar between both sexes. In association with joint damage, male mice developed signs indicative of pain, and this in a biphasic pattern: mechanical allodynia in the ipsilateral hind paw and decreased weight-bearing on the operated limb presented in an acute phase (days 1-5), resolved during the intermediate phase

(weeks 1-2) and reappeared in the chronic phase (weeks 4-12). In contrast, in female mice, both these pain-related behaviors were present throughout the entire time course of the model (day 1-week 12). Direct comparison between males and females revealed that females had greater mechanical allodynia in the intermediate period compared to males, while males had greater weight-bearing deficits at select time points in both the acute (days 1-2) and chronic (weeks 5-6) phases. However, the male mice overall had greater body weights than the female mice, which may contribute to this difference observed in weight-bearing. While the study did not investigate mechanisms underlying the observed sex differences in the development of pain behaviors, it clearly demonstrates that differences exist.

Very few side by side comparisons between male and female mice in OA pain models have been reported in the literature, while a few studies report combined data for animals of both sexes. An interesting recent study investigated sex and age interactions in the rat mono-iodoacetate (MIA) model, and found that MIA induced more pronounced weightbearing deficits and knee joint hypersensitivity in older rats, and this was most pronounced in aged females, suggesting that age significantly impacts OA pain, especially in females [20].

The differences in susceptibility to OA joint damage between the two sexes has been appreciated for a long time, and scientists are increasingly recognizing the importance of sex -like age - as a biological variable in the pathogenesis of joint damage [21]. The study by Temp *et al.* is one of the first to study pain behaviors in an OA model in mice of both sexes side by side. While the use of mouse models to study sexual dimorphisms in chronic pain mechanisms is severely limited because they cannot capture psychological and social factors that may contribute to the observed differences [22], current evidence suggests that there are basic biological pathways that diverge between the sexes. Going forward, we have to hope that the OA research community will increasingly consider these potential sex differences in susceptibility to pain and the underlying mechanisms, in order to increase translational and predictive value of animal models especially with respect to identifying new targets for OA pain.

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