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Chronic Pain and Gender: Biological Mechanisms and Clinical Implications for Personalized Pain Medicine

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ABSTRACT

The 2020 definition by the International Association for the Study of Pain (IASP) characterizes pain as "an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage." This definition emphasizes the individualized nature of pain, influenced by biological, psychological, and social factors. Recent research has focused on understanding the subjectivity of pain and the biological diversity among individuals, particularly examining gender differences in pain perception and management, and exploring the underlying pathophysiological, emotional, and social mechanisms. Epidemiological and clinical data consistently show that women are more prone to develop chronic pain conditions over their lifespan, presenting higher prevalence rates across various painful disorders. Conditions such as osteoarthritis, rheumatoid arthritis, migraine, fibromyalgia, and interstitial cystitis exhibit well-documented female predominance. For instance, a 2019 Spanish study involving 22,842 patients found significantly higher rates of pain among women—25.68% vs. 12.54% for chronic neck pain, 27.03% vs. 18.83% for chronic low back pain, and 15.93% vs. 6.74% for migraine or frequent headaches. Women with pain also more frequently used medications for pain, anxiety, depression, and sleep disturbances. Despite these observations, the mechanisms underlying gender disparities in pain perception and chronicity remain only partially understood. Current evidence suggests a complex interplay between genetic, hormonal, inflammatory, and immune factors that may contribute to both the development and persistence of chronic pain in women. Continued research is essential to unravel these mechanisms and tailor gender-specific approaches for effective pain management and treatment strategies.

Keywords: *Chronic Pain, Patient centered personalised care, gendere medicine*

Introduction

According to the most recent definition by the IASP in 2020, pain is classified as "an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage." Furthermore, it has been clarified that "pain is always a personal experience,that is influenced to varying degrees by biological, psychological, and social factors." In recent years, based on the analysis of this definition, the assessment of the subjectivity of pain and biological diversity has become of fundamental interest. In particular, countless studies have been conducted on gender differences in the perception and management of pain and on its pathophysiological and emotional/social mechanisms.

Clinical evidences and epidemiological data confirm that women are more likely to develop chronic pain during their lifetime, showing a higher prevalence of painful conditions than men. Suffice it to mention, by way of example, clinical conditions such as osteoarthritis, rheumatoid arthritis, migraine, fibromyalgia, or interstitial cystitis, all diseases in which female predominance is well documented [1][2]. In 2019 a Spanish study with a sample of 22,842 patients revealed that the prevalence of all types of pain was significantly higher among women than men. For chronic neck pain, the figures were 25.68% vs 12.54%, for chronic low back pain, 27.03% vs 18.83%, and for migraine or frequent headaches, 15.93% vs 6.74%, in women and men, respectively. Women experiencing pain used prescribed medications for pain, anxiety, and/or depression and sleeping pills more than men [32]. Although the precise mechanisms underlying these differences are not yet fully understood, the literature suggests that a complex interaction between genetic, hormonal, inflammatory, and immune factors may contribute to the development and maintenance of chronic pain [3].

It is much more difficult to determine whether there are significant differences between the sexes in the perception and severity of pain. The analysis of this aspect in the clinical setting is methodologically challenging due to the interference of multiple confounding factors, including sex-specific variations in the pharmacodynamics and pharmacokinetics of analgesics. The aim of this study was to analyze some of the mechanisms that can determine a difference in the therapeutic response to opioids, identify pain responses induced by sex hormones and investigate the difference in the mechanisms of neuroinflammation underlying chronic neuropathic pain.

FOCUS 1 - Sex differences in the opioid system and response to pain treatment

Sex differences in response to opioids are an area of growing interest in pain medicine. Men and women may have significantly different responses to opioid analgesic drugs, differences that depend not only on physiological and biochemical factors—such as enzyme metabolism, gene expression, and hormone levels—but also on variables such as age, hormonal conditions (e.g., menopause or menstrual cycle), psychological state, and the presence of chronic comorbidities.

Similar to what has been observed with other drugs, gender differences in response to opioids can be attributed to both pharmacodynamic (different receptor sensitivity) and pharmacokinetic (absorption, distribution, metabolism, and elimination) factors [4].

One important aspect concerns the different body composition between the sexes: women tend to have a higher percentage of fat mass than men, and this affects the efficacy of opioids, which are notoriously lipophilic. In addition, hepatic metabolism and cytochrome P450 enzyme activity differ between men and women: for example, the CYP2D6 isoform, which is essential for the conversion of codeine to morphine, generally

has greater activity and expression in the male liver than in the female liver. This translates into a potentially lower efficacy of codeine in women.

Preclinical studies have also shown sexual dimorphism in the number and distribution of mu opioid receptors (MORs), the main mediators of the analgesic effect of morphine and its derivatives. For example, a higher number of MORs has been observed in the periaqueductal gray matter of male animals compared to females [5][6]. In addition to quantity, it would also appear that the intracellular response—i.e., the activation of the second messenger cascade following binding to the receptor—is more efficient in males [6].

Consistent with these data, the analgesic efficacy of morphine in male animals was found to be higher than that observed in female animals [5]. These differences may contribute, in part, to explaining the subjective variability in response to pain treatment also observed in human clinical practice.

Over the last twenty years, scientific interest has also focused on genetic variations, particularly on genes involved in pain modulation. The gene encoding the enzyme catechol-O-methyltransferase (COMT) has been one of the most studied due to its close association with both mu-opioid receptors and sex-related differences in pain perception and pharmacological response. The presence of genetic polymorphisms in COMT can significantly influence pain threshold and response to analgesics, with effects that can be modulated by the individual's biological sex [3].

FOCUS 2 - Sex hormones and pain perception

Estrogen receptors (ER) are widely distributed in the central nervous system, including several nociceptive brain areas, such as the amygdala, thalamus, and anterior cingulate cortex (ACC). Several studies have suggested that estrogens in the ACC may significantly influence nociception-related behaviors in mice [7]. The role of estradiol (E2) remains unclear. Estradiol has been shown to increase the facial receptive fields of trigeminal ganglion (TG) neurons in rats and decrease the thresholds of these fields, suggesting that E2 may contribute to TG-mediated pain states specific to women, such as migraine. In the past years, it has been discovered that ERs are more abundant in female rats than males in the TG. These data, combined with those demonstrating that ER agonists lead to dilation of blood vessels in the dura mater, have led to the hypothesis that E2 may contribute to predominantly female pain disorders such as migraine and temporomandibular joint syndrome. In contrast, many data have been published suggesting that estrogens play a protective role against inflammation and pain disorders. Estrogens have been shown to attenuate lymphocyte extravasation following exposure to TNFα, as well as to reduce immune cell trafficking in response to inflammation. In addition, the steroid hormone estrogen 17β-E2 plays a protective role at the blood-brain barrier, helping to maintain tight junctions between endothelial cells. The decrease in E2 after menopause is related to the increase in the proinflammatory cytokines IL-6, IL-1β, and TNFα. [8][11]

The role of estrogens in pain sensitivity is still unclear, and several factors have emerged that indicate a pro-nociceptive and anti-nociceptive function.

For example, it has been shown that the incidence of pediatric fibromyalgia is similar in both sexes until the onset of puberty, when the incidence rate increases in girls. It is curious to note that even in the same woman, hormone fluctuations during the menstrual cycle can alter pain perception. A study was reported on women with fibromyalgia who had normal menstrual cycles and did not use contraceptives, in which sex hormones were measured during the cycle and correlated daily with pain assessment tests. Cortisol and

the sex hormones estradiol, progesterone, and testosterone were analyzed from serum. A mixed linear model was used to determine whether fluctuations in sex hormones were associated with changes in pain severity. In the entire sample, daily variations in both progesterone and testosterone were significantly and inversely correlated with pain severity [9]. Progesterone and testosterone, but not estradiol, were found to be associated with daily variations in self-reported pain intensity. Both progesterone and testosterone were inversely associated with pain, with peaks in these hormones occurring on days when reported pain was lowest. Self-reported fibromyalgia pain was lowest in the mid-luteal phase, corresponding to high levels of progesterone and moderate levels of estradiol and testosterone. Pain was highest during the menstrual phase, when all sex hormones are at low levels. These findings are consistent with previous reports that women with chronic pain show increased sensitivity to pain during the menstrual phase. There is growing evidence that progesterone may have significant mood-regulating properties. Numerous animal studies have demonstrated anxiolytic and antidepressant effects of progesterone administration. Sedative effects and increased fatigue have also been documented with acute progesterone administration in humans. An acute increase in progesterone has also been shown to alter sleep architecture in humans. [9][10]

Testosterone

It has long been believed that testosterone, a predominantly male hormone, plays a protective role in inflammatory and chronic pain conditions. Treatment with testosterone in men reduces the presence of pro-inflammatory cytokines such as tumor necrosis factor α (TNFα), interleukin (IL)-1β, and IL-6 [12][11]. Studies have been conducted that have found that increased testosterone contributes to a decrease in neck and shoulder pain [31] and rheumatoid arthritis in women [28]. It has recently been discovered that testosterone reduces hyperalgesia in female mice in a model of muscle pain by reducing the serotonin transporter [29]. The increase in testosterone levels in males may also help explain the higher prevalence of chronic pain conditions in women [27][11].

FOCUS 3 - Neuroinflammation

Damage to the central or peripheral nervous system can cause neuropathic pain, which has a significantly higher prevalence among females than males [13]. Common causes of nerve damage include autoimmune diseases [14]. Women may be more susceptible to developing neuropathic pain conditions for multiple reasons, both because of their predisposition to autoimmune diseases and because circulating estrogen levels increase proinflammatory cytokines released by mast cells, macrophages, and T lymphocytes. Testosterone has been shown to increase the production of anti-inflammatory cytokines by macrophages, so it is likely that males do not develop as strong an immune response to injury as females. This may affect not only the onset of neuropathic pain, but also its maintenance.

Microglia

Microglia are innate immune cells residing in the central nervous system (CNS) . The differential function between male and female microglia determines sexual differentiation within the brain, as well as sexual dimorphism in pain and inflammation [15]. Spinal microglia interact with the nerve terminals of sensory neurons to influence neurotransmitter release, synaptic plasticity, and signaling between the PNS and CNS [20]. When tissue damage occurs, damaged cells release adenosine 5′-triphosphate (ATP). Microglia detect ATP via purinergic receptors (P2X and P2Y) and activate to respond to tissue damage and inflammation by releasing cytokines such as TNF-α, IL-1β, and IL-6 [16]. This leads to increased activity of excitatory neurons and decreased activity of inhibitory neurons in pain pathways, contributing to the

development of chronic pain [17][18]. Some studies have shown that drugs that inhibit microglia can block the development of pain hypersensitivity after injury [19].

Based on the current literature, microglia activation during neuropathic pain states appears to be a predominantly male mechanism [21]. At baseline, adult male and female microglia have different morphological and functional characteristics. Male microglia typically have larger cell bodies and are more proliferative. When activated, male microglia are more involved in pain signaling than female microglia, as inhibition of microglial signaling in the spinal cord is protective in males but not in females [22].

T cells

T cells are heavily involved in orchestrating the adaptive immune response to antigens. When antigen-presenting cells detect and present antigens to immature T cells, the latter mature and differentiate to control the immune response by releasing cytokines and recruiting other immune cells. The function of T cells is strongly modified by X-linked genes and sex hormone signaling [23]. Furthermore, estradiol signaling on T cells promotes the production of proinflammatory cytokines and T cell proliferation [15][11].

The role of T lymphocytes has a sexually dimorphic effect in states of pain [16]. Recently, a study on immunodeficient knockout mice lacking mature T and B lymphocytes revealed that T lymphocytes mediate certain forms of pain in male mice. It has been observed that the reconstitution of CD8+ T lymphocytes in female and male RAG1 and RAG2 knockout mice resolves tactile allodynia following chemotherapy-induced pain [24] [25]. Similarly, another experiment in male rats with T cell deficiency and nerve injury demonstrated reduced mechanical allodynia following T cell infiltration at the site of injury and in the dorsal horn of the spinal cord [26]. A study conducted on males and females found that CD4+ T cells promote microglial maturation within the brain, indicating that interactions between microglia and T cells may play an important role in the development and function of the immune system in both sexes. Taken together, these data suggest that the activation of macrophages/microglia and T cells likely contributes to different forms of pain in both males and females [11]. Going deeper, some research highlights that the gender difference is inherent in the female production of a greater number of circulating CD4+ and CD8+ T cells than males. This imbalance appears to be linked once again to sex hormones. Males, due to high testosterone levels, have a more dominant Th2 immune population in their circulating CD4+ cells, which results in less pro-inflammatory activity. In contrast, females, due to higher basal levels of estrogen and progesterone, have a dominant CD8+ and Th1 immune population in their CD4+ cells, which results in greater production of the inflammatory cytokines IFN-Y and IL-2[30].

Conclusions

Evidence accumulated in recent years shows increasingly clearly that chronic pain is not a uniform experience between the sexes, but is profoundly influenced by biological differences related to sex, involving neurophysiology, immunology, and pharmacology. In particular, women show a higher prevalence of chronic pain conditions and an often less effective response to opioid analgesics, suggesting a sex-mediated resistance to opioids. This phenomenon seems to derive, at least in part, from differences in opioid receptor expression, intracellular signaling, and hormonal modulation.

Sex hormones, particularly estrogen, progesterone, and testosterone, play a crucial role in modulating both pain sensitivity and immune response. Estrogen, for example, exhibits biphasic and contextual effects: it can amplify the pain response through neuronal

sensitization, but also exert anti-inflammatory effects at specific dosages and in specific contexts. In contrast, testosterone appears to be generally protective, reducing the activity of pro-inflammatory pathways and enhancing analgesia.

Finally, neuroinflammation emerges as a central node in gender divergence in chronic pain. The inflammatory mechanisms affecting glial cells, T lymphocytes, and macrophages differ between males and females. For example, males tend to show greater involvement of microglia, while in females, T cells, particularly $CD4^+$ subtypes, appear to play a more significant role. These differences may influence both the development and maintenance of chronic pain, as well as the response to drug treatments.

In conclusion, research on gender differences in pain still has several challenges to overcome. We still don't have answers to many crucial questions about phisyology and clinical treatment of pain. Understanding the biological basis of gender differences in chronic pain is not only a matter of scientific accuracy, but a fundamental step towards more effective and personalized pain medicine. Although many of the biological, biochemical, and pathophysiological mechanisms underlying male/female differences are still unclear, the hope is to involve more and more researchers in this field in order to identify more effective therapeutic strategies that take into account the needs and requirements of each patient.

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