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GLOBAL YEAR
Sex and Gender Disparities in Pain

FACT SHEET

Biological Mechanisms Underlying Sex Differences in Pain

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There are clear biological differences between men and women including in their anatomy and the function of many different body systems. How these differences can interact with mechanisms causing or maintaining pain has been an area of increasing interest over recent years.

Sex Steroid Hormones

Sex steroids (estrogens, progestogens and androgens including testosterone) are predominantly thought of in the context of reproduction. However, sex steroid receptors are distributed widely throughout the body and we are increasingly aware of the variety of different biological processes they influence. Although they do have a role on the developing fetus and in early life, a marked increase in circulating levels of estrogens and androgens occurs as puberty starts, and they remain high throughout reproductive/adult life before decreasing with age, particularly after menopause in women.

Women have markedly higher levels of estrogens than men, whilst the inverse is true for androgens. However, both hormones are present in both sexes. Across a month (~28 days) hormone levels fluctuate for women, with low levels of estrogens and progesterone during menstruation (periods), increasing estrogens towards ovulation (follicular phase) and high levels of both estrogens and progesterone after ovulation (luteal phase). Progesterone is present in men, but at levels similar to the follicular phase. It is important to remember that hormones are some of the most prescribed medications worldwide—in the form of contraceptives, hormone replacement therapy and treatments for gynaecological, endocrine, dermatological and malignant conditions—and are often used continuously for many years, markedly altering circulating hormonal levels.

Effects of Sex Steroid Hormones on Pain

Hormones can exert an influence on pain in a variety of ways:

- Altering sensitivity to pain by influencing pain processing pathways (e.g., descending modulation)
- Altering biological processes associated with pain (e.g., inflammation)
- Driving hormonally dependent pathologies (e.g., endometriosis)
- Impacting on mood to alter the pain experience

The evidence supporting a menstrual cycle effect on sensitivity to noxious stimuli in healthy women is inconclusive, with most well-designed studies suggesting a small effect

at most [1]. Given that the relationship between individual hormone levels and sensitivity to stimuli is much clearer, it is plausible that the pain-amplifying effects of one hormone are balanced out by pain-suppressing effects of another [2]. Estrogen is a key modulator of pain with a pain-suppressing effect at higher concentrations (activating inhibitory pathways in the spinal cord) and pain-amplifying effect at lower concentrations. Increased estrogen levels have been found to protect against pain conditions like musculoskeletal [3] or chronic posttraumatic pain [4]. However, the latter effect seems only true for females and might even be the opposite for males with high body mass index [4]. The role of progesterone seems to be more pain-amplifying, although pregnancy (a time of very high estrogen and progesterone) is associated with a marked reduction in pain-sensitivity ("pregnancy-induced analgesia"). Testosterone, however, appears to be pain-reducing in both males and females; this may be at least in part due its effect on descending pathways that inhibit pain [2]. In women, the effect of circulating testosterone on responses to experimental pain is independent of the menstrual cycle. In men with chronic pain and low hormone levels, treatment with testosterone reduced pain intensity [5]. Interestingly, menstrual cycle effects do seem more consistent in women with chronic pain, potentially suggesting disruption of the balance between pain-amplifying and pain-suppressing mechanisms. Whilst hormones are commonly used as a treatment for gynaecological pain (period pain, pain associated with endometriosis/adenomyosis) it is well established that they can precipitate pain too, including headaches, migraine, vulval and joint pains. These symptoms occur in women treated with these formulations for non-painful conditions too (e.g., contraception and estrogen-sensitive tumours). Natural reductions in hormone levels as seen peri-/post-menopause are also associated with a change in pain. These relationships are complex, with some pains improving around this time, whilst others worsen and some commence in women who had previously been pain free. Better understanding of the underlying mechanisms will allow us to determine whether there is value in using hormone replacement therapy (HRT) as a treatment for these pains as has already been trialled in some conditions [2].

Qualitative Sex Differences in Pain Biology

Research has recently shifted from documenting, and providing explanations for, quantitative sex differences in pain and analgesic sensitivity to examining the possibility that different genes, proteins (i.e., neuro- and immune-chemicals and their receptors), and even cell types might play a role in pain processing in males and females. Via a comprehensive search of papers published as of January, 2024, at least 49 genes/proteins have been implicated in chronic pain processing in male but not female rodents, and 35 genes/proteins have been implicated in female but not male rodents. The fact that the male list is considerably longer than the female list is almost certainly due to the biased history of using male research subjects in preclinical pain research [6]. This may in fact be the tip of the iceberg, since a number of recent transcriptomics studies in rodents [e.g., 7] and humans [e.g., 8]—which examine gene expression of all genes in a tissue that are up- or down-regulated by pain—have detected large numbers of sex-dependently-expressed genes. Three particular sexual dimorphisms have been investigated in detail:

Immune Cells

Immune cells and pathways are well recognised to play key roles on pain transmission and the development of chronic pain. However, increasing evidence indicates that these cells and pathways are different between males and females (for reviews see [9–11]. Most notably, spinal microglia, purinergic receptors and brain-derived neurotrophic factor (BDNF) signalling are key mediators of chronic neuropathic and inflammatory pain in male, but not female, rodents. In contrast, in female mice chronic pain is dependent on infiltrating T cells of the adaptive immune system. Testosterone appears to be critical in the choice of microglia vs T-cell pathways in male and female rodents, respectively [12]. In addition to sex-specific role of immune cells and signalling pathways in the spinal cord, increasing evidence suggest that such dimorphisms may also occur periphery [13,14] and in the brain [15,16].

Calcitonin Gene-Related Peptide

Calcitonin gene-related peptide (CGRP) has long been implicated in the pathophysiology of migraine, a disorder with a notable sex dimorphism with 2–3-fold more females than males affected. Interestingly application of CGRP to the surface of the brain produces pain hypersensitivity in female, but not male, mice [17], and neuropathic pain is associated with higher CGRP and CGRP receptor expression in the brain of female compared with male rats [18]. Drugs acting at CGRP or its receptor have recently been approved for the treatment of migraine, and analysis of the clinical trial data suggest that these drugs are only effective in women [19].

Prolactin and its receptor. While prolactin is best known for its role in promoting lactation, increasing evidence indicated that prolactin signalling in primary afferents promotes nociceptor sensitization and pain in a female-selective fashion [20]. It has been proposed that the balance of expression of prolactin receptor isoforms may provide protection against pain under physiological conditions, and that disruption of the expression of isoforms may underlie increased risk for pain pathological states specifically for females. Thus, targeting of prolactin and its receptors may provide a novel mechanism to treat pain in women.

Conclusion

Overwhelming evidence supports a multitude of sex-specific biological mechanisms that underlie pain at both a physiological and pathological level. Clinical data is already demonstrating that selective modulation of such mechanisms is more beneficial for one sex over another (e.g. CGRP modulators) and as such uncovering such mechanisms provides opportunities to identify sex-specific treatments for chronic pain.

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