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Gender differences in pain and its relief

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Abstract
There is much evidence to suggest that gender is an important factor in the modulation of pain. Literature data strongly suggest that men and women differ in their responses to pain: they are more variable in women than men, with increased pain sensitivity and many more painful diseases commonly reported among women. Gender differences in pharmacological therapy and non-pharmacological pain interventions have also been reported, but these effects appear to depend on the treatment type and characteristics. It is becoming very evident that gender differences in pain and its relief arise from an interaction of genetic, anatomical, physiological, neuronal, hormonal, psychological and social factors which modulate pain differently in the sexes. Experimental data indicate that both a different modulation of the endogenous opioid system and sex hormones are factors influencing pain sensitivity in males and females. This brief review will examine the literature on sex differences in experimental and clinical pain, focusing on several biological mechanisms implicated in the observed gender-related differences.

Key words
- pain
- sex
- gender

INTRODUCTION

Several reviews on the topic of gender differences in pain mechanisms, control and treatments have been published in the last two decades [1]. The increasing literature refers to a broad range of topics, including preclinical studies on mechanisms underlying male and female differences in nociception and its control, clinical research on gender differences in pain perception and modulation, epidemiological investigations of sex differences in pain prevalence and a growing number of studies examining sex differences in responses to pain therapies [1].

In this brief review, we summarize important findings regarding gender and pain and we will discuss findings regarding sex differences in animal models of pain and in clinical pain prevalence and severity. Moreover, we will review recent research exploring sex differences in responses to pain treatment, followed by a brief discussion of hormonal mechanisms underlying the sex differences in responses to pain and its treatment. We will conclude with a brief commentary on future directions in this interesting field of knowledge.

SEX PREVALENCE AND EPIDEMIOLOGY IN CLINICAL PAIN

Since the pioneering work of Berkley [2], large-scale epidemiological studies have consistently revealed a higher female prevalence of several painful diseases. Women report more severe levels of pain, more frequent pain in more areas of the body and pain of longer duration than men. Such painful conditions particularly involve the head and neck, e.g. migraine, chronic tension-type headache and temporomandibular disorders, but also include fibromyalgia, irritable bowel syndrome and interstitial cystitis [3]. However, while women are more affected by these chronic painful syndromes, the condition is not exclusive to this sex, and there are also conditions more common in men than in women such as cluster headache, a typical male pathology. Moreover, despite these findings the relationship between gender and pain is not simple since other studies have found no sex differences or inconsistent results when examining pain severity in clinical populations [3].

Some of the observed differences can arise from specific recurrent problems occurring over a long period of a woman's life such as gynaecological syndromes, as well as from the greater female longevity, or are related to diseases with a higher male than female prevalence. Furthermore, the prevalence of different kinds of pain in both sexes can change across the lifespan, as occurs for migraine, fibromyalgia, temporomandibular disorders, gastrointestinal, abdominal, joint and back pain. As recently reported, menopause can play an important role in changing pain sensitivity. Interestingly, although the loss of estrogen can lead to a decrease in life-long painful conditions such as headache, menopause can also be accompanied by "new" painful conditions such as osteoporosis and joint inflammation [4]. No sex differences have been reported for some pathological conditions such as cancer [5], although sex differences in the type of cancer and its stage and in the effectiveness of pain treatments in these clinical conditions could

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also influence the presence, magnitude and direction of sex differences in cancer pain [3]. Other confounding factors that can influence sex difference estimates in pain are the reported gender differences in pain symptoms and signs of some syndromes such as appendicitis, migraine, IBS, rheumatoid arthritis and coronary artery diseases [6]. It is recognized that psychological and socio-cultural mechanisms can influence pain perception, expression and tolerance in both sexes, thus confounding gender-related pain analysis. Nevertheless, the overall findings from epidemiological and clinical studies demonstrate that women are at higher risk for many common pain conditions than men. Data on pain intensity are less consistent and influenced by several methodological factors, including mode of patient selection in clinical studies and the sex differences in the effects of pain treatments.

SEX AND EXPERIMENTALLY INDUCED PAIN

Differences in responses to experimental pain in both sexes have been investigated mainly in healthy people using a wide variety of stimuli (mechanical, electrical, thermal, ischemic, chemical). Pain responses have been evaluated by different measures including time and intensity to the first sensation of pain, pain tolerance, and self-report measures of pain intensity. The results varied between studies regardless of the type of stimulus used, indicating that sex differences in nociception depend on multiple factors such as the type of stimulus, testing or end point paradigm, body location, temporal rhythms, reproductive status and age, the presence of disease or illness [6]. In contrast, a recent systematic review concluded that the last ten years of experimental research did not provide clear and consistent results concerning sex differences in human pain sensitivity [7]. However, from the data used for this review and the analysis of the studies, it appears that females feel pain with greater sensitivity than males, although the statistical significance of the sex difference varies across measures, as previously reported [6]. On the other hand, it is interesting to note that despite similar behavioural responses by men and women to a painful stimulus (pain intensity, threshold), some neurophysiological measurements (fNMR, PET) often show a different or opposite response to the same stimulus [8]. These data strongly indicate a different functional involvement of the central nervous system with possibly 'different' plastic changes in those areas probably involved in pain chronicization.

SEX DIFFERENCES AND PAIN TREATMENT

The response to pain therapy (drugs, somatic manipulations, situational adjustment) appears to be sex-related. Several studies based on analgesic and adjuvant drug consumption have documented that women consume and are prescribed more drugs than men, and only a part of this treatment is used to alleviate gynaecological pain [6]. However, lower opioid consumption has also been reported in post-operative women [9], although this result may depend on the type of surgical procedure or arise from increased analgesic side effects in women [10]. A lack of sex-specific effects for μ-mediated opioid analgesia was recently reported, but when the analyses were restricted to patient-controlled analgesia (PCA) or when only PCA morphine studies were considered, robust analgesic effects for women appeared [11]. Similar results were obtained in studies in which analgesic responses were experimentally assessed, suggesting greater morphine analgesia for women. No sex-dependent analgesic effects of mixed opioids such as butorphanol, nalbuphine and pentazocine were found in experimental studies, although in clinical studies it was concluded that women exhibit greater analgesia than men in response to these analgesics [3].

As reported for clinical and experimental studies, sex differences have also been found in investigations of pain treatment. Women received sedatives more often for pain after surgery whereas men were more likely to receive analgesics [12], suggesting that women are at risk for under-treatment of pain. Several studies suggest that the differences in pain treatment between women and men are influenced by both patient and provider characteristics, an effect which may lead to disparities in pain management [13].

In regard to sex differences in non-pharmacological pain interventions, when patients were asked to focus on the sensory components of pain, men reported less pain than woman, whereas when they focused on affective components of pain, women reported more pain than men [14]. In a study examining the effect of acceptance-based coping instructions on cold-pressor pain, women reported a lower pain threshold and tolerance level than men and the acceptance instructions only benefited women [15]. Recently a study investigated whether men and women exhibited different outcomes after an intensive multimodal pain treatment program consisting of individual treatment as well as group therapy [16]. Pre-treatment parameters for pain, disability due to pain, pain duration and pain chronicity stage, as well as age or psychiatric comorbidities, did not differ between genders. The study demonstrated a considerable difference in the benefit for women compared with men, and women consistently improved more in pain-related disabilities in daily life than men. These distinctions did not appear to be due to differences in pain duration, medication, psychiatric comorbidities, pain chronicity stage or application for a disability pension. Therefore, gender differences do not only refer to chronic pain prevalence, pain perception or experimental pain measurement, but also seem to have a clinically relevant impact on the response to pain therapy, even though the results of this kind of study are somewhat variable.

MECHANISMS OF SEX DIFFERENCES IN PAIN

As summarized above, gender differences contribute to individual differences in pain and its relief. However, the specific mechanisms underlying the observed disparity are not yet clear and it has been suggested that an interaction of biological, psychological and socio-cultural factors probably contributes to these differences.

Androgens and estrogens are essential for the development and maintenance of the reproductive system

and many studies suggest that they also play an important role in the observed differences between males and females in the response to pain and pain treatments. Changes in estrogen plasma levels were found to be correlated with recurrent pain in women [17] and postmenopausal women undergoing estrogen replacement therapy showed an increased incidence of temporomandibular (TM) joint pain [18]. However, TM joint pain and fibromyalgia are also related to the menstrual cycle phases, and rapid estrogen changes may also be associated with increased pain [19]. Fibromyalgia symptoms are associated with the luteal phase, when both estrogen and progesterone levels are high [20].

Pain perception varies according to the menstrual cycle phases in women with chronic pain perception, with patients rating pain significantly higher in some phases of the menstrual cycle than in others [21]. In experimental models of pain, estrogens appear to be pronociceptive since male rats injected intracerebroventricularly with estradiol for two days showed higher levels of formalin-induced licking than rats injected with saline [22]. However, estrogens also seem to play an important role in inducing anti-nociception. Simulation of pregnancy in ovariectomized rats, with high plasma levels of estrogens and progesterone, increased the pain threshold [23] and this effect was also present in males [24]. Recently the antinociceptive effect of estrogen was confirmed in a model of neuropathic pain in mice [25]. The authors demonstrated that male and female mice react differently to structural and functional changes induced by sciatic nerve ligature, used as a model of neuropathic pain. Male mice showed a gradual decrease of allodynia and a complete recovery while in females the allodynia and gliosis were still present four months after neuropathy induction. Administration of 17β-estradiol was able to significantly attenuate this difference, reducing the allodynia and inducing a complete recovery also in female mice. Furthermore, 17β-estradiol-treated mice showed a functional improvement of the injured limb, a faster regenerative process of the peripheral nerves and decreased neuropathy-induced gliosis [25]. With regard to the effect of androgens on pain, an inverse relationship was found between plasma testosterone and work-related neck and shoulder disorders in female workers [26]. Other evidence for an analgesic effect of androgens is the clinical finding that the levels of gonadal and adrenal androgens such as testosterone and DHT are lower in both female and male rheumatoid arthritis patients than in controls. Interestingly, androgen administration induces a significant improvement of clinical symptoms, probably through inhibition of the immune system [27, 28]. In male rats, when supraphysiological levels of testosterone were administered to both male and female rats, the licking duration, which was longer in female than male controls, decreased only in females whereas no decrease in flexing or jerking behaviour was observed [29]. These results indicate that a high level of testosterone did not affect the nociceptive input, since jerking and flexing were unchanged, but did induce a 'male-like' response in females with regard to licking, the most complex supraspinal formalin-induced response. This suggests that the already lower licking levels in males are kept low by testosterone and that females are sensitive to changes in testosterone plasma levels. Interestingly, these experimental data were recently confirmed in women [30].

The combined oral contraceptive pill (COCP) has been implicated in the development of a number of chronic pain conditions. Modern COCP formulations produce a low endogenous estradiol, low progesterone environment similar to the early follicular phase of the natural menstrual cycle, with a variable effect on serum androgen levels. Vincent and co-authors used behavioural measures and functional magnetic resonance imaging to investigate the response to experimental thermal stimuli in healthy women, in both a natural and COCP-induced low endogenous estradiol state, to investigate whether alterations in central pain processing underlie these observations in COCP users. Although COCP users generally did not require lower temperatures to obtain a fixed pain intensity, alterations in the brain response to these stimuli were observed. However, lower temperatures were required in a subgroup of COCP users with significantly reduced serum testosterone. Region-of-interest analysis revealed that, in key regions of the descending pain inhibitory system, activity in response to noxious stimulation varied with serum testosterone levels in both groups of women. Of particular interest, in COCP users, activity in the rostral ventromedial medulla increased with increasing testosterone whereas it was significantly reduced compared to controls in those women with low testosterone. These findings suggest that, in a low endogenous estradiol state, testosterone may be a key factor in modulating pain sensitivity via descending pathways. Specifically, failure to engage descending inhibition at the level of the rostral ventromedial medulla may be responsible for the reduction in temperature required by COCP users with low circulating testosterone.

Other experiments aimed at evaluating the long-term effect of a painful stimulus in rats confirmed that male gonadal hormones have an inhibitory, adaptive effect on the behavioural and neuronal responses to repeated nociceptive stimulation [31]. These data are not surprising considering the distribution of sex hormones and their receptors in areas of the peripheral and central nervous systems associated with nociceptive transmission [32, 33]. Furthermore, sex hormones appear to modulate cortical processing of pain-related stimuli [34-36]. A regional increase in baseline μ-opioid receptor availability and greater activation of endogenous opioid neurotransmission during pain in women in the high-estrogen state was also reported. During the low estrogen condition, however, significant reductions in endogenous opioid tone were observed at the level of the thalamus, nucleus accumbens and amygdala, which were associated with hyperalgesic responses [37]. The important effect on gonadal hormones by pain killers should be underlined. Data are clear concerning the hypogonadism induced by opioids and other commonly used analgesics [38]. Thus the endocrinopathies occurring in these patients can strongly affect their quality of life and the possibility to completely recover from

the original pathology. These findings suggest that the interaction of the opioidergic system with gonadal hormones plays a role in the observed sex-based differences in pain sensitivity.

Several studies have indicated that genotype may contribute to sex differences in pain. Since the early experimental data of Liebeskind and collaborators on mice strain differences in swimming-induced analgesia, preclinical research has shown that genotype influences nociception, and these findings have been extended to humans in recent years [39]. For example, hereditary sensory and autonomic neuropathies (HSANs) are monogenic pain disorders in which pain sensibility is substantially absent. Rare inherited disorders may provide models to explain genetic variability in more common pain states and these syndromes appear to be linked to genes encoding proteins of different functional classes, e.g. ion channels, enzymes, transcription factors and trophic factors. From genetic association studies, a wide variety of genes have now been associated with both experimental and clinical pain states, and success in this field will lead both to a better understanding of basic pain mechanisms and to the development of new therapies.

Many studies have suggested that interactions between the immune system and the nervous system modulate nociception via the crucial role of microglia. Recently, Sorge and collaborators [40] explored whether nociception can be processed in female mice through a pathway that is independent of microglia. The authors induced mechanical allodynia in mice of both sexes and found that intrathecal injection of glial inhibitors reversed allodynia in males but not in females. The transient depletion of microglia blocked allodynia in the male mice but not in the females. Furthermore, allodynia was reversed in male but not in female mice by blocking signalling mediators linked to microglia-neuron nociception pathways such as P2X4 receptor, p38 MAP kinase or brain-derived neurotrophic factor. From these data the authors suggested that microglia are essential for mechanical nociception in male mice, whereas other mechanisms are probably used in females. To test whether adaptive immune cells are involved, the authors studied allodynia in nude or recombination-activating gene 1-knockout (Rag1-/-) mice, which lack T cells and B cells. The administration of glial inhibitors reversed allodynia in both male and female nude or Rag1-/- mice. In contrast, in female Rag1-/- mice receiving an adoptive transfer of splenocytes, allodynia could not be blocked by glial inhibitors, suggesting that female mice process nociception via lymphocyte-dependent mechanisms but can use microglia-dependent pathways when lymphocytes are absent. Sex hormones also regulate the expression of peroxisome proliferator-activated receptors (PPARs), which in turn can modify the expression of cytokines associated with nociception. Examining the sexually dimorphic expression of PPARs, the authors found that a PPARα agonist reversed allodynia in males, but not in females or castrated males, whereas a PPARγ agonist reversed allodynia in females but not in males or testosterone-treated females. These findings appear to be important for future research on pain since they indicate the need for sex-separated experimental studies and further suggest that different clinical strategies could be adopted to optimize pain management in men and women.

CONCLUSIONS

Differences between men and women in pain prevalence, the seeking of medical treatment of pain syndromes, pain behaviour and responses to analgesic drugs have long been reported. The role of social, cultural and biological factors in the sex difference in pain perception has been discussed. During the last two decades, a large amount of data has been collected on differences between the sexes in responses to pain, including pain thresholds, tolerance and response to pain treatments. Sex differences in nociception have been well documented in the literature. It has been shown that women perceive more pain than men and this has been demonstrated for clinical pain and for experimental pain in humans and animals. Sex differences in pain perception are frequently substantial, with moderate to large effect sizes. Multiple factors are considered responsible for sex differences in pain perception and for the great prevalence of chronic pain conditions in women. Biological factors such as sex hormones are thought to be one of the main mechanisms explaining sex differences in pain perception. Further research to elucidate the mechanisms underlying sex differences in pain responses is needed to reduce these disparities in pain.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias the conduct and findings of this study.

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