Sex, Gender, and Pain: Women and Men Really Are Different

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Sex-related differences in the experience of both clinical and experimentally induced pain have been widely reported. Specifically, females are at greater risk for developing several chronic pain disorders, and women exhibit greater sensitivity to noxious stimuli in the laboratory compared with men. Several mechanisms have been proposed to account for these sex differences. Psychosocial factors such as sex role beliefs, pain coping strategies, mood, and pain-related expectancies may underlie these effects. In addition, there is evidence that familial factors can alter pain responses, and these intergenerational influences may differ as a function of sex. Sex hormones are also known to affect pain responses, which may mediate the sex differences. Although the magnitude of these effects has not been well characterized, there are potentially important practical implications of sex differences in pain responses. These implications are discussed, and directions for future research are delineated.

Pain is a complex multidimensional experience influenced by a variety of biologic and psychosocial variables. One set of organismic factors that has received increased attention in recent years is the role of sex and gender on pain responses. In general, the term sex refers to the biologic status of an individual as being female versus male, whereas gender refers to the sex-related social role(s) with which an individual identifies. Several lines of evidence, including epidemiologic studies, laboratory pain research in both humans and nonhuman animals, and investigations of various clinical pain populations, indicate sex-related influences on the experience of pain.

This article reviews the recent literature regarding sex, gender, and pain. First, the epidemiologic and clinical evidence for sex differences are presented. Then, the findings from studies of responses to experimental pain in humans is reviewed. Next, possible mechanisms contributing to sex-related influences of responses to pain is discussed. Finally, practical implications of these findings and directions for future research are considered.

Sex, Gender, and Clinical Pain

As summarized in several recent reviews [1•,2,3], women are overrepresented in several chronic pain conditions. For example, migraine and tension-type headaches, temporomandibular disorders, fibromyalgia, and irritable bowel syndrome are all more prevalent in women, with female to male ratios ranging from 2:1 to 9:1 [4–8]. Moreover, epidemiologic and survey research has typically demonstrated greater frequencies of pain-related symptoms among females than males in the general population [9–14]. Because these epidemiologic data are based on population-derived samples, the sex differences in pain prevalence cannot be attributed to the greater tendency among females to seek treatment [15,16]. Thus, females appear to be at increased risk for experiencing pain-related symptoms.

In addition to differences in the frequency of pain, several studies in clinical settings suggest that women and men may differ in their adjustment to pain. In one study of a heterogeneous chronic pain population, no sex differences were observed on total depression scores; however, certain depressive symptoms were more common among females, including body image distortion and fatigue [17]. These investigators have also reported that age and gender interact to influence depression in patients with chronic pain, with greater depressive symptoms among younger women and older men [18]. Haley *et al.* [19] reported that depression was associated with pain severity among female patients with chronic pain, whereas depression was related to activity impairment among male patients. Weir *et al.* [20] found no overall sex differences in psychosocial adjustment to chronic pain in a heterogeneous sample; however, the predictors of adjustment varied for women and men. Specifically, women's adjustment was accounted for primarily by cognitive variables, such as the meaning they attributed to their pain, whereas for males social support was the strongest predictor of adjustment. In addition, psychosocial adjustment was related to health expenditures for women but not men. More recently, a self-reported history of traumatic events was associated with poorer affective adjustment among male patients with chronic musculoskeletal pain, but trauma history was not related to adjustment among female patients [21]. We have reported that high levels of anxiety are associated with increased pain severity and greater pain-related disability among men but not women in a sample of patients with primarily musculoskeletal pain [22]. These findings suggest that the predictors of adjustment to chronic

pain may be sex-dependent; however, the nature of these effects remains unclear.

Sex, Gender, and Experimental Pain

Considerable research has examined the question of whether females and males differ in their responses to experimentally induced pain, and these studies recently have been reviewed by us [23,24•] and others [1•]. Overall, the data indicate increased sensitivity to several forms of laboratory pain among females relative to males; however, there is substantial variability in the magnitude of the effects. Riley *et al.* [24•] performed a meta-analysis of this literature and found moderate to large sex differences in pain threshold and tolerance across several types of noxious stimuli. Notably, the least consistent effects emerged for thermal (heat) pain, which may be the most frequently used experimental pain stimulus. In a subsequent study, we reported that females demonstrated enhanced temporal summation of thermal stimuli, although no sex differences emerged for discrimination of noxious heat [25], and the significance of sex differences in heat pain threshold was influenced by the assessment method and the rate of increase in temperature [26]. Thus, the stimulation parameters and assessment method likely contribute to the lack of consistency observed across studies of sex differences in thermal pain perception.

Mechanisms Underlying Sex Differences in Pain

Several mechanisms have been proposed to explain sex differences in the experience of both clinical and experimental pain, and these mechanisms are often broadly characterized as psychosocial versus biologic. It is important to recognize the artificiality of this distinction, because this classification is based more on the level of analysis than on the actual mechanism of action. For example, one commonly cited "psychosocial" mechanism explicating sex differences in pain perception is that the feminine sex role permits acknowledgement of pain whereas the masculine sex role discourages expression of pain. However, at a more biologic level of analysis, one might conclude that the environmental and biologic factors that produce the perceptual and behavioral responses associated with feminine sex roles also influence nociceptive processing. Such factors could include expectancies, conditioning, ovarian hormones, and endogenous pain regulatory systems, all of which are known to alter the neurophysiology of pain. Thus, when conceptualizing these putative mechanisms underlying female-male differences in pain responses, it is important to remember that psychosocial and biologic explanations may refer to the same underlying processes described at different levels of analysis.

Sex role expectancies

As alluded to above, one potential explanation for sex differences in pain is based on the notion that feminine sex roles encourage expressions of pain whereas masculine sex roles discourage pain behavior. Despite its common sense appeal, evidence supporting this proposition is scant, and this issue has primarily been examined in the context of experimental rather than clinical pain. Otto and Dougher [27] reported that for males, high masculinity scores were associated with higher pain thresholds, whereas neither masculinity nor femininity was associated with pain threshold for females. However, even after accounting for masculinity-femininity scores, the sex difference in pain threshold remained significant, but after accounting for the sex of the subject, sex role scores were not related to pain measures. In another study designed to manipulate sex role expectancies, male and female subjects rated cold pressor pain for either a female or a male experimenter, both of whom were selected to be attractive and who dressed to accentuate feminine and masculine stereotypes, respectively [28]. Males reported significantly less pain in the presence of a female experimenter, whereas females' ratings did not differ as a function of experimenter gender. In contrast, other studies have not found significant effects of experimenter gender [27,29]. Thus, empiric support for a mediating influence of sex role expectancies is not strong.

Cognitive-affective factors

It is also plausible that cognitive-affective factors, including emotional distress, pain coping strategies, and pain-related expectancies may contribute to sex differences in pain. These psychologic variables have been related to both clinical and experimental pain, and there may be important sex differences in how these factors influence pain [30–34]. For example, psychologic symptoms such as depression and anxiety are more prevalent among females than males and are associated with increased pain and other physical symptoms [12,35,36]. In addition, affective distress has been related to greater experimental pain sensitivity [37–40]; therefore, the greater emotional distress among females may contribute to both increased clinical pain and enhanced experimental pain responses. However, we have reported that anxiety is associated with poorer adjustment to chronic pain [22] as well as increased experimental pain sensitivity [41] among males but not females, suggesting that anxiety produces greater effects on pain responses in men than in women.

In addition to these affective variables, cognitive factors such as coping and self-efficacy may be important determinants of sex-related differences in pain. Regarding coping strategies, catastrophizing has been associated with poorer adjustment to clinical pain [42–44] as well as decreased tolerance of laboratory pain [30]. Notably, we [45] and others [46] have reported higher levels of catastrophizing among females relative to males, which may contribute to their increased risk for experiencing pain. In addition, measures of self-efficacy or perceived ability to control or decrease pain have been associated with better adjustment to chronic pain [31,47], reduced pain from medical procedures

[43], and reduced sensitivity to experimental pain [48]. We previously found that greater perceived ability to tolerate, control, and decrease pain was related to decreased pain sensitivity among females but not males [41]. It is important to note that the pain-reducing capacity of cognitive variables such as pain-related expectancies, self-efficacy, and coping strategies can be reversed by the opioid antagonist naloxone [49–51]; therefore, sex-related influences of these variables may represent evidence that endogenous opioid activation differs for women versus men.

Familial factors

Familial aggregation of pain has been reported for many pain-related conditions, including fibromyalgia [52–54] and headache [55–60] and among a heterogeneous sample of patients with chronic pain [61]. Several studies have also reported that a self-reported family history of pain is associated with increased pain complaints in community-based samples [11,14,62,63]. Interestingly, some evidence suggests that the influence of family history on pain may be sex-related. For instance, Edwards *et al.* [62] reported that the relationship between family history and pain complaints was stronger for females than males. Also, Neumann and Buskila [64] found that both female and male relatives of fibromyalgia patients were characterized by higher tender point counts than controls; however, only female relatives exhibited lower pressure pain thresholds, and female relatives of fibromyalgia patients had poorer health status than male relatives of fibromyalgia patients and controls. More recently, we reported that a self-reported familial pain history was associated with increased clinical pain and greater experimental pain sensitivity for females but not males [65]. However, other authors have reported that a family history of pain was associated with increased pain complaints equally in females and males [11,63].

If indeed familial factors are associated with pain responses in a sex-dependent manner, there are several potential mechanisms whereby this could occur. One possibility is that social learning contributes to the increased pain reported by individuals with a family history of pain. Indeed, exposure to pain models has been demonstrated to alter pain responses [66–68]. Such social influences could be more pronounced for females than males, because females are more responsive to nonverbal communication signals than males [69–74]. In a recent study, females reported a significantly greater number of familial pain models than males, suggesting that females are more aware of pain in others [63]. Thus, females' greater awareness of nonverbal cues may render them more susceptible to the social learning influences created by exposure to family members with pain.

Another explanation for intergenerational effects on pain involves genetic factors. Several chronic pain disorders involve genetic influences, including migraine headache [75–78], rheumatoid arthritis [79,80], and fibromyalgia [75,81]. Interestingly, these disorders are more prevalent among females, raising the possibility that their genetic contributions may be sex-linked. Mogil [82] has generated considerable animal research indicating that genetic factors affect experimental pain sensitivity, and some of the genetic influences on pain and analgesia are sex-related. In humans, a recent study of pressure pain thresholds in monozygotic and dizygotic twins revealed strong correlations between pain thresholds within twin pairs; however, monozygotic twins showed only slightly higher correlations than dizygotic twins, suggesting stronger environmental than genetic contributions [83]. As a whole, these lines of evidence indicate that familial factors may exert sex-specific effects on both clinical and experimental pain responses, due to some combination of social learning and genetic influences.

Hormonal factors

One obvious difference among females and males is their exposure to gonadal hormones throughout the life cycle. Especially during the period between menarche and menopause, females are exposed to cyclic variations in estrogen and progesterone, and these ovarian hormones are present in much higher concentrations among females than males. Sex steroids are known to influence multiple peripheral and central nervous system pathways involved in nociceptive processing [84], and nonhuman animal research indicates that basal nociception as well as analgesic responses vary across the estrous cycle [1•]. In addition, pain-related symptoms among women can be influenced by the menstrual cycle phase [85–89]. Moreover, some predominantly female pain disorders, such as migraine headache and temporomandibular disorders, show their peak prevalence during the reproductive years [2,90], and the use of exogenous hormones has been associated with increased risk for temporomandibular disorders [91•]. Thus, ovarian hormones appear to play an important role in some clinical pain conditions. Experimental pain responses have also been found to vary across the menstrual cycle in healthy females, with most studies demonstrating greatest sensitivity to painful stimuli during the luteal (*ie,* premenstrual) phase of the cycle [92]. Taken together, these findings suggest that gonadal hormones can substantially affect nociceptive responses, and this may contribute to sex differences in the experience of pain.

Endogenous pain inhibition

The perception of pain is modulated by multiple endogenous systems, and there is evidence that these systems may operate differently for females and males. One form of endogenous pain modulation is stress-induced analgesia (SIA), and multiple nonhuman animal studies indicate greater SIA among males relative to females [1•,84]. Notably, even when SIA was quantitatively equivalent in female and male animals, there were qualitative differences. Specifically, Mogil *et al.* [93] demonstrated that male

and female mice had equal degrees of swim SIA, but this analgesia was reversed by either opioid or *N*-methyl-D-aspartate receptor blockade in males but not in females.

Similar results have been reported by Kavaliers and Choleris [94]. Direct evidence of sex differences in endogenous pain inhibition among humans is lacking. For example, diffuse noxious inhibitory controls, the inhibition of one source of pain by the application of pain at a remote site, was found to be similar for females and males [95]. However, we previously reported that higher resting blood pressure was associated with lower pain sensitivity in males but not females, and sex differences in pain responses were attenuated after accounting for resting blood pressure [96], suggesting that the pain inhibitory effects of elevated blood pressure may be stronger for males. These animal data suggest both quantitative and qualitative sex-related differences in endogenous analgesia; however, few human studies addressing these issues have been conducted.

Practical Implications

It is important to remember that sex and gender represent only one set of biopsychosocial factors that can affect the experience of pain, and the importance of sex-related influences on pain, relative to other factors (*eg,* disease activity, age, race, coping skills, and so forth), remains unknown. However, enhanced knowledge regarding sex differences in pain responses could be of practical significance in at least three ways.

First, investigating sex differences may improve our understanding of the etiopathogenesis of certain forms of clinical pain. For example, menstrual-cycle–related changes in the symptomatology of female-predominant pain conditions suggest the involvement of gonadal hormones on disease specific or nonspecific pathophysiologic processes. Second, it is conceivable that pain treatment would be tailored based on sex differences. For instance, recent research has indicated sex differences in responses to opioid analgesics [97], and it appears to be the case that certain classes of opioid analgesics provide more effective pain relief for females than males. In addition, if psychosocial variables (*eg,* coping, mood) influence pain responses differentially for women versus men, then the efficacy of cognitive-behavioral treatments for pain may also vary as a function of sex. Third, understanding sex differences may lead to new treatments for pain, especially in the area of hormonal manipulations. Indeed, antiestrogenic agents such as tamoxifen appear to be effective in the treatment of cyclical mastalgia in women [98,99] and gynecomastia in men [100].

It seems plausible that such therapies would be effective in the treatment of other chronic pain conditions that are hormonally influenced (*eg, rheumatoid arthritis,* temporomandibular disorders, fibromyalgia). Moreover, these treatments could potentiate the effects of other analgesic agents, which would provide an enhanced clinical effect. The influence of sex steroid treatments on symptoms of chronic pain remains an important yet unexplored area of research. Clearly, additional research is needed to facilitate the clinical application of findings regarding sex-related differences in the experience of pain.

Conclusions

A considerable amount of evidence from both laboratory research and clinical investigation demonstrates the existence of sex differences in the experience of pain. Thus, the obvious answer to the question, "Are women and men different?" is "yes." However, the more interesting and important questions have yet to be resolved. For example, what are the mechanisms underlying sex differences in responses to pain? Several likely candidates have been reviewed in this article (*eg,* cognitive-affective factors, sex roles, familial factors, hormonal factors), but their relative contributions remain unknown. In addition, sex differences may be qualitative rather than quantitative, as previous animal studies have demonstrated equipotent endogenous and exogenous analgesic responses in female and male mice, but the neurochemistry underlying the analgesic was different for the two sexes [93,94]. A better understanding of the sex-related neural mechanisms supporting nociceptive and analgesic responses will lead to more effective treatment of pain in both women and men.

Another important question is, "What is the relationship between the greater clinical pain and enhanced experimental pain sensitivity observed among women?" These two findings may be coincidental; however, it is possible that females' greater responsitivity to experimental pain is a risk factor for the development of certain clinical pain conditions. Additional research exploring the predictive validity of laboratory pain responses is warranted. Another important question is, "What are the adaptive benefits of greater pain sensitivity among women?" There appears to be an assumption that greater sensitivity to pain is undesirable, which is undoubtedly true under certain pathologic conditions. However, enhanced somatosensory awareness may allow females to seek treatment earlier and avoid more severe tissue damage. In addition, recent research suggests that disclosing negative emotions has beneficial health effects [101], and it may be that disclosing pain and other physical symptoms has similar benefits. Thus, many important questions remain regarding sex, gender, and pain, and this promises to be a fruitful and clinically relevant area of investigation for the future.

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