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Drs Dao and LeResche have provided a scholarly review that presents the various biologic and psychosocial factors that contribute to the effect of gender or sex on pain perception and pain conditions.[1] The underlying hypothesis advanced by the authors is that the prevalence of chronic orofacial pain is greater in women than men due to sex differences in pain mechanisms and due to yet-to-be identified factors unique to the craniofacial system. The weight of evidence supporting this view comes from the epidemiologic and experimental studies reviewed by the authors. As noted by the authors, several—but surely not all—persistent or chronic pain conditions show a higher prevalence in females than in males. However, females appear to be over-represented in the clinical populations that suffer from a variety of painful head and neck disorders, as well as painful conditions associated with deep visceral disorders (eg, irritable bowel syndrome) and certain musculoskeletal disorders (eg, fibromyalgia). Similarly, the authors note that the weight of experimental studies show that females are slightly more sensitive to a variety of noxious stimuli applied under controlled laboratory conditions.

Do the Subtle Sex-Dependent Differences in Pain Perception Contribute to the Higher Prevalence of Facial Pain in Women?

An interesting and yet unresolved question relates to whether one's sensitivity to experimentally administered noxious stimuli is predictive of one's risk for developing a variety of chronic sensory disorders. As noted by the authors, while most experimental studies have reported that females are more sensitive to noxious stimuli compared to males, the differences are modest on a population basis.[1] Hormonal changes associated with the menstrual cycle also produce subtle but measurable changes in ischemic pain perception.[2] The subtle nature of these changes may lead one to question whether these differences have any real meaning from a pathophysiologic perspective and brings into question whether one's sensitivity to experimentally applied noxious stimuli is an adequate probe of the processes or mechanisms that lead to clinically relevant persistent pain conditions. In my view, the small group of females who show substantially enhanced pain sensitivity to noxious stimuli represents an important "signal" buried in the large amount of "noise" present in the rest of the population. Group findings can be misleading and may blur or obscure the identification of significant biopsychosocial factors that contribute to the pathophysiology of a variety of persistent pain conditions seen in a small percentage of the female population. For example, if only about 2% to 5% of females in the United States have biopsychosocial profiles that impact upon the peripheral and/or central pain processing of sensory stimuli, this could result in a cluster of clinically significant chronic sensory disorders in several million women.

A more fundamental aspect of this question is whether the assessment of pain perception in a highly controlled laboratory environment has any relationship to clinical pain report, dysfunction, and suffering—which are features of many chronic sensory disorders. This question has not been adequately addressed, but it is clear that musculoskeletal conditions such as temporomandibular disorders (TMD) and fibromyalgia are associated with a generalized enhancement in pain sensitivity.[3,4] The most pain-sensitive TMD patients also report more clinical pain for a longer duration than those who are less sensitive to experimentally applied noxious stimuli.[5] To

address this important question more fully, prospective studies are required to address whether pain sensitivity is a significant predictor of persistent pain conditions.

The authors have also noted that it is not clear whether the reported sex differences in pain perception result from ". . . a response bias phenomenon shaped by various psychologic, social, and cultural factors or biologic differences in pain-processing mechanisms." Recent studies by Maixner et al[4] and Fillingim et al[6] have partially addressed this issue. Both male and female subjects, as well as TMD and non-TMD patients, demonstrate comparable capacities to discriminate small increments of noxious stimuli. In contrast, female subjects and TMD patients show a greater ability to temporally summate nociceptive stimuli when compared to males or control non-TMD patients. These findings suggest that there are sex-dependent differences in pain processing and that this difference is quite prominent in females with TMD. In my view, it is currently somewhat artificial and overly reductionistic to conceptualize or to cast sex-dependent differences in pain report in the context of a mind/body dualism (ie, response bias influenced by psychosocial and cultural variables versus biologic response). Both body and mind have an underlying neurobiology that affects the peripheral and central processing of nociceptive stimuli. The capacity of the nervous system to process and interpret sensory events is shaped by a variety of interactive biologic, environmental, and psychosocial events that influence the development of and phasic changes in the nervous system's structure and function. As a consequence, there is individual variability in the perceptual, emotional, and physiologic responses to pain-evoking stimuli.

Are There Sex-Dependent Differences in Pain Transmission and Pain Modulation?

The biologic factors that contribute to sex-based differences in pain perception remain unknown, but the authors suggest that a variety of biologic factors, such as gonadal hormones, nitric oxide, substances derived from the sympathetic nervous system, estrogen-evoked increases in nerve growth factor production, and sex differences in opioid and non-opioid pain regulatory systems, likely contribute to these differences.

As noted by the authors,[1] evidence is beginning to emerge that sex-dependent differences in pain regulatory systems in the central nervous system (CNS) may partially explain sex-dependent changes in the perceptual, emotional, and physiologic responses to noxious stimuli.[7] One pain regulator that appears to differ between men and women is related to resting arterial blood pressure.[8] Several studies have established that arterial blood pressure is inversely related to pain sensitivity in both rodents and humans.[9,10] In general, higher levels of resting arterial blood pressure are associated with decreased behavioral and perceptual responses to a variety of noxious stimuli. The association between resting blood pressure and pain sensitivity has been consistently observed in men but is much more difficult to demonstrate in females. The mechanism by which resting arterial blood pressure alters pain perception has not been fully examined. One possible mechanism, which has received experimental support, is through the activation of carotid sinus baroreceptors, which in turn engage central nervous system pain regulatory networks. Several studies have shown that the activation of carotid sinus baroreceptors diminishes nociceptive reflexes in rats and diminishes pain perception in humans.[9,11] We have proposed that painful TMD, which are associated with myalgia, result from an alteration in baroreceptor effects on CNS inhibitory processes.[5] We have also recently obtained additional evidence of a disruption in the association between arterial blood pressure and pain perception in TMD patients.[12]

Central opioid mechanisms that regulate pain perception also appear to differ between males and females.[7] In rats, females are less sensitive to morphine and evoke a smaller stress-evoked analgesia than male rats. Phasic and developmental effects of gonadal hormones also impact both stress analgesia and morphine analgesia in rodents. Recent clinical studies also show that males and females differ in their sensitivities to different opioid-receptor agonists.[13]

More and more evidence is accumulating that central pain regulatory systems differ between men and women, and although speculative, it appears likely that the traditionally examined opioid and non-opioid regulatory systems are less active or functional in females and may be disrupted in a variety of sensory disorders that have a strong female representation.[7] It is very likely that both phasic and developmental effects of reproductive hormones influence the functional integrity of both opioid and non-opioid regulatory systems and that dysregulation of the hypothalamic-gonadal axis is likely to contribute to the development of a variety of female-biased chronic sensory disorders.

Why Are There Sex-Dependent Differences in Pain Perception?

A fundamental question that has not been adequately examined or addressed in this field of investigation is: Why are there sex-dependent differences in pain perception and associated pain regulatory systems? In a recent review,[7] we suggested that sex-dependent differences in pain perception and pain regulatory systems result from strong evolutionary pressures that act to increase the reproductive potential of a species. Several humoral factors associated with the hypothalamic-pituitary-adrenal axis impair almost all levels of the reproductive axis. β-endorphin inhibits the release of luteinizing hormone. Glucocorticoids impair luteinizing hormone release, gonadal function, and tissue responses to gonadal hormone actions. Catecholamines such as norepinephrine and epinephrine can excite the pituitary-adrenal axis and impair reproductive potential. It thus seems likely that men and women have evolved different pain regulatory systems that explain, at least partially, the sex-dependent differences in opioid and non-opioid associated pain regulatory systems. The contribution of these putative and fundamental differences in pain regulatory systems to the pathophysiology of female-biased chronic sensory disorders remains an important and little explored question.

Why Is There a Higher Prevalence of Orofacial Pain in Females Than in Males?

Although several female-biased disorders are associated with a variety of complaints that arise from a variety of anatomic structures, it is not clear why orofacial pain is such a prominent feature of these disorders. As previously noted,[5] it seems plausible that the predominance of head and neck pain observed in female-biased patient populations with impaired pain regulatory systems may be explained partially by the relatively high density of head and neck sensory input to the somatosensory system compared to other body structures. The orofacial region is richly innervated, almost constantly in use, and prominently represented in somatosensory regions of the CNS. Thus, an impairment in CNS inhibitory systems may be more likely to contribute to a pain complaint associated with the head and neck than to other body regions by enhancing the processing of sensory information from richly innervated peripheral sources (eg, muscles and joints). Impairments in CNS inhibitory systems may also contribute to the pain observed in patents with TMD and other related musculoskeletal disorders by permitting the expression of central neural generators within CNS sensory structures that have a prominent orofacial representation. This could produce painful sensations without requiring input from peripheral orofacial sources.

Summary

The authors have provided a provocative review and discussion of several of the biopsychosocial factors that are likely to contribute to sex-dependent differences in pain perception. They raise a number of important questions and point the way to new research topics that require investigation if we are to understand more fully how gender or sex influences pain perception and the pathophysiology of persistent pain conditions.

Acknowledgments

Supported by NIH grants DE07509 and DE13079-01.

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AUTHORS' RESPONSE TO CRITICAL COMMENTARIES

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Linda LeResche, ScD

We thank Drs Eli,[1] Giamberardino,[2] and Maixner[3] for their insightful comments and the valuable information and perspectives they add to our focus article from their own areas of expertise. We are also pleased to see that there are many areas of agreement between their viewpoints and our own in this highly controversial and complex area of research, and that our differences appear to be more a matter of emphasis than of outright disagreement. One area of differing emphasis relates to the importance of experimental research in understanding clinical pain. As Maixner points out, the question of whether "assessment of pain perception in a highly controlled laboratory environment has any relationship to clinical pain report, dysfunction, and suffering" is a fundamental one. We agree with Giamberardino that "experimental studies designed specifically to address the issue of gender differences in algogenic perception are an indispensable step toward a better understanding of the diversities observed in clinical reality." However, we also agree with Eli that the interpretation of experimental pain studies of gender differences is confounded by gender differences in anxiety, social role expectations, attentional processes, and control, which can all affect pain response, and that "complexity increases enormously with regard to clinical pain."

To support the relationship between clinical and experimentally induced pain and the link between gender differences in clinical prevalence and psychophysical data, Maixner cites evidence that some musculoskeletal conditions such as temporomandibular disorders (TMD) and fibromyalgia are associated with enhancement in sensitivity to laboratory pain stimuli. Key to interpreting these findings is understanding whether the enhancement in pain sensitivity in patients is the cause or the consequence of the disorders, since sensitization of the peripheral and central nervous systems can be induced by chronic pain. As pointed out by Maixner, prospective studies (which should be population-based, or at least based on larger samples, as noted by Giamberardino) are required to address whether pain sensitivity can predict susceptibility to the development of persistent pain conditions. It is certainly not unreasonable to be cautious given the fundamental differences between acute/experimental and chronic pain. However, we wish to emphasize that exercising caution in extrapolating experimental data to the clinic is not synonymous with negating the importance of these data.

One of the most intriguing aspects of Maixner's commentary is his suggestion that gender differences in clinical pain conditions (and the minor gender differences generally observed in the laboratory) may be attributable to a relatively small group of women who show substantially enhanced pain sensitivity, rather than to global differences between the sexes. This hypothesis is certainly worthy of investigation through experimental, clinical, and epidemiologic study, as are other