

Introduction

Sex Makes a Difference: Experimental and Clinical Pain Responses

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In exploration, large discoveries precede smaller ones. In the case of geographic exploration, large landmasses were found and then, eventually, bays, rivers, and creeks were identified and mapped. Much the same process occurred in the case of scientific exploration. With the passage of time, broad principles were refined and exceptions led the way to new rules. It was necessary, to discern the finer details, to step away from models that aggregated data over large populations and, instead, deliberately analyze differences among groups, clusters, or subsets.

Medical researchers were slow to develop an interest in interindividual factors. Variables such as the patient's sex, age, or ethnic background were often regarded as largely irrelevant or nuisance factors. Only recently, for example, has the National Institutes of Health mandated including members of both sexes in human biomedical and behavioral research projects.

Although many pain investigators embraced the biopsychosocial model, it still took years for them to carefully consider the role of biological sex or gender identity in influencing the prevalence of pain conditions, the response to treatment, or the mechanisms used to cope with challenging pain syndromes. Only lately have scholars identified the imbalance in the numbers of males and females diagnosed with many acute and chronic pain states,^{1–3} established a special interest group of the International Association for the Study of Pain to

focus on sex-related factors in the experience of pain, or edited a reference volume on Sex, Gender, and Pain.⁴

Typically, the preponderance of patients for many pain disorders is female. This, of course, is in addition to gynecological problems and includes such conditions as headache, rheumatoid arthritis, fibromyalgia, irritable bowel disorder, and temporomandibular disorder. Epidemiological inquiry is a necessary first step, but the data on prevalence need to be supplemented by research on biological, psychological, and sociocultural factors with an eye to understanding the underlying mechanisms, reducing the incidence of the problems, and improving the treatment of acute and chronic pain.

The basic studies and review articles in this special collection provide the reader with an excellent overview of the state of the field. Three of the papers examine biological factors, emphasizing sex differences in the effects of opioid analgesics, the role of gonadal hormones, and the response of mechanisms that react to stress. The other three articles focus on psychological and sociocultural factors, paying particular attention to sex differences in anxiety, spousal relationships, gender roles, coping mechanisms, and negative affect.

Craft provides a detailed examination of the literature on sex differences in opioid analgesia. The findings suggest that agonists that act preferentially at mu receptors (and, generally, at kappa receptors) are more potent or effective in male rodents than in female ones, but, intriguingly, have the reverse effect in humans. These data are highly provocative, but Craft cautions that the studies have come from few laboratories and that procedural factors (efficacy of the opioid tested, nature of the noxious stimulus, pain test employed, intensity of the stressor,

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and corrections for baseline sensitivity) can play a crucial role in determining the outcome of laboratory studies on nociception. The possible mechanisms underlying these sex differences may deal with the pharmacokinetics of the drugs (rate and amount of distribution to receptor sites or formation of metabolites) or their pharmacodynamics (sex differences in receptor density, affinity to opioids, or neural response to receptor signaling). Female rats, for example, seem to have fewer mu receptors or less efficient mu opioid mediated signal transduction than males. Craft reports the provocative finding, from a PET study,⁵ that reproductive-age women have greater mu opioid receptor binding potential than men in numerous cortical and subcortical areas, possibly underlying their greater response to such opioids. If this biological enhancement is confirmed, and if it is diminished by a depletion of sex hormones at menopause, it could help explain the increased risk for several pain disorders that occurs in women in later life. Interestingly, other female pain problems, such as migraines, diminish after menopause.⁶ Craft notes that both baseline pain sensitivity and sensitivity to opioid analgesics in female animals seems to be dependent on their gonadal steroid hormone state. Female rats receiving morphine at a point around the middle of their estrous cycle achieve significantly less analgesia than when they are in estrus.

Aloisi's review examines these issues in considerable detail. Gonadal hormones seem to be prime candidates in explaining sex differences in pain, since it is clear that they also modulate many other biological and cognitive functions. Estrogens and androgens, which critically direct bodily structures and functions throughout prenatal and postnatal development, have been demonstrated to affect many of the peripheral and central areas that underlie neural plasticity and pain reactivity. For example, estrogen receptors in the spinal cord of both male and female animals are strongly concentrated in the substantia gelatinosa and increase in density when estrogen plasma levels are high. High levels of estrogen and progesterone produce an elevation of pain threshold in ovariectomized female rats⁷ and in male rats.⁸ Steroid-sensitive cells are also found in a large number of central structures which are activated by nociceptive inputs and whose activity (and, indeed, gonadal hormone level) is modified by stress. These interrelationships are complex: stress decreases estrogen levels in female rats,⁹ pain decreases estrogen levels in female rats,¹⁰ stress increases pain,¹¹ and pain increases stress.¹²⁻¹⁴ Moreover, stress can induce ovarian dysfunctions¹⁵ and cause abnormal activation of the hypothalamic-pituitary-adrenal axis, possibly causing the abnormal neuroendocrine patterns seen in such disorders as fibromyalgia,^{16,17} chronic pelvic pain,¹⁸ and temporomandibular pain dysfunction.¹⁹

As Aloisi notes, "it would be of particular interest to evaluate whether the 'modulator' effect of stress on gonadal hormones can make stressed subjects more susceptible to both acute and chronic pain."

Zimmer et al pay particular attention to sex differences in stress responses following noxious stimulation. Male and female volunteers gave saliva samples, which were analyzed for the stress hormone, cortisol, at various points before and after immersion of the hand in ice water. Cortisol levels increased significantly in both men and women, but significantly more so in males. Moreover, men were able to tolerate the pain for significantly longer periods than women. The authors note the temptation to conclude that a common mechanism underlies the higher pain tolerance and elevated cortisol response, but caution that their correlational data are open to other interpretations, particularly ones tied to the temporal peaks of the neuroendocrine and pain responses.

Biological research has begun to carefully separate the multiple components of pain: the sensory, affective, and cognitive.^{20,21} While there is a growing body of literature that suggests male and female rats differ in susceptibility to anxiety,²² human research on the relationship between sex differences in pain and sex differences in anxiety is more firmly established. Edwards et al, in their contribution to this collection, review the research on this topic and provide an extension between laboratory-induced pain and clinical pain. Earlier research had indicated that stress and anxiety were more strongly linked to pain among females than among men, but a number of recent studies found the opposite. They set out to examine this issue in detail, looking, in particular, at the relationship between sex, anxiety, and treatment outcome in a multidisciplinary program which typically included regional injections and, subsequently, cognitive-behavioral therapy. For the sorts of pain experienced by these patients, generally reported at the back, legs, or neck, only the blocks and injections were successful, markedly reducing pain in both sexes. For males, but not females, a scale that measured pain-related anxiety responses correlated highly with the initial rating of pain. Interestingly, the relation between pre-treatment anxiety and post-treatment pain relief differed between the sexes. For women, those with higher anxiety showed less pain reduction; for men, the opposite was true. The authors speculate on the nature of this sex-specific relationship between anxiety and pain relief, considering the small literature on sex differences in attentional focus and placebo responses, and express the hope that further research will lead to clinical interventions that can tailor the treatment to the individual's sex and psychosocial profile.

Fillingim et al, in their paper, examine the studies that indicate the behavior of the spouse has a strong impact on the pain and disability expressed by chronic pain patients. Since the findings show greater pain, disability, and pain behavior among those whose spouses are supportive and solicitous, researchers have tended to interpret them in light of the operant theories of pain behavior that see spousal solicitousness as a reinforcer of pain expressions. To determine whether these effects are sex-related, the authors examined the nature of the relationship for both male and female patients experiencing chronic musculoskeletal pain. The study included numerous measures of pain affect and disability; the main conclusion was that spousal solicitousness was related to greater pain in both sexes. Several associations were sex-dependent (solicitousness with self-reported disability in men, solicitousness with pain-related interference, low activity level, opioid use, and poorer functional performance in women). The correlational data raise a number of intriguing issues, particularly whether the sex of the patient or the sex of the spouse is the variable that deserves attention and, in either case, whether solicitousness encourages pain behavior or, alternatively, whether greater distress brings on greater solicitousness. If so, as the authors note, "female patients may need to display greater pain-related disability to elicit supportive responses from their husbands, while the wives of male patients require less pain-related disability to provide increased support." This interpretation is aided by the earlier finding²³ that the wives of male pain patients are more strongly affected by their husbands' pain and disability than the husbands of female patients.

These sorts of findings, which place pain behavior within a powerful psychosocial context, are explored in great depth in the review paper presented by Myers et al. They formally address the terminology used in this area, distinguishing between "sex" as a name used to describe biologically determined differences between males and females and "gender" which emphasizes the socioculturally influenced behaviors and characteristics. This brings them to stereotypical masculine and feminine pain behaviors and the view that "males are thought to be more motivated than females to appear impervious to pain." A review of the literature on young children suggests that stereotypical behavior is demonstrated at an early age; recent evidence from the Gender Role Expectations of Pain Questionnaire developed by this group indicates that adults apply these same expectations to the behavior of others and themselves. Myers et al examine the broader question of sex-related differences in cognitive processing of information about pain, finding data that show women rely more than men on social support, feel

less in control, and engage in more maladaptive coping strategies such as catastrophizing.

The studies and reviews presented in this issue represent important milestones in understanding the role of sex and gender in accounting for individual pain behaviors. The findings are compelling and provocative, but the authors acknowledge that we still have far to go. For one, we are at an early stage in understanding genetic factors related to pain reactivity.^{24,25} What aspects of pain response and modulation are governed by sex-specific genomic mechanisms? We do not yet know how the biologic and psychosocial factors discussed here affect the predisposition to chronic pain, the immediate neural and emotional reactions to injury and disease, or the mechanisms that maintain abnormal neurochemical, structural, or psychological responses during chronic pain.²⁶

Many of the animal and human studies on sex differences have used phasic pain in the laboratory; we need to extend our use of animal models of chronic pain and our examination of self-expectancy, anxiety, and coping among chronic pain patients and to test whether sex differences are influenced by the intensity, location, duration, or quality of pain. Are there sex differences in the long-term efficacy of opioids, non-steroidal anti-inflammatory drugs, and other analgesics or in the benefits from psychological therapies or physical interventions?

Our developmental perspective is weak in relation to sex differences in pain behavior. Can we, or, for that matter, should we alter child rearing practices in a way that will reduce the incidence of pain behaviors in some individuals? What messages are we giving patients (or medical personnel) in papers such as those presented here? Are hypervigilance, anxiety about abnormal bodily states, medical attention seeking, or expression of the need for emotional support from a spouse or friend desirable or undesirable characteristics?

We need to better understand the influence of the menstrual cycle,^{27,28} menopause,^{6,29} and the use of estrogen replacement therapy³⁰ on women's responses to acute and chronic pain and the effects of pharmacological treatments. There is very little information about the relation between male androgen levels and pain reactivity, and, more significantly, very little interest in urological³¹ or other pain disorders that preferentially affect men.

Finally, it deserves to be emphasized that behavior is determined by an interaction of biological, psychological, and sociocultural factors.³² No matter what group data indicate about sex differences or gender stereotypes, each patient must be treated as an individual, whose pain and suffering are conscientiously evaluated and managed.

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