MESSAGE FROM THE SIG CO-CHAIRS

Dear Members of the Sex, Gender and Pain SIG,

This newsletter contains abstracts from the SIG meeting in Prague held in conjunction with the 4th Congress of EFIC (European Federation of IASP Chapters) on 2nd September 2003. Professor Richard Rokyta of the University of Prague hosted the meeting. Professor Anna Maria Aloisi organized the detailed program and the publication of the abstracts. We thank both of these colleagues most warmly for their work for the SIG. During the meeting, following the presentations by Anita Holdcroft and Victoria Grace, a discussion arose about the definitions of the words ‘Sex’ and ‘Gender’ as defined in the National Academy of Sciences publication ‘Understanding the Biology of Sex and Gender Differences’ (Eds. Wiseman and Pardue, 2001). It became clear that a number of languages use one word to describe both sex and gender and that the American interpretation of these words may differ across the world. If you have a contribution to this language diversity, please send us your letters and stories.

Since the last newsletter, we were asked to respond to the Pain of Urogenital Origin SIG initiative to develop definitions of urogenital pain based on the IASP Taxonomy Committee publication. We have responded as follows: (1) a classification of pain by position should enable the inclusion of many of the multiple pains described by women; (2) wherever applicable, the prevalence of a pain syndrome should be described for males and females separately; and (3) suggested therapies could be broadened to include all types of multidisciplinary pain management programs because males and females may respond differently. The resulting chapter in the Core Curriculum is now available for comment before publication on the Members Only page of the IASP Web site: www.iasppain.org. SIG members are encouraged to submit any further comments via the email on the page.

The next SIG meeting will be held in Siena, Italy during the weekend of Saturday 18th and Sunday 19th September, 2004. It will follow a joint meeting by the University of Siena and the Royal Society of Medicine, London, on ‘Traditional and Innovative approaches to Pain’ starting on 16th September. The SIG meeting will have the theme of ‘The Hormonal Modulation of Pain.’ Please put the date in your diary and encourage your colleagues to attend.

We wish you all Season’s Greetings and Best Wishes for the New Year.

Anita Holdcroft, MD and Jeff Mogil, PhD


Please send contributions, comments and questions to:
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Sex differences in responses to opioid analgesics have been increasingly investigated in recent years. While findings regarding sex differences in the analgesic effects of kappa opioid agonist-antagonists have garnered considerable attention, it is important to note that several studies have also addressed sex differences in responses to mu-opioids. For example, Sarton and colleagues (2000) reported more robust and longer lasting morphine analgesia among women compared to men using experimentally induced electrical pain. Similarly, Zacny (Zacny 2002) found that three μ-opioid agonists, morphine, meperidine, and hydromorphone, produced greater analgesia among women than men for cold pressor pain. Sex differences are not limited to analgesic effects, as Dahan and coworkers (1998) have reported greater morphine-induced respiratory depression in women, and women showed greater narcotic-induced emesis in the emergency department (Zun et al. 2002). Two recent studies of postoperative pain provide additional data relevant to the question of whether there are sex differences in the responses to μ-opioid agonists.

First, Cepeda and colleagues (2003) examined the records of more than 8,800 patients who had received morphine, meperidine, or fentanyl at one of 35 hospitals. The reasons for opioid administration varied widely and included acute/procedural pain, chronic pain, cancer pain or relief of other symptoms. Overall, 26% of patients experienced nausea and vomiting and women were significantly more likely to experience nausea and vomiting than men. This study did not report on pain or analgesic effects; however, a more recent study by Cepeda, M.S. and Carr, D.B. (2003) examined pain perception and morphine consumption after surgery in 423 women and 277 men. After patients reported a pain rating of 5 or greater on a 0-10 scale, 2.5 mg of IV morphine were administered every 10 minutes until the pain rating was less than or equal to 4. Women reported greater pain and consumed 30% more morphine than men. These findings suggest greater adverse effects but diminished analgesia from morphine among women compared to men. The findings regarding nausea and vomiting are consistent with previous research, but the greater analgesia among men contrasts with prior results in the postoperative pain setting (Miaskowski and Levine, 1999) and in the laboratory (Sarton, et al., 2000; Zacny, 2002). Thus, the presence and direction of sex differences in opioid analgesia appears to vary across studies and likely depend on several factors, including the pain model used, the patient population, the specific opioid agonist, and possibly the dosage. Clearly, additional research is needed to further elucidate the conditions under which sex differences in analgesia emerge, as well as the mechanisms underlying these effects.

References:

BASIC SCIENCE RESEARCH CORNER
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As I noted in my previous column, one of the drawbacks of preclinical research on sex differences in pain and analgesia to date has been the preponderant use of acute pain models. That is, a majority of researchers (myself included) who have compared nociception and antinociception in male vs. female rodents have employed only common tests of phasic pain such as the tailflick and hotplate tests. In contrast, clinically significant pain in humans usually involves inflammatory processes and/or neuropathy, which lead to persistent pain, hyperalgesia and allodynia that may be difficult to treat. It is not known to what extent the preponderant use of acute pain models in rodents has contributed to the apparent, puzzling discrepancy between results obtained human vs. rodent studies examining sex differences in opioid analgesia, for example (for review, see Craft, 2003). This possibility is addressed by a recent study conducted in the laboratory of Dr. Mitch Picker.

In “Capsaicin-induced hyperalgesia and mu-opioid-induced antihyperalgesia in male and female Fischer 344 rats” (JPET 307:237-245, 2003), Barrett et al. characterize thermal hyperalgesia produced by capsaicin injection into the tail, as well as
sensitivity to the antihyperalgesic effects of several mu agonists using this model of tonic pain. In their previous studies using this strain of rat, this group demonstrated either no sex difference in nociceptive sensitivity to acute thermal stimuli (Cook et al., 2000) or greater sensitivity in females (Barrett et al., 2002a; Terner et al., 2002; 2003); females were also more sensitive than males to a noxious mechanical stimulus (Barrett et al., 2002b). These results generally agree with studies in humans demonstrating greater sensitivity to acute mechanical (and sometimes thermal) pain in women than in men (for review, see Fillingim and Maixner, 1995). In the present study, Barrett and colleagues demonstrate that capsaicin was significantly more potent in female than male rats in producing thermal hyperalgesia. A particularly commendable aspect of this study is the careful examination of the possible impact of size differences in male and female rats on the results: The authors demonstrate convincingly that sex differences in thermal hyperalgesia are not explained by sex differences in tail length or circumference. Sex differences in capsaicin-induced hyperalgesia appeared to be gonadal steroid-dependent: gonadectomized males were more sensitive, and gonadectomized females were less sensitive to capsaicin-induced hyperalgesia than their respective gonadally intact controls. This group similarly demonstrated that sex differences in sensitivity to an acute thermal stimulus are gonadal steroid-dependent in the F344 strain (Terner et al., 2002). Taken together, these results suggest that sex differences in thermal nociception in this strain do not depend on the physiological state of the organism: sensitivity to noxious thermal stimuli is greater in females than in males under normal, and under inflamed tissue conditions.

In the second part of the study, Barrett et al. evaluate sex differences in the antihyperalgesic effects of several mu opioid agonists. For the most part, there were no significant sex differences in the antihyperalgesic effects of morphine, buprenorphine or deozinc given systemically (s.c.), intracerebroventricularly (i.c.v.) or locally (into the tail). However, it is important to note that in the few cases in which sex differences were observed (buprenorphine administered locally and i.c.v.), it was females who showed a better response. These results differ dramatically from this group’s (and others’) previous results obtained using standard tests of acute thermal pain, in which opioids are often reported to be more potent in male than in female rats (Craft, 2003). Therefore, the present study suggests that sex differences in opioid analgesia may depend on the physiological state of the organism: whereas opioids may be more potent or efficacious in males than females against acute pain, under conditions of inflammation, opioids may be more effective in females than in males. Clearly this hypothesis merits further careful analysis in both animal and human studies. It is intriguing to consider that the presence/absence of inflammation may contribute to the apparent discrepancies between rodent and human studies on opioid analgesia published to date.

The only drawback to the present study was the lack of estrous stage evaluation in female rats. Previous studies in both rats and humans suggest that pain and analgesia may fluctuate across the estrous/menstrual cycle (for reviews, see Riley et al. 1999; Fillingim and Ness, 2000; Craft et al., in press). In fact, the gonadectomy results in the present study suggest that gonadal hormone fluctuation in females is likely to significantly influence sensitivity to capsaicin-induced thermal hyperalgesia. We have found that small sex differences in opioid analgesia, such as those we have reported in Sprague-Dawley rats, may be entirely dependent on the stage of estrus in females (Stoffel et al., 2003). Thus, all investigators characterizing sex differences in pain and analgesia are encouraged to include estrous stage analyses in their studies. Although I can personally attest to the tediousness of these experiments, we really need to better understand the cyclic influence of gonadal steroid hormones on pain and analgesia in females, and how this might contribute to the discrepancies across studies of sex differences in pain and analgesia.

References:
Do birth partners help or hinder women’s experience of elective caesarean section?
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Women tend to engage in more support seeking coping behaviors, especially emotional support, whereas men use problem-focused strategies. Childbirth is an event that places some women under extreme physical and psychological strain. Childbirth also often involves emotional support from a birth partner. However, contradictory evidence exists in terms of how helpful birth partners can be; some studies report positive, whereas other report negative effects. We report preliminary results from a study that aims to determine the role that birth partners have in influencing mother’s experience of caesarean section, such as amount of post-operative pain and emotional state. Results revealed that birth partner’s fear did not influence mother’s fear or pain during a caesarean, but that it is associated with increase in mother’s post-operative fear and pain. Further research into the emotional impact of birth partners is recommended.

Sex-specific influence of attention on pain perception
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The scarce literature on potential sex-specific influences of attention on pain perception was reviewed and compared to data from studies of the author. These sources suggest that the influence of attention on pain perception cannot be verified in women – in contrast to men - when experimental pain induction is massive (very intense, tonic, concurrent stimulations). Similarly, the differential effect of different attentional strategies cannot be verified under the same experimental conditions in women. In situations with more moderate intensities of experimental pain stimulation, attentional distraction from pain can be demonstrated in women as in men. The author suggests that women use distraction manoeuvres according to instruction in the less threatening experimental situations but switch to manoeuvres with individually proven efficacy in the more threatening experimental situations with the result that both the experimental and the control groups use similar manoeuvres in the latter case.

Modulation of endogenous pain mechanisms by female and male sex hormones
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We previously demonstrated that female and male sex hormones play different role on formalin-induced nociceptive responses by comparing the responses of normal and gonadectomized rats (Gaumond, et al., 2002). The goal of the present study was to verify: 1) the specific effects of testosterone, progesterone and estrogen in gonadectomized female and male rats and to 2) whether the gender differences recorded during the different phases of the formalin test are opioidergic-dependent.

The rats were divided into twelve groups (n = 8/group): one group of intact males, one group of intact females and the ten others were castrated (CAST) males and ovariectomized (OVX) females. Males and females received a supplementation of either: 17β-estradiol, progesterone, 17β-estradiol and progesterone, testosterone or a vehicle. In the second study, intact females and males rats received a subcutaneous injection of different doses of naloxone ranging between 0 and 10 mg/kg. In the first study, testosterone significantly reduced the nociceptive responses during phase I (acute) and phase II (tonic phase) but not during the interphase (inhibitory). The combination of 17β-estradiol and progesterone re-establish the weaker nociceptive pain reduction during the interphase as it is observed in the intact female. Interestingly, the effect of these hormones is not gender specific since they have the same action in females and males. Preliminary results suggest that that naloxone almost totally abolishes the interphase inhibitory response but only in females. Results also suggest that testosterone plays an important role in nociceptive responses. Moreover, as female hormones act mainly on pain inhibition mechanisms (interphase), this suggests that certain chronic pain conditions could be related to a deficit of these pain inhibitory mechanisms rather than an increased nociception. Finally, the effect of female sex hormones during the interphase seems to be opioidergic.

“Understanding what women want”
An exploration of women’s experiences of chronic pelvic pain and the multidisciplinary approach
Catherine Stephens, Assistant Psychologist, Department of Medical Psychology, Leicester Royal Infirmary, UK

A few studies have reported the effectiveness of using a multidisciplinary team approach to assess and manage chronic pelvic pain (CPP) (Kames et al 1990; Peters et al 1991). To date no studies have examined women’s perspective of the
multidisciplinary approach: what is it that women want from healthcare professionals? And what does it feel like to be a woman living with CPP? In-depth interviews were conducted by staff of the multidisciplinary clinic for CPP in Leicester, UK with 16 women who had been through the clinic. Interview transcripts were analysed using grounded theory, a qualitative methodology that generated several themes.

Results showed that one of the main themes was “patient-professional interaction” – did the gender of the professionals matter? There were various schools of thought around this issue, which were not necessarily exclusive. Women tended to hold a number of different views concurrently and struggled to resolve them, which gave the overall impression they did not know what they wanted. Higher-order analysis suggested that patient-professional interaction was best illustrated by a dual theme termed “professional fallibility / patient expert.” “Professional fallibility” referred to the limited knowledge and understanding the professionals were thought to have, no matter whether male or female. “Patient expert” was the corresponding role, and represented the vast body of views, experiences and theories women had about their bodies and their pain.

Results suggest that professional tasks could be made easier if women with CPP were acknowledged and treated in the role of the patient expert by forming a fourth and fifth arm for patients and peers alongside gynaecology, pain management and psychology. A support group has been set up for women with CPP in Leicester as a first step to achieving this. Our research also demonstrates the value of qualitative methods in pain research which provides an important mechanism to give patients some control over treatment.

Critical reflections on the sex and gender distinction:
Assessing its usefulness for pain research
Victoria Grace, University of Canterbury, New Zealand

The Institute of Medicine (USA) recently published a book-length report on an investigation into the question of the biological contribution of sex to human health. The IOM endorses the distinction between ‘sex’ and ‘gender’, and advocates that researchers use this distinction for the purposes of all biomedical and clinical research on sex differences. This is a particularly significant development in the light of the concurrent emphasis the report places on a new era of research on sex differences that is evolving for the purpose of devising a ‘gender-specific medicine’. The IOM claims regarding the sex/gender distinction raise a number of questions. This paper develops a critical analysis of the use of the sex/gender distinction as outlined by the IOM report, with a particular focus on pain research. The paper argues that the critical insights in pain medicine regarding the limitations of a dualistic approach to the mind and body, to culture and biology, in understanding and explaining pain are not facilitated by adopting the sex/gender distinction as a conceptual framework for research on sex differences in pain.

Does gender influence analgesic drug pharmacology?
Dr. Anita Holdcroft, Chelsea and Westminster Hospital, Faculty of Medicine, Imperial College London, United Kingdom

The division between ‘sex’ and ‘gender’, as defined by the USA Institute of Medicine [1], is not considered to be mutually exclusive when considering drug pharmacology because interactions between sex and gender occur as well as age-related changes. For example, females ask for more analgesic medications than men, but in terms of side effects females demonstrate more adverse reactions from pain medications. The former situation is gender-related whereas the latter are more sex-specific. The mechanisms for these effects are either sex dependent e.g., physical factors, or sex specific e.g., hormonally mediated. Hormones have either non-genomic (activational) or genomic (organisational) activity. For instance, sex steroid hormones can activate inhibitory descending pathways with the potential to synergistically interact with opioids, or through organisational effects can influence transcription factors involved in nociceptive transmission.

Through retrospective and prospective studies of patients after surgery [2], gender influences in opioid use have been measured. Males regularly use more opioids than females and have more pain on movement. Psychological and biological differences have been suggested to explain these findings and now the question is how to best put these results into practice. Drug delivery systems may have to be programmed specifically for the patient’s sex (as is the case for the opioid remifentanil) and patient information purposely designed for males or females in order to enhance benefits or reduce risks of analgesics.


Opioid therapy and quality of life in women and men suffering with chronic non-malignant pain
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The gonads, through their products, have important effects on cognitive functions such as emotion, attention, learning and memory. Gonadal hormones act during development, shaping the brain in a male or female fashion. In addition, throughout life, androgen and estrogen act through receptors that are present in many brain areas. Cholinergic, adrenergic as well as glutamatergic systems, all involved in pain modulation, have been found to be greatly modulated by gonadal hormones and, consequently, to induce sex differences in the behavioural, hormonal and neuronal response to pain. Female rats are more affected than males by painful stimulation; this higher reactivity is suggested to be the basis for the higher incidence of chronic pain states in women than in men.
Sex differences in pain perception during early development in rats
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Two different systems for the transmission of thermal and mechanical pain perception at the spinal cord level in adult rats have been described. In the present study, the evolution of these two systems during ontogeny was investigated. The ontogenetical evolution of thresholds obtained using three types of nociceptive stimulation was compared. Pain threshold of thermal (tail-flick and plantar test) and mechanical (Randall-Selitto test) stimulation were utilised in early postnatal days from the 3rd up to the 28th day. There were no significant sex differences in measurement done on the same day. The results obtained by two thermal stimulation methods were significantly different. The results obtained by thermal tail flick and the mechanical methods varied in the same sense and did not present differences during ontogeny. The results from thermal nociceptive thresholds measured with plantar test and those obtained from mechanical simulation were developed differently. They are similar until the 16 PD, then their evolution goes in opposite directions. Results are consistent with the hypothesis of two different systems of transmission of the noxious messages during ontogeny. Obtained results may be explained by the involvement of transmission mediators that are acting in two different nociceptive systems.

The International Journal of Sex Difference in Health, Disease and Aging

Aims and Scopes:
Normal cellular and integrative physiological, pathological and pharmacological functions in biology are influenced by sex-based differences. XX vs. XY: The International Journal of Sex Differences in the Study of Health, Disease and Aging is focused on advancing our understanding of sex differences in the pathobiology from conception to aging. Particular emphasis is placed on studies that advance:

- The knowledge base on and research priorities for animal and cellular models that may determine where sex differences exist and where they are relevant to biological function at the cellular, developmental, organ, and organismal level.
- The biologically relevant aspects of sex differences that lead to greater understanding of the significance of sex in human biology and health.
- The basic mechanisms by which sex differences exert their effects on health and disease.

XX vs. XY invites applied and basic research contributions in sex differences in disciplines including, but not limited to, anesthesiology, biology, cardiology, endocrinology, epidemiology, genetics, geriatrics, immunology, molecular and cell biology, neurobiology and psychological disorders, pediatric, physiology, pharmacology, and rheumatology (see Instructions to Authors at http://xxvsxy.syr.edu). Please send submissions regarding pain research to Roger Fillingim (rfilling@ufl.edu).

SIG on Sex, Gender and Pain Objectives:
The scientific focus is on the issues of sex, gender and pain. The proposed activities are:
1. Encourage basic and clinical research on how sex and gender affect pain mechanisms and all realms of its management.
2. Provide a central information resource on these issues.
3. Develop multidisciplinary e-mail discussion groups on sub topics.
4. Encourage the production of periodic reports for IASP on possible applications of emerging information to clinical practice and future clinical and basic research.