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MESSAGE FROM THE SIG CO-CHAIRS

We would like to introduce ourselves as the new co-chairs of the Sex, Gender and Pain SIG. Nomita Sonty and Anne Murphy have also been elected to serve as secretary and treasurer, respectively. First, we would all like to thanks Jeff, Anita, Rebecca and Ed for their hard and diligent work as the previous executive board. The four of you have left big shoes to fill!

Over the next three years, there are several goals we would like to accomplish:

(1) We would like to finalize the work of the previous board and organize an experts workshop for the development of comprehensive guidelines for the conduct of pain research with regard to sex and gender for basic, translational and clinical studies. The idea is to develop a consensus on important issues to take into account when designing experiments to examine sex and gender issues in pain. These guidelines will be published in PAIN, thereby increasing the awareness of basic and clinical scientists on the importance of sex and gender when designing experiments and analyzing data. With the aide of the Research Center for the Neuroendocrine Influence on Pain at the University of Maryland, fund raising has already begun. Our goal is to hold the workshop in the Fall 2006.

(2) A second goal for this board is the development of a SIG website in order to highlight important issues to the SIG as well as convey information to the general public. We are in the process of interviewing web designers and our goal is to have this website up and running by next year.

(3) We highly encourage SIG members to submit workshop proposals to the next World Congress in Scotland in 2008. There were two workshops and a plenary lecture at the meeting in Sydney and we should try to at least match that in Glasgow.

We believe that the three goals outlined above are achievable with the help of our SIG members. Additionally, we are open to suggestions and comments from members of the SIG and encourage your input on any matters.

Sincerely,
Richard Traub
Stefan Lautenbacher

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Peripheral Mechanisms Contribute to Innate Biological Sex Differences in Pain
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The recent article by Rebecca Craft in the Newsletter’s Basic Science Research Corner drew attention to studies indicating that sex differences in pain and analgesia have an “innate biological basis”. Here we expand upon this evidence and briefly review investigations that also reveal that there are physiologically based sex differences in peripheral nociceptive mechanisms.

A number of common chronic musculoskeletal pain syndromes, such as fibromyalgia and temporomandibular disorders (TMD), have a greater prevalence in women than in men, but the lack of obvious pathology associated with them makes it unclear to what extent physiological factors may underlie these sex-related differences in their [8,10]. There is however some evidence, such as findings that masticatory muscle pressure pain thresholds vary through the menstrual cycle in both healthy women and TMD patients [11,13], which associates sex hormones, and in particular estrogen, with sex-related differences in the prevalence of these pain conditions [10]. Furthermore, basic animal studies have revealed a significant interaction between sex, sex hormones and primary afferent activity. In the trigeminal system for example, the mechanoreceptive field size of facial skin afferent fibers varies with the stage of the estrus cycle and is enlarged in estrogen-treated ovariectomized female rats compared to males [1]. Of greater relevance to TMD AND fibromyalgia manifested in the orofacial region are the properties of the small-diameter myelinated and unmyelinated nociceptive afferents supplying the temporomandibular (jaw) joint (TMJ) and masticatory muscles, which are the primary locations of the pain complaints or neuromuscular dysfunction (e.g. jaw movement limitations) characterizing these conditions. The mechanical threshold of rat masticatory muscle nociceptors varies through the estrus cycle [3], and TMJ nociceptors recorded in female goats display a range of force necessary for maximum afferent firing rate that is smaller than that in males [14]. These findings suggest that changes in mechanical sensitivity of joint and muscle nociceptors could partly underlie the observed variability in chronic musculoskeletal pain in conditions such as TMD and fibromyalgia.

Our laboratories have also used injections of glutamate into deep craniofacial tissues as a tool to investigate the possible role of physiological mechanisms in sex-related differences. Glutamate is an algesic chemical found in peripheral tissues as well as the CNS, and peripheral glutamate levels and glutamate receptors are elevated in inflammatory pain conditions [9]. Injection of glutamate into the TMJ reflexly evokes a concentration-dependent increase in jaw muscle activity in both sexes but evokes greater jaw muscle activity in females than in males [6]. This sex-related difference disappears if female rats are gonadectomized and reappears if gonadectomized female rats are given estrogen replacement therapy, consistent with findings of estrogen receptors in the TMJ and other musculoskeletal tissues [15]. Further evidence for a peripheral basis underlying these effects comes from our findings that glutamate injection into deep craniofacial tissue evokes an afferent fiber discharge that is also significantly greater in female than in male rats, which suggests that a peripheral mechanism contributes to the observation of enhanced glutamate-evoked jaw muscle reflex responses in female rats [4].

These afferent and reflex responses to glutamate are mediated, at least in part, through activation of peripheral both N-methyl-d-aspartate (NMDA) and non-NMDA receptors [7]. Furthermore, the glutamate-evoked reflex responses can be suppressed by morphine acting principally through peripheral μ opioid receptors [2] and by GABA agonists acting through peripheral GABA receptor [5], and there is a sex difference in the peripheral action of morphine. Thus, female rats are more sensitive than male rats to the excitatory action of glutamate on peripheral NMDA and non-NMDA receptors in craniofacial musculoskeletal tissues, and may lack the protective inhibitory effect of peripheral μ opioid receptors afforded male rats.

But does any of this data in rats have relevance to human pain responses? The answer is clearly yes, since in parallel human experiments with other colleagues in Toronto and Denmark [4,16], we have shown that injection of glutamate into the human masseter muscle evokes NMDA-dependent pain and allodynia, and the intensity and extent of the pain are significantly greater in women than in men [4,16]; analogous sex-related differences in muscle pain intensity have also been reported after injection of serotonin into the masseter muscle [12]. Furthermore, the glutamate-evoked pain is associated with a significantly facilitated jaw-stretch reflex in men but not in women [7]. Since one possible function of facilitated jaw-stretch reflex responses during jaw muscle pain may be to reduce jaw mobility and thus protect against further exacerbation of an existing painful injury, the finding of a sex-related difference in myofascial pain and in the modulation of jaw-stretch reflex responses may prove to be important in clari-
flying why the prevalence of TMD is greater in women than in men.

The results of these various investigations indicate that peripheral, physiologically based mechanisms may contribute to the sex-related differences in pain and its control. In the particular case of glutamate, animal and human studies suggest that elevation of peripheral glutamate levels in deep tissues may be involved in the neuromuscular changes, pain spread and referral, allodynia, hyperalgesia, pain at rest, and the female predominance manifested in many pain conditions such as TMD and fibromyalgia. Nonetheless, further studies are needed for a better understanding of the role of peripheral glutamate receptors in the mechanisms underlying these pain conditions.

References:


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There is increasing interest in the non-verbal expression of pain. There are a number of reasons for this ranging from practical clinical need, as when trying to assess pain within very young children, through to more theoretically based questions relating to the uniqueness of pain expressions. For example, there have been debates as to whether we can say that there is a facial expression of pain, and if there is, whether such expressions are unique, in that they are distinct from other discrete emotions such as anger, fear and happiness. Many of these arguments and relevant evidence has been summarized in the excellent Behavioural and Brain Science review by Amanda Williams (2002).

Turning to potential sex differences, there is now good evidence to suggest that males and females may generally differ in their expression of emotions (McClure, 2000). Given that pain can be communicated through facial expressions, and that men and women are generally through to differ in their expression of pain, it is perhaps understandable that there should be interest into whether males and females differ in facial pain expressions. For example, a study by Guinsburg et al. (2000) found that within neonates, females are more expressive during a painful medical procedure (heel lance) than males. For this issue of the newsletter I wish to report on a new experimental study on sex differ-
ences in facial pain expressions by Kunz, Gruber and Lautenbacher (submitted). They examined 40 healthy volunteers (20 male, 20 female) with the goal of investigating potential sex differences in facial expression to experimentally administered painful and non-painful stimuli. They made use of a thermal heat pain induction task, in which pain was administered to the thigh, and subjective pain assessed using a visual analogue scale. The faces of participants were videotaped throughout the study and facial action coding (FAC) used to assess facial expressions. Facial muscle movements of four specific action units thought to be important in pain were examined (Prkachin et al., 1983): brow lowering, orbital (eye) muscles, nose wrinkling/upper-lip raising and eye closure. Somewhat surprisingly, no sex effects were found for either subjective pain reports or facial expressiveness (action units) during the heat trial. However, when correlations were conducted between subjective pain and the facial action units, differences were found between men and women. For women, a relationship was found between self-reported pain and the action unit for brow lowering. No such relationships were found within men.

Further research is clearly needed to extend this potentially interesting avenue of research in order to not only determine whether men and women are similar (or different) with respect to facial expressions associated with pain, but to also examine how these non-verbal cues relate to subjective pain experiences. As Kunz et al. (submitted) conclude “future studies investigating the relationship between self-report and non-verbal pain behaviours should consider sex as an important modulating factor”. It would also be of interest to see such methods applied to different groups. For example, are the facial pain expressions of patients moderated by sex, and if so, are there differences in how such expressions are detected (and acted on) by male and female clinicians.

References