MESSAGE FROM THE SIG CO-CHAIRS

Dear SIG members,

Just a quick update on the activities of the SIG over the past few months. Stefan and Nomita are busy designing the SIG website which should be operational by the next newsletter. Anne and Rich are working with several other people to put together a meeting to develop guidelines for conducting research on sex, gender, and pain that was initially proposed by Jeff Mogil and Anita Holdcroft. We will keep you informed.

Another reminder that workshop proposals are due at the end of March for the IASP meeting in 2008. If you submit a proposal, please let us know.

Sincerely,
Rich Traub and Stephan Lautenbacher

SIG Initiative in Europe

We are preparing an initiative, using the European platform of EFIC. The European chapters will be encouraged via the EFIC mailing list to plan contributions at the national and regional conferences, which direct attention to sex- and gender-related topics in pain research and pain management. Support will be offered by establishing contact with international experts in this field and by announcing such events via the SIG newsletter and SIG homepage.

SIG Homepage

The SIG homepage is active in a test run and can be viewed by using the link: http://www.unibamberg.de/fakultaeten/ppp/faecher/psychologie/professur_fuer_physiologische_psychologie/sig_sex_gender_and_pain/. New columns presenting literature and up-comings events relating to our SIG group as well as the SIG guidelines are in preparation. Suggestions by the SIG members for form and content of the SIG homepage are very welcome.

Please send newsletter contributions, comments and questions to:
Gernot Ernst
Blefjell Hospital Kongsberg, Anesthesiology
Drammensvei 4
3612 Kongsberg, Norway
Tel: 004732725500; Email: gernot.ernst@blefjellsykehus.no

Table of Contents: Message from Co-Chairs............. 1
Basic Science Research corner......... 2
Clinical Research corner............. 3
Epinephrine – A Molecule Linking Stress, Sex and Pain

Michael S. Gold, PhD
University of Maryland Baltimore, Department of Biomedical Sciences and Program in Neuroscience, Baltimore, MD 21201, USA

A glance at a daily newspaper or the evening news and one gets the distinct impression that the level of stress in the world is rising. Take a walk through inner city USA and one does not need mass media to get the same impression. While acute stress may actually be a good thing, resulting in the activation of a number of protective mechanisms, not the least of which is the suppression of pain, chronic stress appears to have a number of deleterious consequences including the exacerbation of ongoing pain. Given that the response to stress is sexually dimorphic, it is reasonable to hypothesize that the impact of chronic stress on nociceptive processing will also be sexually dimorphic. Indeed, recent data from a polyarthritis model indicates that hyperalgesia associated with the development of arthritis, which is a stressor in its own right, occurs earlier and with a greater severity in females than in males (2). Levine and colleagues have recently published results from several animal studies designed to tease apart the processes underlying the link between sex, stress and pain.

**Stress**

Acute stress results in the activation of the hypothalamic-pituitary-adrenal (HPA) axis characterized by the release of corticotropin-releasing hormone (CRH) in the hypothalamus which mediates the release of adrenocorticotropic hormone (ACTH) from the pituitary which in turn mediates the release of corticosterone from the adrenal cortex. Along with mediating a number of other physiological functions, corticosterone is thought to be the principal mediator acting in the hypothalamus to inhibit HPA activation. In contrast, chronic stress appears to be associated with the loss of this feedback inhibition and, among other things, the recruitment of the sympatho-adrenal (SA) axis. This axis is characterized by the activation of brainstem adrenergic circuitry resulting in an increased drive on sympathetic preganglionic neurons which in turn increases the release of epinephrine from the adrenal medulla.

**Stress and Sex**

Stress-induced activation of HPA and SA axes are sexually dimorphic and regulated by gonadal hormones. Testosterone inhibits HPA function while estrogen enhances it (6). Consequently, the response to acute stress, as measured by the release of ACTH and corticosterone is considerably smaller in males than in females. This hormonal mediated regulation of HPA function appears to reflect, at least in part, the actions of gonadal hormones at androgen and estrogen receptors with the hypothalamus. In contrast, hormone mediated regulation of the SA axis, appears to reflect, at least in part, regulation of adrenal output. The first evidence out of the Levine lab in support of such a suggestion came in the form of a plasma extravasation study in which it was demonstrated that estrogen increases the release of a factor from the adrenal gland that suppresses plasma extravasation, while testosterone increased the release of this factor (4, 5). The suggestion that estrogen may be acting directly on the adrenal gland is suggested by the observation that ERα is expressed in the adrenal medulla (5).

**Stress, Sex and Pain**

So what is the connection between stress, sex and pain? The answer appears to be epinephrine. Epinephrine is capable of generating hyperalgesia via activation of β2 adrenergic receptors, most likely present on the peripheral terminals of nociceptive afferents (1, 9). Interestingly, males are more sensitive to the hyperalgesic actions of epinephrine than females, a difference that is mediated by the actions of estrogen (3). Estrogen appears to mediate this difference by driving an increase in the production of epinephrine in the adrenal medulla and consequently plasma epinephrine concentrations (which, according to the HPLC analysis are more than 2 time higher in females than in males, are attenuated with gonadectomy and restored with estrogen replacement) (7). High resting epinephrine levels should result in adrenergic receptor desensitization and a lower sensitivity of the hyperalgesic actions of epinephrine in females than in males (7).

It turns out the sex differences in nociceptive threshold may also reflect estrogen-induced regulation of epinephrine levels. While the presence of a sex difference in nociceptive threshold has been hotly debated and thoroughly reviewed (several times), and clearly depends on a number of factors, it appears to be relatively robust in the rat when assessed with an analgesy meter (i.e., a Randall-Selitto device) (2, 7): Males have a higher nociceptive threshold than females. Again epinephrine raises its head as this difference appears to reflect, in part, an estrogen mediated regulation of epinephrine production in the adrenal medulla. Nociceptive threshold is increased in females by gonadectomy, adrenal-medullectomy and adrenal denervation, while it is normalized to levels observed in intact females with estrogen replacement or epinephrine replacement (7). However, while epinephrine levels appear to be critically involved in the determination of both epinephrine-induced hyperalgesia and the regulation of nociceptive threshold, mechanisms...
underlying these processes appear to be distinct. This is particularly true in males where adrenalectomy has no influence on epinephrine-induced hyperalgesia but results in an elevation in nociceptive threshold which not reversed by epinephrine replacement.

So how does stress fit into the mix? It turns out that non-habituating stress results in sensitization of primary afferent to actions of bradykinin (8). The factor responsible for the stress-induced sensitization of primary afferents appears to be epinephrine as the stress-induced effects were blocked by adrenalmedulectomy and reconstituted with epinephrine replacement (8). Interestingly, chronic stress appeared to have no influence on hyperalgesia induced by prostaglandin E2, another mediator thought to act directly on the primary afferent terminals. This observation suggests that epinephrine regulation of nociceptive function is quite specific. Given that these results were obtained in male rats, they suggest a mechanism that could account for the differential influence of epinephrine on nociceptive threshold and hyperalgesia, whereby epinephrine influences specific channels and/or second messenger pathways underlying the actions of specific inflammatory mediators but has no influence on channels underlying mechanical activation of nociceptive afferents.

What does it all mean...
The combined influences of stress and estrogen make for a bad situation if one is talking about a chronic pain syndrome. Chronic stress results in the suppression of nociceptive and anti-inflammatory circuitry, resulting in both increased pain and tissue damage associated with injury. Chronic stress may also result in elevated levels of epinephrine, which, in the intact female should decrease nociceptive threshold. Estrogen should further increase epinephrine levels resulting in an even greater suppression of nociceptive threshold. The result of all of these factors may be the seeds for the development of a chronic pain syndrome.

References:

CLINICAL RESEARCH CORNER
Edmund Keogh, PhD
Pain Management Unit, University of Bath & Royal National Hospital for Rheumatic Disease, Claverton Down, Bath BA2 7AY, UK

For this issue of clinical corner I wish to draw your attention to a recent Health Technology Assessment (HTA) report published by the United Kingdom’s National Health Service (http://www.ncbiota.org). Whilst I realize that this may initially seem to be of more local interest, there are some potentially important issues that I hope will be of general interest to all SIG members.

The report in question, authored by Bartlett et al. (2005), describes an investigation into the extent that socio-demographic factors, such as gender, age and ethnicity, are taken into consideration within clinical trials. It also considers the potential causes and effects of exclusion, by outlining some of the social, legal and ethical issues associated with such practice. What makes this report particularly interesting is the evidence base they draw on, which includes reviews of randomized controlled trials, as well as examination of large patient cohort databases. Specifically, the authors consider two patient conditions, coronary heart disease (CHD) and osteoarthritis, and respectively focus on issues associated with the use of statins and non-steroidal anti-inflammatory drugs (NSAIDs). Their review com-
prised of 27 randomized controlled trials involving statins use in CHD and 25 trials for NSAID use in osteoarthritis, as well as examined need, prescription differences and adverse effects for both drugs using large cohort databases. With respect to the gender-related effects associated with NSAID it seems that women were represented in almost 70% of the clinical trials that were reviewed. Although not perfect, this figure is initially encouraging. However, closer inspection reveals that although men and women may be included such trials, outcomes were not reported by socio-economic groups. Interestingly, the authors point to potential differences between the USA and Europe, with trials originating in the US seeming to be more likely to report such effects. The examination of side effects within the large cohort of patients revealed that the risk of gastrointestinal problems associated with NSAIDs increased with age, although this seemed to be dependent on gender – with males showing an increased risk. With respect to potential prescribing differences, the report also suggests that around 4% of adults used prescribed analgesics for pain associated with osteoarthritis, with this being more common within females and those over the age of 65.

As members of this SIG might expect, the authors of this report note that exclusion of specific groups, such as gender, can potentially compromise the generalizability of results, and the exclusion of such groups from clinical trials is a potential problem. They also call for both sex and age to be considered together, especially in light of the potential susceptibility of older men to the adverse effects of NSAIDs. What is potentially useful, within the UK at least, is that the findings from these HTA reports feed into decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE). Although it remains to be seen how, or even whether, such recommendations are implemented, reports such as this highlight the need to consider socio-demographic factors, such as gender, in the treatment of a range of clinical conditions including pain.

Reference


SIG Objectives

The Special Interest Group on Sex, Gender, and Pain is comprised of scientists and clinicians who have an interest in understanding the influence of sex-related factors on the experience of pain. As stated in our charter, the SIG pursues the following objectives:

- To encourage basic and clinical research on how sex and gender affect pain mechanisms and all realms of its management
- To provide a central information resource on these issues
- To develop multidisciplinary discussion groups on subtopics of these issues

SIG Membership

Please remember to pay the $20.00 SIG dues in addition to your IASP membership dues. Membership in SIGs is open only to members of IASP. Members wishing to join the SIG should indicate their preference on the annual membership renewal form or contact the IASP main office directly at: Email: members@iasp-pain.org

SIG information:

The SIG currently has 115 members representing 21 specialties in 24 countries.

The current balance in the SIG account is: US$6,754

The ‘Call for Workshop and Plenary Proposals’ has gone out for the 12th World Congress on Pain, Glasgow, Scotland, UK, August 17-22, 2008. The deadline for submission is: March 31, 2006. Please send proposals to:

Dr. J. Castro-Lopez, Chair,
Scientific Program Committee;
email: jclopes@med.up.pt
Fax: 351-22-557-3758

Next Newsletter Deadline and Publication Dates

Deadline  Publication
June 15, 2006  July 1, 2006

Please send all Newsletter contributions and suggestions to: Gernot Ernst
Blefjell Hospital Kongsberg, Anesthesiology
Drammensvei 4
3612 Kongsberg, Norway
Tel: 47-32725500; Email: gernot.ernst@blefjellsykehus.no