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MESSAGE FROM THE SIG CO-CHAIRS

Dear SIG Members,

The summer’s World Congress on Pain in Sydney is quickly approaching. Don’t forget to mark in your calendars the time of our SIG Meeting: Wednesday, August 24, 2005 (Jeff’s birthday, as it turns out), at 16:30-17:30 hours in the Sydney Convention Center. Please be sure to attend, as we will be discussing ongoing project plans, electing new officers, and enjoying refreshments. The location of the meeting has not yet been disclosed, but should be prominently featured in the final Congress program given to all attendees. The #1 issue on the agenda will be how to take forward our plan to hold an expert workshop to arrive at a consensus on experimental standards (Guidelines) in this subfield. As you all know, we have developed a set of questions to be discussed, and identified possible attendees. The sticking point is finding an institution willing and able to sponsor the costs of this workshop. We have made informal and formal presentations to a number of pharmaceutical companies, but so far to no avail. So bring your ideas and your Rolodex to the World Congress on Pain in Sydney. In the meantime, those who offered to develop ideas on the Guidelines at the SIG meeting in Italy are invited to email Anita, Anna Maria, or Serge so that short presentations can be arranged and topics discussed before, as well as during, the meeting.

Sincerely yours,
Anita Holdcroft, MD and Jeffrey S. Mogil, PhD

NEEDED: Newsletter Editor.

Beginning in summer 2005, the Sex, Gender and Pain SIG will need a new editor for its newsletter. The editor works with the Executive Committee, IASP and the SIG membership to coordinate submissions of columns, announcements and other articles for the newsletter, which is published three times annually. This position involves a minimal time commitment, typically to secure and organize submissions and to provide light editing. If Interested, please contact Becky Papas (rpapas@sbcglobal.net) or any of the SGP SIG officers.

Meetings:
The 1st World Congress on Gender-Specific Medicine, Sept. 8-11, 2005, Intercontinental Hotel, Berlin, Germany, www.gendermedicine.com
Sex, Gender and Pain SIG Business Meeting, August 24, 2005, Convention Center, Sydney, Australia

SIG information:
The SIG currently has 99 members representing 18 specialties in 23 countries.

The current balance in the SIG account is: US$ 6769.00
To be a member of the SIG on Sex, Gender and Pain, please indicate this SIG on your IASP dues form, or contact IASP via email: members@iasp-pain.org

Please send newsletter contributions, comments and questions to:
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Many recent studies provide evidence that sex differences in pain responses are, at least in part, psychosocial in nature—including learned, gender role-specific responses of study participants to the noxious stimulus as well as to the researcher observing/recording their pain responses (e.g., Myers et al., 2003; Kállai et al., 2004). One approach to distinguishing between the contributions of psychosocial/cultural vs. innate biological influences on pain sensitivity is to compare pain responses in very young male vs. female subjects, who presumably haven’t yet acquired gender role expectations. In fact, recently born human female neonates have been found to express significantly more pain than male neonates during a painful procedure (Guinsburg et al., 2000), suggesting that there may indeed be a “pure” biological sex difference in pain processing—one that develops very early in life.

Sternberg and colleagues (Sternberg et al., 2004) recently examined the question of early sexual differentiation of nociception and opioid antinociception using very young mice. Female and male mouse pups were tested on the day of birth or 1 week later, on two standard nociceptive tests that are widely used in adult rodents. Whereas there was no sex difference in hotplate latencies, females had longer warm water tail withdrawal latencies than males. These sex differences were similar in the day-old and week-old pups. Similar to reports in adult rodents, neonatal male mice were more sensitive than neonatal females to the antinoceptive effects of morphine, though again only on the tail withdrawal test. This sex difference was also observed in both day-old and week-old pups. The authors noted that the test-discrepant basal nociception results, though not readily explainable, are characteristic of the adult rodent literature on this topic. I’ll second this, and add that in my own laboratory, sex differences in (and gonadal hormone modulation of) nociceptive baselines may depend on a number of other variables about which we’d all rather not concern ourselves. These include handling/habituation (unpublished data) and perhaps other experimental minutiae that differ from lab to lab, and even within labs from experiment to experiment (yup, like who’s collecting the data). So, although I would certainly like to see another lab attempt to replicate this experiment, the findings are intriguing in that they suggest that sex differences in nociception and opioid antinociception can be demonstrated in very young mice, as early as the first day of life.

Sternberg and colleagues noted two previous studies that suggest that early developmental effects of hormones are responsible for adult sex differences in opioid antinociception (Cicero et al., 2002; Krzanowska et al., 2002). The Cicero and Bodnar labs both demonstrated that neonatal testosterone manipulation on the first day after birth eliminated adult sex differences in morphine antinociception. That is, preventing males from being exposed to testosterone from early in life to adulthood made them considerably less sensitive to morphine as adults—more like females. Conversely, exposing females to testosterone early in life made them considerably more sensitive to morphine as adults—more like males. We have attempted to replicate this finding in my laboratory, with an added twist. Thus far, we have found that early castration indeed makes male rats “female-like” in their adult response to morphine, suggesting that males’ greater morphine sensitivity stems from their early exposure to testosterone. However, when we give adult males that were castrated as neonates a mere two weeks’ exposure to testosterone as adults, the “normal male” phenotype is completely restored. That is, with just a brief exposure to testosterone as adults, males that have been testosterone-deprived from birth to adulthood respond to morphine just like normal males would, males that have been testosterone-exposed during their whole lives. Thus, males castrated as neonates retain their testosterone sensitivity—at least insofar as adult testosterone restores normal morphine potency—and neonatal castration does not actually “change them into females” (females do not typically show increased morphine sensitivity when given testosterone as adults). Rather, whatever masculinizing effects that testosterone has on the nervous system or body that makes males particularly morphine-sensitive appear to occur pre-natally. Our finding therefore corroborates Sternberg and colleagues’ recent paper showing that sex differences in morphine antinociception are already present on the day of birth. To determine exactly how early this sexual differentiation emerges will require manipulation of hormones during the pre-natal period. That study, as we are getting fond of saying in my lab, “will take some grant money.”

Taken together with the human neonatal study described above, these rodent studies indicate that adult sex differences in pain and analgesia very likely do have an “innate, biological basis.” It will be interesting to learn the extent to which, and how, these early sex differences are muted or enhanced by psychosocial and cultural influences.

References:


For those interested in sex differences in pain and pain-related behaviors, a question often asked is “why do such differences exist?” Clearly there are a multitude of possible mechanisms, the number reflecting the multidisciplinary approach to understanding this phenomenon. Such mechanisms are considered important as they not only point to potential theoretical explanations as to why such relationships exist, but in doing so also allow us to consider how best to tackle this issue in practice.

There are a number of methods that allow us to isolate potential mechanisms, although some can be more difficult to apply when dealing with human clinical pain. Fortunately, methods have been developed, originating within the social sciences, that allow us to ascertain the mechanisms by which one variable (e.g., sex) may be related to another (e.g., pain). Rather than go into a detailed description as to how such procedures are performed, I will instead focus on three recent studies that have examined the same potential mechanism for understanding sex differences in pain (Dixon et al., 2004; Edwards et al., 2004; Keogh et al., 2005).

Those interested in understanding how such procedures are conducted, however, are directed to the highly accessible papers by Baron and Kenny (1986) and Holmbeck (1998; 2002) on mediation effects.

The mechanism under investigation in these three studies is a psychological construct known as ‘catastrophizing’ (Sullivan et al., 1995; 2001). For those of you less familiar with this construct, catastrophizing refers to the tendency of engaging in the cognitive process of exaggerated negative rumination and worry. Not only is pain-related catastrophizing related to increased experimental and clinical pain reports, but it also seems to occur more frequently in women than men. Not surprisingly, therefore, catastrophizing has been proposed as a potential mediator of sex differences in pain. Indeed, five years ago Sullivan et al. (2000) and Keefe et al. (2000) showed respectively in healthy volunteers and chronic pain groups that the variance associated with differences between men and women in pain can be accounted for by levels of catastrophizing. More recently, catastrophizing has been examined further, in an attempt to understand the conditions under which this mechanism may occur. As will become apparent, not all is as clear as it may first seem.

The first study was conducted by Edwards et al. (2004). They recruited 198 healthy participants (of which 83 were male), all of whom completed a battery of measures including a measure of catastrophizing. Pain was assessed using two methods: a self-report measure of pain experiences over the past month, and an experimental thermal pain induction task (a smaller subset also completed ischemic pain and cold pressor pain tasks). As expected men reported significantly fewer pain experiences (less bothersome pain, fewer pain sites) and demonstrated a greater tolerance to thermal pain. Men were also found to report a lower use of catastrophizing. Importantly, Edwards et al. (2004) also found that catastrophizing mediated the sex differences in pain experiences. However, when it came to examining the sex differences in thermal pain (or cold pressor pain for that matter), catastrophizing did not serve as a mediator. Thus although catastrophizing was found to mediate some of the sex differences in pain, this study points to the potential fragility of such effects, as well as suggesting that such a mechanism may depend on the nature of the methods used to examine pain.

In a second study, the effect of sex on chronic pain patients’ responses to an interdisciplinary pain management program was investigated. Keogh et al. (2005) assessed 98 chronic pain patients (65 females) at the start of an interdisciplinary pain intervention, at the end of the intervention (2-3 weeks later) and then again 3 months post-intervention. Measures of pain experiences, emotional distress (including catastrophizing, anxiety and depression) and disability were taken. Overall, both males and females showed improvements in pain, emotional distress and disability just after the intervention. Additionally, both groups maintained this improvement on measures of disability, pain-related anxiety and depression. However, sex differences were found with respect to the longer term improvements in pain experiences and pain-related catastrophizing. For both measures, males maintained this improvement 3-months post-intervention, but females did not. Furthermore, change in female pain reports from post-intervention to 3-month follow-up was mediated by changes in catastrophizing. Catastrophizing may, therefore, be important in understanding sex-specific changes in pain reports following an intervention, although this is not necessarily the case for all pain behaviors.

The final study to be considered here is one conducted by Dixon et al. (2004). They used structural equation modeling to examine differences in how men and women respond psychologically and physiologically to cold pressor pain. They recruited 112 females and 91 males and measured blood pressure and cortisol changes to experimental pain tolerance, as well as examining the role of psychological factors such as emotional vulnerability and catastrophizing. The model they examined provided a good fit to the data, with the main findings revealing that psychological factors are important when considering mediators of sex differences in pain. As expected, it was through pain catastrophizing that sex was related to pain tolerance. Additionally, Dixon et al. (2004) sought to determine which factors explained the sex difference in catastrophizing. They found that emotional vulnerability, which is a sex-specific personality characteristic, served as the mechanism by which sex differences in pain-related catastrophizing occurred. Thus the reason why females may be more susceptible to catastrophizing may be due partially to a more general emotional vulnerability factor. This study demonstrates that even mechanisms can have mechanisms!

The papers presented here all investigated the role that catastrophizing may have in explaining sex differences in pain and/or pain-related behaviors. They are important because they all use methods to empirically determine the extent to which this proposed mechanism helps to explain sex differences in pain. Although there is still much to learn regarding potential mechanisms, the use of such techniques to help answer this important question is an issue worthy of future discussion.
The Development of Guidelines for Conducting Research on Sex, Gender and Pain by the IASP Sex, Gender and Pain SIG: Issues to Be Considered.

1. Should the terms “sex” and “gender” be used more discriminatorily?
2. What is the cost vs. benefit of single-sex vs. dual-sex studies? If only females are examined, what information should be collected routinely (e.g., phase of menstrual cycle, age, oral contraceptive use and type)?
3. What is the best way to analyze group data so that potential sex differences will not be lost?
4. What are the best ways to determine reproductive cycles in subjects?
   a. Is it always important to test at different stages of the cycle?
   b. What times during the cycle are of greatest interest and why?
   c. Should non-cycling or irregularly cycling subjects be excluded?
   d. Is it always necessary to document hormonal cycles via blood or other physical samples? What are the most efficient, reliable, cost-effective ways to do this?
   e. How should the designations “pre-estrus, estrus, metestrus, diestrus” and “menstrual, follicular, ovulatory, luteal” be defined?
5. What are the advantages and limitations of using gonadectomy to examine the role of gonadal steroids in pain and analgesia?
6. How should replacement hormones be administered? (How can different hormone replacement regimens affect conclusions about the role of gonadal steroid hormones in pain and analgesia?)
7. In what ways is it important to take subject age into account in studies of sex differences in pain and analgesia?
   a. On what basis should experimental subjects be classified as “child” vs. “adult” (or neonate vs. sub-adult vs. adult, etc.)? How shall puberty be defined?
   b. On what basis should experimental subjects be classified as “post-menopausal” (“post-estrus”)?
8. How should the possible effects of experimenter sex/gender be dealt with?
9. How should the possible effects of the environment (psychosocial context) be investigated?
10. Choice of pain test:
    a. Should multiple tests be used? (e.g., does modality of the noxious stimulus matter?)
    b. Are there certain parameters of pain testing that should be included whenever possible? (e.g., pain threshold and tolerance? multiple intensities of pain?)
    c. Do some pain tests in animals have better predictive validity than others? (i.e., how do we better bridge the gap between preclinical and clinical research?)
11. In what ways can sex differences in factors such as body weight, body composition, activity level, stress-reactivity, anxiety, depression, etc., contribute to sex differences in pain and analgesia?
12. In what ways can sex differences in side-effects of analgesic drugs contribute to sex differences in their analgesic effects?
13. Are circadian (and circannual?) influences on pain and analgesia important to take into account?
14. What patient groups should be studied, and how does the choice of patient group influence the conclusions that can be drawn (e.g., is one sex disproportionately represented in some patient groups)?
15. How should the variables of clinical pain history, clinical pain type (e.g., reproductive vs. non-reproductive), and reproductive history (e.g., parity) be taken into account?
16. Is there enough evidence to warrant sex-specific pain interventions?