The hormonal modulation of pain

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Factors relevant to sex differences

<p>| Table 1. Factors decidedly or likely relevant to sex differences in experimental studies of human pain |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Context</th>
<th>Individual</th>
<th>Response measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morality</td>
<td>Threatability</td>
<td>History</td>
<td>Threshold</td>
</tr>
<tr>
<td>Location</td>
<td>Stress</td>
<td>Age</td>
<td>Tolerance</td>
</tr>
<tr>
<td>Timing</td>
<td>Time attending</td>
<td>Coping</td>
<td>Suprathreshold scaling</td>
</tr>
<tr>
<td>Neuromodulator gender</td>
<td>Genetic background</td>
<td></td>
<td>Stimulus discrimination</td>
</tr>
<tr>
<td>Phasing</td>
<td>Congruency</td>
<td>Sex authenticity</td>
<td>Reflex</td>
</tr>
<tr>
<td>Sleep history</td>
<td>Hormonal status</td>
<td></td>
<td>Imaging</td>
</tr>
<tr>
<td>Co-stimulation</td>
<td>Anxiety (trait and state)</td>
<td></td>
<td>Cardiovascular system</td>
</tr>
<tr>
<td>Context, sound, etc.</td>
<td>Reproductive status (female)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social environment</td>
<td>Communication (extent and style)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Attention</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Expectation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mood state</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Greenspan et al., Pain 2007
Overview

Brief introductory to gonadal steroid hormones

Are sex differences in pain mediated by gonadal hormones?

What mechanisms may be involved?

Do hormones also influence analgesic drug responses?

Future directions

Gonadal steroid hormones

Hormones produced by ovaries and testes are referred to as gonadal steroids

Gonadal steroid hormones:

• Estrogens: e.g., estradiol
• Progestins: e.g., progesterone
• Androgens: e.g., testosterone (precursor of estradiol)

Important for primary and secondary sex characteristics

Early-life sexual differentiation:

• Testosterone exposure during critical period of neuronal development: development of masculine patterns
• Low testosterone levels: development of feminine patterns
Gonadal steroid hormones

**Females**
- LH stimulates progesteron synthesis
- FSH stimulates estrogen synthesis

**Males**
- LH stimulates testosterone production
- FSH stimulates sperm maturation

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**Humans**

<table>
<thead>
<tr>
<th>Estradiol (pg/ml)</th>
<th>Progestrone (ng/ml)</th>
<th>LH (mIU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Graph A" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- ~ 28 day cycle (range 25-35)

**Rats**

<table>
<thead>
<tr>
<th>Estradiol (pg/ml)</th>
<th>Progestrone (ng/ml)</th>
<th>LH (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Graph B" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- ~ 4-5 day cycle

Becker et al., Endocrinology 2005
How can we examine hormonal modulation of pain?

• Examine different stages of reproductive cycle

• Examine different stages of menstrual cycle. Self-reports of menstrual cycle effects are often unreliable. Important to take temperature, test for ovulation and determine blood serum concentrations

• Endocrine ablation (gonadectomy in animals) + add on hormone replacement therapy with steroids that are within the physiological range

Are sex differences in pain mediated by gonadal steroid hormones?

What are the effects of varying hormone levels across the menstrual cycle on experimental pain sensations?
Are sex differences in pain mediated by gonadal steroid hormones?

Meta-analysis of 16 studies on perception of experimentally induced pain across menstrual cycle phases of healthy females:

For pressure stimulation, cold pressor pain, thermal heat stimulation, and ischemic muscle pain, higher pain thresholds and tolerance to pain are found in the follicular phase than the luteal phase.

Electrical stimulation was different than the other stimulus modalities, showing the highest thresholds for the luteal phase.
Are sex differences in pain mediated by gonadal steroid hormones?

Pressure pain

Sherman and LeResche, Am J Physiol Regul Integr Comp Physiol 2006

Ischemic pain

Sherman and LeResche, Am J Physiol Regul Integr Comp Physiol 2006
Are sex differences in pain mediated by gonadal steroid hormones?

Menstrual cycle effects on experimental pain are observed, but inconsistently.

Differences are relatively minor, and differ for stimulation type.

Logistic difficulties in getting subjects in at the right time, defining cycle phases, or hormonal variability across the cycle may contribute to inconsistencies.

- > Clinical pain and the menstrual cycle?
Are sex differences in pain mediated by gonadal steroid hormones?

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Reported effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Migraine headache</td>
<td>Migraine increases at end of luteal phase compared with other phases</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>Intensity of pain associated with TMD increases at end of luteal phase</td>
</tr>
<tr>
<td>Chronic low back pain</td>
<td>Pain increased in luteal and menstrual phase</td>
</tr>
</tbody>
</table>

Kuda et al., Brain Res Bull 2005

Prevalence of pain syndromes during the reproductive stages

More prevalent in cycling than postmenopausal women:
- joint pain
- chronic widespread pain
- fibromyalgia

More prevalent in perimenopausal and postmenopausal women than premenopausal women:
- burning mouth syndrome
- atypical facial pain
- atypical odontalgia

Kuda et al., Brain Res Bull 2005
Are sex differences in pain mediated by gonadal steroid hormones?

**Hormone replacement therapy**

In general, women receiving hormone replacement therapy have increased incidence of pain as compared with postmenopausal women who are not using hormone replacement therapy.

LeResche et al., *Pain* 2003

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**Pregnancy**

Pain thresholds and symptoms appear to improve over the course of pregnancy and will increase again postpartum.

During pregnancy both progesterone and estradiol rise continuously, among other hormonal changes.

LeResche et al., *J Orofacial Pain* 2005; Bajaj et al., *Pain* 2002
Are sex differences in pain mediated by gonadal steroid hormones?

Nothing compares to labor pain?

No effects were found on tolerance values of subjective pain ratings

Pain thresholds for cold pressor test were higher for women with child bearing experience

Hapidou and DeCatanzaro, Pain 1992

Are sex differences in pain mediated by gonadal steroid hormones?

Hormonal modulation of pain seems to occur in both experimental pain and in clinical pain syndromes

Estradiol seems mainly pro-nociceptive, but anti-nociceptive effects may also occur, depending on the pain disorder and experimental pain modality

At the least, reproductive stage and menstrual cycle effects need to be taken into account in studies on sex differences
What mechanisms may be involved?

Pain modulation by gonadal steroid hormones is very complex.

Gonadal hormone receptors are distributed both peripherally and centrally and may directly affect pain pathways or indirectly by acting on other pathways.
What mechanisms may be involved?

Progesterone versus estradiol? First insights

Do hormones also influence analgesic drug responses?

- Should pain management be targeted differently for females and males?
- More specifically...should hormonal factors during the female reproductive cycle be taken into account?
Do hormones also influence analgesic drug responses?

Are there sex differences in efficacy of analgesics?

<table>
<thead>
<tr>
<th>Species</th>
<th>M &gt; F</th>
<th>M = F</th>
<th>F &gt; M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat*</td>
<td>35 (66%)</td>
<td>16 (30%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Mouse</td>
<td>7 (33%)</td>
<td>13 (62%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Rhesus Monkey</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Human</td>
<td>0 (0%)</td>
<td>4 (29%)</td>
<td>10 (71%)</td>
</tr>
</tbody>
</table>

*Approximately 60% of sample is the Sprague-Dawley strain; 57% of sample is from two laboratories.

Craft, Clin J Pain 2003

Do hormones also influence analgesic drug responses?

Is analgesic efficacy influenced by hormonal variations?

Great deal of variability. Current hypotheses:

- Testosterone may enhance opioid potency in male rodents

- Opioids in intact cycling female rodents are least effective in estrus stage compared to other stages

- Estradiol, and not progesterone, is probably responsible for cycle-related changes in opioid analgesia

Craft et al., Eur J Pain 2004
Do hormones also influence analgesic drug responses?

Differences in mu-opioid receptor activation induced antinociception between cycles: microinjection of morphine in the ventral periaqueductal grey

Sex differences in opioid receptor binding

Females in low estradiol state had significantly lower opioid system activation in several brain areas compared to high estradiol state

Decreased opioid activation correlated with higher pain ratings & estrogen variations
Future directions

Our overall goals

• Determine which mechanisms contribute to higher prevalence of pain in females in many syndromes

• Discover how sex-specific mechanisms of pain/analgesia can improve pain management

Possible directions

• Improve study methodology: consensus report and guidelines as established in Greenspan et al., Pain 2007

• Examining whether (anti-)estrogen compounds may be used as therapy in treating chronic pain conditions that are influenced by hormonal variations

• Examine genetic contributions to sex differences (sex chromosome)

• What are the cellular and molecular bases of hormonal modulation of pain?
Thank you

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