Hormonal Modulation of Pain: Estrogen Modulation of Visceral Nociception

Victor Chaban, Ph.D., MSCR

Department of Internal Medicine
Charles R. Drew University of Medicine and Science
Department of Medicine
David Geffen School of Medicine
University of California, Los Angeles
Background

The brain is one of the specific target tissues for sex steroid hormones. Estrogens, progestins and androgens are able to induce several effects in brain areas of the central and peripheral nervous system, through the binding with specific receptors. It has recently been demonstrated that the spinal cord is an active production center of neuroactive steroids including pregnenolone, dehydroepiandrosterone, progesterone, allopregnanolone and estrogen.

General Hypothesis:

Steroid hormones may be involved in the modulation of nociceptive mechanisms
Clinical Relevance:

Functional- disorders for which no pathophysiological cause can be identified?

Visceral pain-associated functional syndromes
- Irritable bowel syndrome (IBS)
- Interstitial cystitis (IC) a.k.a Painful Bladder Syndrome (IC/PBS)
- Chronic pelvic pain (CPP)

IBS estimated to affect 25% of the population in many countries and accounts for 40-50% of GI consultations worldwide. Symptoms description of IC/PBS (urgency, frequency, and bladder pain generally relieved by voiding) is parallel to the description of IBS-diarrhea predominance (urgency, frequency, and abdominal pain relieved by defecation)

Chronic pelvic pain (CPP) covers a wide range of reproductive disorders including dysmenorrhea, endometriosis, and pelvic congestion as well as bowel (IBS) and urinary tract problems (such as IC/PBS)

Incidence of episodic or persistent visceral pain associated with functional disorders is 2-3x higher (IBS) or even more (IC/PBS) in women than men

**Hypothesis 1:** *Estradiol modulates nociceptive signaling associated with pelvic pain*
The Estrogen Trinity: Membrane, Cytosolic, and Nuclear Effects

- **Membrane Receptor** interacts with Estrogen, leading to an Ion Channel.
- **Intracellular Messenger** activates a Kinase, which phosphorylates Target Proteins.
- **ER α/β** binds to CAEB, regulating Target Genes.

### Alternative Effects
- ER interacts with Target Proteins, affecting various cellular processes.

### Direct Nuclear Action
- ERα/β directly binds to DNA, activating or repressing gene expression.

This diagram outlines the complex interactions of estrogen at different cellular levels, showcasing its diverse effects on cell function.
Alternative mechanisms of action of estrogens:

- The rapid time course of the primary effect is too fast to be compatible with RNA synthesis or protein translation (seconds to minutes)

- Dependence (or independence) on the presence of classic ERs (inhibition of the effect by ICI-182780)

- The extracellular membrane-delimited primary effect might be achieved by estrogen conjugated to membrane-impermeant molecules (E-6-BSA)
Activation and Sensitization of Primary Afferents

**Activation**

- P2X
- VGCC
- ER
- Acid
- Mechanical
- Chemical

**Pain and Auto-sensation**

- Voltage gated sodium channels

**Generator potentials**

**Action potentials**

---

Ligand-gated Ion Channels

Voltage gated

Ca^{++}

Na^{+}

Ligand gated

P2X

Acid Capsaicin Heat

VR1

Ca^{++}

Na^{+}
Voltage-gated Ion Channels

Neurotransmitter release

Efferent Function

Afferent Function

Voltage-gated

Na⁺, K⁺, Ca²⁺
G-protein Coupled Receptors

PGE$_2$ increases excitability

Decrease excitability

MOR

AC

PLC

Ca$^{++}$

K$^+$

Na$^+$

Voltage gated

Ligand gated

Acid Capsaicin Heat

Gi$\alpha$

Gi$\beta\gamma$

VGCC (N, P/Q)

cAMP

IP$_3$

PKC

PKA

VR1
Previous findings:

17β-Estradiol inhibits ATP-induced $[\text{Ca}^{2+}]_i$ influx in DRG neurons

17β- Estradiol attenuates the ability of opioids to inhibit ATP-induced $[\text{Ca}^{2+}]_i$ response

17-β Estradiol attenuates the inhibition of PGE$_2$-induced $[\text{cAMP}]_i$ production in cultured DRG neurons mediated through MOP
ESTRADIOL INHIBITS ATP-INCREASED [Ca^{2+}]_i IN DRG NEURONS

Chaban et al. Neuroscience 118., 2003

Tissue Damage

ATP

P2X

VGCC

ER

Pain
Estradiol do not inhibit ATP-induced [Ca^{2+}]_i in ERαKO mice

RT-PCR analysis of estrogen receptor (ER)α & ERβ gene expression. Samples without reverse transcriptase (RT-) have no amplicon. Lane M: DNA size-marker.

Chaban & Micevych, 2005
Pharmacological profile of estradiol-modulated ATP-induced $[\text{Ca}^{2+}]_i$ increase in Wt mice

Chaban & Micevych, 2005
17β-estradiol inhibits ATP-induced [Ca$^{2+}$]$\text{i}$ response in small DRG neurons from Wt and ERβKO mice

The effect on the pharmacology of an ER:
- $E_2$ effect is stereo-specific since 17α-estradiol had no effect
- $E_2$ effect is steroid-specific- blocked by ICI 182780.

Mediated via membrane-associated ERα
- E-6-BSA mimics the effect of $E_2$ in Wt mice
- $E_2$ did not attenuate ATP-induced [Ca$^{2+}$]$\text{i}$ flux in DRG neurons from ERαKO mouse
Proposed mechanisms of visceral nociception modulation

ATP released by tissue damage acts on P2X3 that activate VGCC - signaling nociception. 17-E₂ modulates L-type VGCC in DRG neurons via the direct interaction of a membrane ERα with the mGluR₂/₃ inhibiting adenylyl cyclase (AC) activation of L-type VGCC

(Chaban et al. American Journal of Translational Research, 2013)
Hypothesis II:  
*Primary afferent neurons as site of convergence for different pelvic organs (In vivo studies):*

Communication between somatic and visceral organ systems has been demonstrated. Unclear where systems converge  
**DRG may be a site for viscero-visceral cross-sensitization**

**Methods:**
Retrograde labeling of DRG neurons innervating uterus /colon or hind paw by retrograde tracers determined modulation of intracellular calcium influx induced by ATP (P2XR- agonist) or α,β- me ATP (P2X3R agonist) in visceral and cutaneous primary sensory neurons.
A subset of DRG neurons innervate both visceral organs: uterus and colon

Chaban et al., Neuroreport, 2007

Conclusions

Estrogen down-regulates intracellular signaling associated with nociception and decreases anti-nociceptive opioid signaling in primary afferent sensory neurons. Thus, depending on the presence or absence of opioid receptor agonists, estrogen can be either anti-nociceptive or pro-nociceptive (Chaban et al., 2004-2014).

Estrogen differently acts on visceral and cutaneous sensory neurons.

Gonadal hormones are necessary for reproduction, but it appears that no body region, no neuronal circuit, and virtually no cell is unaffected by them. Thus, increased attention toward these hormones appears to be obligatory.

Supported by NIH grant NS063939