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Mini-Review

# Estrogen modulation of visceral nociceptors

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## ABSTRACT

A large body of literature supports the idea that estrogen modulates nociceptive responses in pelvic pain syndromes; however, whether this hormone is pro- or anti-nociceptive remains unresolved. The dorsal root ganglion (DRG) is an important site of visceral afferent convergence and cross-sensitization. Within the context of our hypothesis visceral nociception and nociceptor sensitization appear to be regulated by purinergic $P2X_3$ and vanilloid TRPV1 receptors and 17β-estradiol modulates DRG neuron response to ATP (P2X agonist) and capsaicin (TRPV1 agonist) suggesting that visceral afferent nociceptors are modulated by estrogen in the DRG. 17-β estradiol (E2), the most common form of estrogen, acts on functional properties of $P2X_3$ and TRPV1 receptors in DRG neurons *in vitro*. The localization of estrogen receptors (ER) in DRG neurons and the attenuation of ATP/capsaicin-induced intracellular calcium concentration $[Ca^{2+}]_i$ strongly suggest that E2 modulates visceral pain processing peripherally. Moreover, E2 appears to have different actions on nociceptive signaling depending on the input. Based on our data we propose that E2 can gate primary afferent response to increase or decrease nociception.

**KEYWORDS:** DRG, calcium, P2X, TRPV1

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## INTRODUCTION

In women, pain symptoms and nociceptive thresholds vary with reproductive cycle and our previous data strongly suggest the role of estrogen receptors in modulating nociceptive signaling [1-3]. 17β-estradiol (E2), the most potent estrogen of a group of endogenous estrogen steroids may be a causative factor inducing inflammation that contribute to the observed sex difference in visceral pain associated with functional pain syndromes. Most of the current literature pertains to specific functional syndromes defined by medical subspecialties. These include: irritable bowel syndrome: IBS (gastroenterology); chronic pelvic pain: CPP (gynecology); interstitial cystitis/painful bladder syndrome: IC/PBS (urology); fibromyalgia (rheumatology) and others. Many reports have described substantial overlaps between two or more of these syndromes [4-5]. Moreover, clinical presentations of functional syndromes lack a specific pathology in the affected organ but may respond to a viscero-visceral cross-sensitization in which increased nociceptive input from an inflamed organ (i.e., uterus) sensitizes neurons that receive convergent input from an unaffected organ (i.e., colon or bladder). The site of visceral cross-sensitivity is unknown. Recent data from our laboratory and others showed that viscero-visceral cross-sensitization occurs in the dorsal root ganglion (DRG) where it is modulated by E2. Nociceptive transmitter ATP release within sensory ganglia [6] suggests a site and mechanism for cross-sensitization, but depending on the prevailing conditions, E2 can have anti-nociceptive or pro-nociceptive actions.

The incidence of episodic or persistent visceral functional pain disorders such as IBS, IC/PBS, are

2-3 times more prevalent in women than men [7-10]. Pain symptoms and pain perception may vary across the menstrual cycle [11]. Moreover, sexual intercourse triggers symptoms in a large percentage of female IBS patients suggesting the involvement of sex steroids in the reproductive tract [7, 11]. Our hypothesis is that E2 modulation of cross-sensitization of visceral inputs in the DRG accounts for the observed changes in pain perception and symptoms in functional pain syndromes. E2 attenuation of ATP/capsaicin-induced $[Ca^{2+}]_i$ response, and decreased expression of P2X3 and TRPV1 receptors in estrogen receptor-α knockout (ERαKO) and estrogen receptor-β (ERβKO) knockout mice [3] strongly suggest that E2 modulates pain processing peripherally. Moreover, E2 appears to have different actions on nociceptive signaling depending on the input.

**Transduction of nociceptive signals**

The cell bodies of primary visceral spinal afferent neurons are located in the lumbosacral (L1-S1) DRGs that transmit information about chemical or mechanical stimulation from the periphery to the spinal cord. Nociceptors are small to medium size DRG neurons whose peripheral processes detect potentially damaging physical and chemical stimuli. ATP and capsaicin have emerged as putative signals for visceral pain. ATP is released by distention of the viscera and tissue damage (for review see [12-13]). Visceral nociceptive capsaicin-sensitive C-fibers are activated by ATP and excitatory amino acids that are released by noxious stimuli from cells in target organs (paracrine action), from afferent terminals themselves (autocrine action [14], or in sensory ganglia [6, 15]). In our studies we observed that DRG neurons innervating viscera have a greater $[Ca^{2+}]_i$ response to subsequent ATP and capsaicin and NMDA stimulation than somatic afferents [16]. These observations indicate that viscerally-specific neurons express receptors with higher permeability to $Ca^{2+}$, which can modulate transduction of nociceptive signals and suggest that *visceral* afferents are functionally different from *somatic* afferents (Figure 1). Sensitization of primary afferent neurons may play a role in the enhanced perception of visceral sensation leading to pain. Endometriosis, acute and recurrent/chronic pelvic pain in women or abdominal pain from IBS are all visceral pain sensations that may result in part from sensitization [17-18]. Mechanisms of peripheral sensitization may involve an increase in the excitability of the afferent nerves by molecules that decrease the excitation threshold [19]. Sensitization can develop in response to inflammation. Phosphorylation-dependent modulation of the vanilloid receptor TRPV1 is one of the key mechanisms mediating the hyperalgesic effects of inflammatory mediators, such as prostaglandin E2 (PGE2) in mouse sensory neurons [20]. Significantly, inflammation dramatically alters TRPV 1 receptor-mediated transduction and purinoception by causing a several fold increase in ATP-activated currents, and enhances the expression of P2X receptors increasing neuronal hypersensitivity [21].

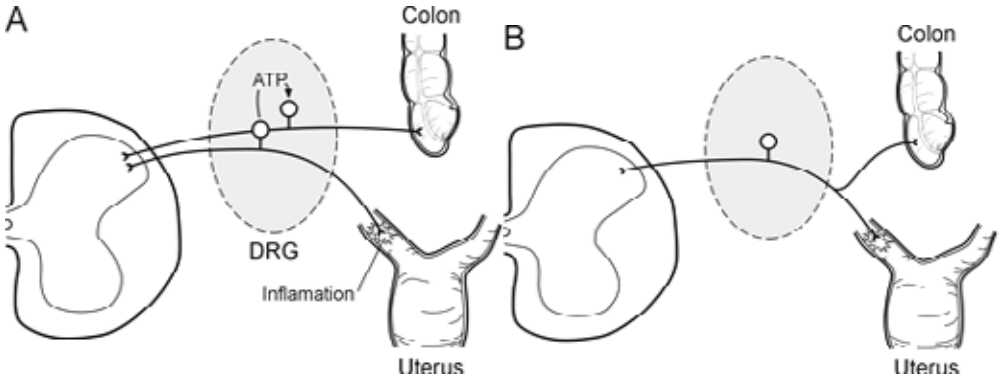


**Figure 1.** Non exclusive models of two possibilities for viscero-visceral cross-sensitization in the DRG. In (A), ATP released by a neuron innervating the inflamed uterus acts on a neighboring neuron sensitizing its responses to colonic distention. In (B), the same neuron innervates the uterus and colon. Uterus inflammation directly sensitize the neuron to colonic distention.

**Inflammatory activation of DRG neurons**

Number of molecules and neurotrophic factors are involved in hyperalgesia and overall sensory neuron sensitization [22]. The inflammatory process produces mediators which activate nociceptors by interacting with ligand-gated ion channels or by sensitizing primary afferents [23]. One mechanism for sensitization involves phosphorylation of ion channels and receptors including P2X3 and TRPV1 receptors. Inflammation does not change the percentage of total cells responding to ATP but sensitizes the ATP response by increasing the expression of P2X3 [21]. Thus, the greater behavioral sensitivity during the inflammation is due to a twofold to threefold increase in ATP responses suggesting that a small amount of ATP would evoke depolarization sufficient to elicit action potentials in DRG neurons [21]. This pathological response arises from sensitization of DRG to external stimuli [21]. Furthermore, inflamed tissues augment nociceptor responsiveness by acting on TRPV1 [24]. Gastrointestinal inflammation modulates the intrinsic properties of nociceptive dorsal root ganglia neurons, which innervate the GI tract and these changes are important in the genesis of abdominal pain and visceral hyperalgesia. Neurons exhibit hyperexcitability characterized by a decreased threshold for activation and increased firing rate [25]. Inflammation upregulates the activity of N-methyl-D-aspartate receptors (NMDARs) in all DRG neurons within ganglia innervating viscera [26]. Sensitization may also account for a lowered nociceptive threshold to mechanical manipulation of the inflamed area. Within the context of our cross-sensitization hypothesis, inflammation sensitizes non-inflamed viscera that are innervated by the same DRG and/or cross-sensitization occurs as a result of intra-DRG release of sensitizing mediators such as ATP within the DRG.

**Peripheral E2 modulation of nociception**

Several lines of evidence indicate that E2 directly influence the functions of primary afferent neurons. Both subtypes of estrogen receptors (ERα and ERβ) are present in DRG neurons including the small-diameter putative nociceptors [27]. *In vitro*, ATP-sensitive DRG neurons respond to E2 [2-3], which correlated well with the idea that visceral afferents are E2 sensitive: i) visceral pain is affected by hormonal level in cycling females [28]; ii) there are sex differences in the prevalence of functional disorders involving the viscera [7, 29]; and iii) putative visceral afferents [16] fit into the population of DRG neurons that are sensitive to E2 [3]. These data suggest that in addition to CNS actions of E2 [30-31], E2 can act in the periphery to modulate nociception [1] (Figure 2).

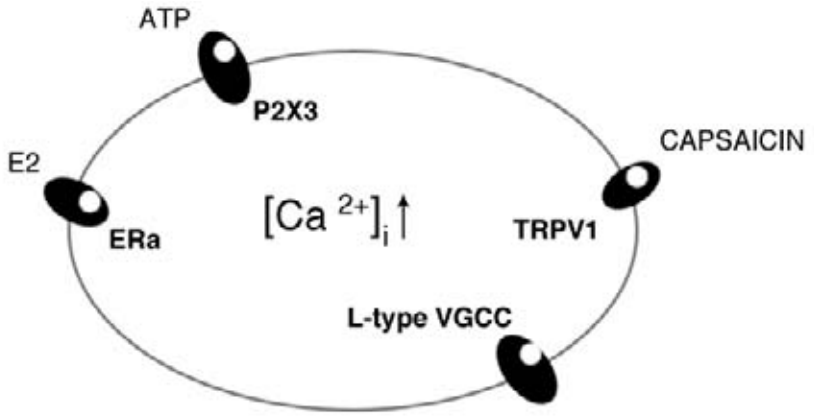


**Figure 2.** Proposed mechanism of 17-βestradiol (E2) effect on ATP-induced $[Ca^{2+}]_i$ signaling in primary sensory neurons. ATP released by tissue damage acts on $P2X_3$ receptor resulting in activation of the L-type voltage-gated calcium channel (VGCC). ERα modulates ATP-induced P2X3- mediated as well as capsaicin-induced TRPV1-mediated $[Ca^{2+}]_i$ increases.

ERα/ERβ receptors were traditionally envisioned as E2-activated transcription factors. However, more recent studies indicate that E2 has a multiplicity of actions: membrane, cytoplasmic and nuclear (reviewed in [1, 32]). E2 modulates cellular activity by altering ion channel opening, G-protein signaling, and activation of trophic factor-like signal transduction pathways. These effects have been ascribed to membrane-associated receptors [33]. Moreover, estrogen receptors (ERs) are distributed in regions of the central and peripheral nervous system that mediate nociception. For example, ERs are expressed in dorsal horn neurons of the spinal cord and DRG neurons [27, 34]. Results from our laboratory and others indicate that E2 acts in DRG neurons to modulate L-type voltage-gated calcium channels (VGCC) [35-36] and through group II metabotropic glutamate receptors [2]. E2 has a significant role in modulating visceral sensitivity, indicating that E2 alterations in sensory processing may underlie sex-based differences in functional pain symptoms [37]. However, reports of E2 modulation of visceral and somatic nociceptive sensitivity are inconsistent. For example, elevated E2 levels have been reported to increase the threshold to cutaneous stimuli but decrease the percentage of escape responses to ureteral calculosis [38]. However, nociceptive sensitivity appears to increase when E2 levels are elevated [39-40]. Indeed in most clinical studies, women report more severe pain levels, more frequent pain and longer duration of pain than men [9].

### Significance and discussion

Little is known about E2-mediated mechanisms in peripheral nervous system, but the fact that DRG neurons express ERs and respond to E2 treatment suggest that they are a potential target for mediating nociception. From a public health prospective, the outcome of this study will have a substantial impact on our knowledge of nociceptive functional diseases and help achieve a deeper understanding of gender differences presented in clinical aspects of these symptoms. Only a thorough understanding of the mechanism implicated in these phenomena can truly contribute to the designing of new and more efficient therapies. Many illnesses affect women and men differently. Some disorders are more common in women, and some express themselves with different symptoms. Many studies confirmed that differences between the sexes exist in the prevalence and severity of a broad range of diseases, disorders and conditions. In the United States, pain accounts for nearly 20% of all primary health care visits. Proposed studies address a crucial question in women's health. Reaching further than the concrete basic science contribution, this project is a liaison between the basic science work and the clinical aspects that are addressed through other disciplines such as anesthesiology (pain management), gastroenterology and OB&GYN.

## CONCLUSION

In summary, a large body of literature supports the idea that E2 modulates nociceptive responses in pelvic pain syndromes; however, this mechanism remains unresolved. Within the context of our hypothesis E2 modulation of nociceptive response depends on the type of pain, its durations and the involvement of other nociceptive-mediated mechanisms. Visceral nociception appears to be regulated by ATP/capsaicin and E2 in the periphery at the level of DRG. The DRG is an important site of visceral afferent convergence and cross-sensitization.

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## CONFLICT OF INTEREST STATEMENT

There is no conflict of interest to disclose for this manuscript.

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