Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.jzus.zju.edu.cn; www.springerlink.com
E-mail: jzus@zju.edu.cn

Review:

Estrogen modulation of visceral pain*

Li-hong SUN, Wen-xin ZHANG, Qi XU, Hui WU, Cui-cui JIAO, Xin-zhong CHEN†‡

Department of Anesthesiology, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou 310006, China

†E-mail: chenxinz@zju.edu.cn

Received Nov. 18, 2018; Revision accepted Mar. 21, 2019; Crosschecked June 13, 2019

Abstract: It is commonly accepted that females and males differ in their experience of pain. Gender differences have been found in the prevalence and severity of pain in both clinical and animal studies. Sex-related hormones are found to be involved in pain transmission and have critical effects on visceral pain sensitivity. Studies have pointed out the idea that serum estrogen is closely related to visceral nociceptive sensitivity. This review aims to summarize the literature relating to the role of estrogen in modulating visceral pain with emphasis on deciphering the potential central and peripheral mechanisms.

Key words: Estrogen; Visceral pain; Hyperalgesia; Ovariectomization
https://doi.org/10.1631/jzus.B1800582 **CLC number:** R741

1 Introduction

Visceral pain, commonly known as a prominent symptom of many clinical diseases, is one of the most frequent reasons for patients seeking medical intervention (Malykhina, 2007). Being characterized as diffuse and poorly localized, and often referring to a superficial and remote location in the body, visceral pain is different from somatic pain (Cervero and Laird, 1999). The fundamental neurobiological mechanism underlying the pathophysiology of visceral pain is not fully understood. A growing number of studies have suggested that women tend to show lower thresholds and less tolerance to some nociceptive functional diseases, such as irritable bowel syndrome (IBS), interstitial cystitis, and chronic pelvic pain (CPP) (Riley et al., 1998; Aloisi and Bonifazi, 2006). Furthermore, it has been reported that symptoms and pain perception fluctuate with the menstrual cycle (Ji et al., 2008). Given the existence of sex differences and the variation of symptoms across the estrous cycle, it is highly possible that gonadal hormones are involved in modulation of pain signal processing. Therefore, attention has shifted to investigating the mechanisms underlying the modulation of visceral pain by gonadal hormones (Aloisi and Bonifazi, 2006; Traub et al., 2014). Estrogen is a type of steroid hormone, like progestins and androgens. Estradiol (E2), progesterone, and testosterone are examples of such hormones in circulation (Heitkemper and Jarrett, 2001; Sherman and LeResche, 2006). Estrogens exert function on body systems by binding to specific estrogen receptors (ERs).

The ERs include classical ERs (ERα and ERβ), and extranuclear receptors (G protein-coupled ER (GPER), membrane ER (mER)-Gαq, ERαΔ4, and ER-X). It is envisaged that ERs engage in integrated action, travelling dynamically among membrane, cytoplasm, and nuclei, regulating both upstream nongenomic cascades and the downstream genomic responses (Marino et al., 2006). Early research found that ERα and ERβ acted as nuclear transcription factors mediating protein synthesis and DNA transcription. Apart from these "classical mechanisms," it was later discovered that ERα and ERβ can also be

‡ Corresponding author
* Project supported by the National Natural Science Foundation of China (No. 81471126)
ORCID: Li-hong SUN, https://orcid.org/0000-0003-1726-059X
© Zhejiang University and Springer-Verlag GmbH Germany, part of Springer Nature 2019

trafficked to the plasma membrane and activate the metabotropic glutamate receptors (mGluRs), initiating membrane-associated intracellular signaling pathways (Micevych et al., 2007; Sinchak and Wagner, 2012; Rudolph et al., 2016). The extranuclear ERs are localized in the membrane, including plasma and endoplasmic reticulum, and are involved in mediating activation of various protein-kinase cascades. They can also be translocated into the nucleus to modulate genomic mechanisms (Eyster, 2016; Li et al., 2016). Given the abundant distribution of ERs in the central nervous system and visceral organs, their involvement in visceral pain regulation is anatomically possible. Indeed, Pfaffl et al. (2003) later demonstrated that estrogens account for sex differences in the incidence rate and the pathomechanisms of many kinds of visceral pain. For instance, the incidence of IBS in females changes with the age-related variation in estrogen levels, while the prevalence of IBS in males hardly changes with age (Garcia Rodriguez et al., 2000). Estrogen is reported to modulate visceral pain by enhancing neuronal activities or regulating neuronal plasticity processes at the level of the peripheral nervous system, spinal cord, and supraspinal nervous system (Vanderhorst et al., 2002; Shibuya et al., 2003; Ter Horst et al., 2009).

2 Peripheral modulation of visceral pain processing by estrogen

The dorsal root ganglion (DRG) is a crucial site of the convergence of afferents innervating visceral organs. Alteration of signal transduction in DRG neurons results in an enhanced or weakened perception of visceral pain sensation. Many studies have reported that estrogen modulates sensory inputs at the primary afferent level (Papka and Storey-Workley, 2002; Rowan et al., 2014; Chaban, 2015). ERs are widely spread throughout the body, including primary afferent neurons, the central nervous system, and some visceral organs, such as the gastrointestinal tract and reproductive organs. Thus, they provide an anatomical basis for potential target sites of estrogen action on the transmission and projection of visceral sensory neurons (Campbell-Thompson et al., 2001; Pfaffl et al., 2003). IBS usually causes diarrhea and recurrent abdominal pain, and is a common visceral pain disease (Bokic et al., 2015). Activated by 17-β-estradiol, which is a commonly used potent endogenous estrogen, ERs have been found to modulate colonic motility and exert anti-inflammatory and analgesic effects in an IBS-induced visceral pain model in mice (Zielińska et al., 2017). Both ERα and ERβ participate in conducting nociceptive information at a peripheral level, especially in small-diameter DRG neurons. It has been reported that activation of GPERs could trigger the production of neuron-derived nitric oxide (NO), which is strongly implicated in regulating gastrointestinal motility by acting as an inhibitory neurotransmitter (Lefebvre, 1995). The expression of NO in the gut is greatly upregulated in patients with inflammatory intestinal disorders, such as IBS, inflammatory bowel disease (IBD), and celiac disease. The GPER agonist G-1 stimulates NO production in cultured myenteric neurons, via a process dependent on increased expression of neuronal nitric oxide synthase (nNOS). Furthermore, immunofluorescence labeling has shown that GPER is co-expressed with nNOS in the myenteric plexus (Reinders et al., 2005; Li et al., 2016). These findings indicate that estrogens influence gastrointestinal motility and mediate abdominal pain potentially by regulating NO levels in the enteric nervous system (Reinders et al., 2005).

Estrogen alters signal transduction and cellular activity by regulating the response of neurons to nociceptive receptors and ion channels (Chaban, 2012; Pan et al., 2016). The transient receptor potential ion channel (TRPV) and purinergic receptors (P2X2R and P2X3R) are known to participate in visceral nociceptive integration (Basbaum, 2009). Sensitization of visceral nociceptors is one of the neuronal mechanisms accounting for primary hyperalgesia (Cervero and Laird, 1999). For example, in a visceral pain model induced by bladder distension, exogenous application of capsaicin increased intracellular Ca^{2+} and evoked NO release. This process required the activation of TRPV1 receptors (TRPV1Rs), which were highly expressed in the mucosa and muscle of the bladder (Birder et al., 2002). The action potentials in DRG neurons initiated by painful stimuli can be mediated by TRPV1 and P2X3. The P2X3 activator, adenosine 5-triphosphate (ATP), is known as one of the most common bioactive compounds in the body. In the transduction of noxious stimuli, ATP released

by tissue damage activates purinergic P2X receptors on visceral nociceptive C-fibers (Dunn et al., 2001). Estrogen inhibits the response of DRG neurons to ATP (an activator of P2X3R) and capsaicin (a TRPV1R agonist). This process may be mediated by interaction of the membrane-associated ERα and the mGluR in DRG neurons (Chaban, 2012). Another mechanism proposed for estrogen's role in encoding nociception is that it inhibits the L or N type high-voltage activated calcium channels expressed on primary afferents (Meleine and Matricon, 2014). It is a clinical phenomenon that females tend to be less sensitive than males to μ-opioid receptor (MOR) agonist analgesia of visceral pain (Cepeda and Carr, 2003). The underlying pharmacological mechanism of this phenomenon is not fully understood. The difference in levels of serum estrogen has been implicated as one of the factors accounting for this sex difference in the analgesic potency of the MOR agonist. Peripheral administration of morphine, which is a widely used MOR agonist, to treat noxious colorectal distention (CRD) has higher analgesic potency in ovariectomized (OVX) rats than in rats treated with estradiol, indicating that estradiol inhibits the pharmacological effect of MOR agonists (Aubrun et al., 2005; Ji et al., 2007). Studies have established the connections between estrogen and the modulation of the analgesic potency of μ-opioid agonists (Sandner-Kiesling and Eisenach, 2002; Aubrun et al., 2005; Ji et al., 2006). However, the underlying mechanisms accounting for the different analgesic potency of the μ-opioid agonist in the presence or absence of estrogen are not fully understood. One of the mechanisms proposed is that estrogen treatment decreases the expression and inhibits the activity of MORs (Ji et al., 2006). Note that the μ-opioid agonist can cause an increased expression of ERs in the ovary, indicating that the interaction between estrogen and MORs is bi-directional (Vodo et al., 2013).

3 Spinal mechanisms in estrogen modulation of visceral pain

The spinal cord is well established as a primary central station where neurons respond to noxious visceral stimulation. Estrogen takes part in modulating the descending inhibition system or altering the inhibitory processing in spinal dorsal horn neurons (Vanderhorst et al., 2002). Estrogen may control synaptic transmission by modulating the activity of some ion channels in the spinal cord. *N*-methyl-D-aspartate (NMDA) receptor, a type of ionotropic glutamate receptor, is quite important in regulating synaptic plasticity and memory function in nerve cells (Moriyoshi et al., 1991). NMDA receptors (NMDARs) in the spinal cord are known to contribute to hyperalgesia and neuron hyperexcitability (central sensitization) at the spinal level in response to visceral or somatic nociceptive stimuli (Zhou et al., 2011). Functional NMDAR is a heterotetramer with two GluN1 subunits and two GluN2/3 subunits (GluN2A-D or GluN3A). NMDAR activity can be regulated by many factors including ischemia, inflammation, aging, and sex hormones (Hardingham and Bading, 2010). There is strong evidence that estrogens regulate the activity of spinal NMDARs, which serve as an important mechanism for modulating visceromotor response (Liu et al., 2007). ERα and NMDARs are co-expressed in the superficial dorsal horn, the deeper laminae, and lamina X of the spinal cord, providing an anatomical basis for NMDAR's role in estrogen modulation of pain processing at the level of the dorsal horn (Chaban et al., 2003). In a visceral pain model caused by colonic inflammation in OVX rats, intrathecal treatment of 2-amino-5-phosphonopentanoic acid (APV, an NMDAR antagonist) attenuated the visceromotor response to CRD. Estrogen replacement decreased the potency of APV in inhibiting CRD-induced visceromotor response. Estrogen treatment significantly increased the phosphorylation of spinal GluN1, which was shown to contribute to estrogen-mediated facilitation of nociceptive processing (Tang et al., 2008). Meanwhile, studies have shown that the activity of the GluN2B subunit can also be modulated by estrogen. Ji et al. (2015) found that estrogen enhanced the activity of GluN2B containing NMDAR in the spinal cord, which underlies the potential mechanism of estrogen-facilitation of colonic inflammation-induced visceral hyperalgesia. There are many potential mechanisms accounting for the effect of estrogen on NMDARs in the spinal cord. Estrogen modulates neuronal activity via phosphorylation of NMDAR subunits NR1 and NR2. The phosphorylation process can be triggered by estrogen-mediated activation of protein kinase C (PKC) and PKA (Romeo et al., 2005). Ji et al. (2015) showed that

estrogen enhanced the CRD-induced activation of extracellular signal-regulated protein kinase (ERK) in spinal dorsal horn neurons. ERK belongs to the mitogen-activated protein kinase (MAPK) family, which plays a key role in the processing of noxious stimuli. ERK phosphorylation is involved in the ER α-mediated enhancement of visceral sensitivity at the spinal level (Ji et al., 2011). The process of ERK phosphorylation can be very complicated. On the one hand, NMDAR activation can trigger the phosphorylation of ERK. As elaborated above, estrogen increases the activation of spinal NMDARs following noxious visceral stimulation. One pathway of ERK activation involves NMDAR activation–Ca^{2+} influx–PKA activation–ERK phosphorylation. On the other hand, phosphorylated ERK (p-ERK) can be an upstream stimulator of NMDARs. PKA-ERK activation could evoke activation of NMDAR subunits in the spinal cord (Thomas and Huganir, 2004). Another possible mechanism for estrogen's effect on NMDAR is that estrogen directly activates the protein tyrosine kinase Src, which then phosphorylates and increases the activity of NMDARs (Nilsen et al., 2002).

Epigenetic regulation, involving DNA methylation, chromatin remodelling, and non-coding RNAs, is also involved in estrogen's modulation of visceral sensitivity in the spinal cord. With histones being basic structures of chomatin, histone acetylation and hyperacetylation are well-known for regulating transcriptional activities (Nilsen et al., 2002). Cao et al. (2015) found that 17-β-estradiol treatment increased the magnitude of visceromotor response to CRD in OVX rats. However, the estrogen-facilitated visceromotor response was attenuated by spinal application of the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA), indicating a critical role of histone hyperacetylation in estrogen modulation of visceral pain at the spinal level. They further demonstrated that histone deacetylase inhibition increased the binding of acetylated histone 3 and ERα to the promoter of the *mGluR2* gene, which could cause an upregulation of mGluR2 mRNA and protein. Furthermore, spinal administration of the mGluR2 antagonist LY341495 inhibited the antinociceptive effect of SAHA (Cao et al., 2015). Thus, the evidence above indicates that ERs interact with mGluR2 to modulate visceral pain via epigenetic mechanisms in the spinal cord.

4 Supraspinal mechanisms in estrogen modulation of visceral pain

It is increasingly evident that estrogen exerts multiple downstream actions in the neurons of the central nervous system by activating many kinase pathways. Estrogen binding sites are widely distributed in many brain structures which are also involved in the processing of pain signals (Heitkemper and Jarrett, 2001). Numerous studies indicate that estrogen modulation of visceral pain is mediated in certain areas of the central nervous system, including the amygdala, prefrontal regions, cingulate, and insula (Chaloner and Greenwood-van Meerveld, 2013; Labus et al., 2013; Gao et al., 2017). In OVX rats receiving implantation of estrogen in the amygdala, the visceromotor response to colorectal distension increased (Myers et al., 2011). The presence of nuclear ERs in the astrocytes of the central nervous system has been well demonstrated. In a high estrogen state, the expression of excitatory amino acid transporters decreased in the astrocytes of the midbrain (García-Ovejero et al., 2002; Pawlak et al., 2005). ERs have been shown to interact with the glutamate transportation system, leading to the development of neuron plasticity in chronic pain. The excitatory amino acid transporter (EAAT) was found to be involved in the maintenance of glutamatergic synapses and plays a vital role in various visceral pain states (Bradesi et al., 2011). An estrogen-related reduction of EAAT uptake in the brain was linked to a decreased threshold for colorectal distension. In a magnetic resonance imaging (MRI) study conducted by Hubbard et al. (2016), estrogen was found to alter visceral nociceptive processing in the brain and modulate viscerosensitivity following acute stress. Functional MRI in rats showed that noxious visceral stimulation enhanced the activation of some brain regions in an estrogen-stress dependent manner. These regions included the insula, anterior cingulate, amygdala, parabrachial nuclei, and cerebellum. The potential mechanism of estrogen's significant role in modulating visceral sensitivity in different brain areas is very complicated. It has been reported that estrogen increases synapse density and NMDAR-binding activity in the hippocampus (Daniel and Dohanich, 2001; Chen et al., 2014). Estrogen enhances neuron excitability in the hypothalamus by increasing NMDAR

phosphorylation and expression (Romeo et al., 2005). Estrogen was also reported to decrease the binding of NMDARs and AMPA (α-amino-3-hydroxy-5-methy-4-isoxazolepropionic acid) receptors in the frontal cortex and the nucleus accumbens (Magnusson and Martin, 2002). Furthermore, it has been speculated that opioid receptors may be implicated in the central action of estrogen in modulating visceral pain.

The analgesic potency of the μ-opioid agonist in treating visceral pain is mediated by estrogen at the supraspinal level. The MORs exist in many brain areas, such as the cerebral cortex, hippocampus, striatum, and locus coeruleus (Kalyuzhny et al., 1996). In OVX rats combined with short-term estrogen treatment, the number of opioid binding sites in the brain decreased, resulting in a reduction of the analgesic effect of MOR agonists (Ratka and Simpkins, 1991). The potential mechanisms accounting for the estrogen-mediated reduction in analgesia potency of the μ-opioid agonist are still not fully understood. Given that the MOR belongs to the G-protein-coupled receptor (GPCR) family, it has been proposed that a rapid increase of estrogen may inhibit the analgesic function of the μ-opioid agonist by altering the linkage of G proteins to the respective effector system (Qiu et al., 2003; Ji et al., 2006).

5 Discussion

In recent years, a growing body of evidence has pointed to the involvement of different gonadal hormones in the modulation of pain signal processing. In this review, we have examined the evidence of the important role of serum estrogen in regulating visceromotor response. Estrogen plays an important part in modulating visceral noxious stimulation-evoked nociceptive sensitization at the level of peripheral, spinal, and supraspinal sites.

The effects of gonadal hormones on visceral pain can be contradictory. For example, estrogens are generally thought to be pronociceptive in visceral pain, while some studies have revealed that estradiol can be antinociceptive. In some studies, OVX rats displayed long lasting visceral hyperalgesia, which could be relieved by exogenous administration of estrogen. Spinal ERβ activation can have antinociceptive effects by attenuating the visceromotor response in a CRD model of visceral pain (Gaumond et al., 2002, 2005; Cao et al., 2012). The conflicting results may be due to the different species, techniques, protocols, pain models, and various estrogen concentrations applied in different experiments. Furthermore, different methods of estrogen administration, acute or chronic, intravenous or subcutaneous, can have different effects on visceral hyperalgesia. It is also reasonable to speculate that the opposite effects of estrogen on visceral pain may be mediated by the different types of ERs and different estrogen-evoked pathways involved in the peripheral and central nervous systems.

Being diffuse and poorly localized, visceral pain is more difficult to treat than other kinds of pain. Currently, visceral pain is generally treated with pharmacotherapy. A better understanding of estrogen-mediated differences in visceral pain may be helpful in unveiling some of the key mechanisms contributing to the development of visceral pain, and may provide new targets for the development of therapeutic strategies. From a public health perspective, targeting ERs or the downstream pathways may be a potential approach to relieve visceral pain. Furthermore, by taking into account the varying estrogen levels across the menstrual cycle or during the different stages of pregnancy, the promise of personalized and precise treatment of visceral pain could be closer to reality.

6 Future directions

This review has highlighted the importance and complexity of estrogen modulation of visceral pain at the primary and central levels. The evidence presented may increase our knowledge of the gender-based biomedical difference in visceromotor response and help to achieve a deeper understanding of the multiple mechanisms underlying estrogen modulation of visceral pain. Determination of these mechanisms is still in progress. In response to call for new and more efficient therapies targeting visceral pain, there is an urgent need for more powerful studies focusing on these mechanisms. A growing number of papers have pointed out the importance of the immune system

contributing to sexual differentiation of visceral pain. Taking into consideration the changes in levels of other sex hormones in relation to the gender difference, the roles of progestin and androgen in regulating pain processing remain to be further investigated.

Contributors

Xin-zhong CHEN was responsible for the initial idea, proofreading, and checking of this manuscript. Li-hong SUN and Wen-xin ZHANG participated in accessing relevant literature and editing the manuscript. Qi XU, Hui WU, and Cui-cui JIAO contributed to the design and writing of the article. All authors have read and approved the final manuscript.

Acknowledgments

We sincerely thank Dr. Li-na YU (School of Medicine, Zhejiang University, Hangzhou, China) for her guidance.

Compliance with ethics guidelines

Li-hong SUN, Wen-xin ZHANG, Qi XU, Hui WU, Cui-cui JIAO, and Xin-zhong CHEN declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Aloisi AM, Bonifazi M, 2006. Sex hormones, central nervous system and pain. *Horm Behav*, 50(1):1-7. https://doi.org/10.1016/j.yhbeh.2005.12.002

Aubrun F, Salvi N, Coriat P, et al., 2005. Sex- and age-related differences in morphine requirements for postoperative pain relief. *Anesthesiology*, 103(1):156-160.

Basbaum AI, 2009. Change is coming! *Pain*, 141(1-2):1. https://doi.org/10.1016/j.pain.2008.11.011

Birder LA, Nakamura Y, Kiss S, et al., 2002. Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. *Nat Neurosci*, 5(9):856-860. https://doi.org/10.1038/nn902

Bokic T, Storr M, Schicho R, 2015. Potential causes and present pharmacotherapy of irritable bowel syndrome (IBS): an overview. *Pharmacology*, 96(1-2):76-85. https://doi.org/10.1159/000435816

Bradesi S, Golovatscka V, Ennes HS, et al., 2011. Role of astrocytes and altered regulation of spinal glutamatergic neurotransmission in stress-induced visceral hyperalgesia in rats. *Am J Physiol Gastrointest Liver Physiol*, 301(3): G580-G589. https://doi.org/10.1152/ajpgi.00182.2011

Campbell-Thompson M, Reyher KK, Wilkinson LB, 2001. Immunolocalization of estrogen receptor α and β in gastric epithelium and enteric neurons. *J Endocrinol*, 171(1): 65-73. https://doi.org/10.1677/joe.0.1710065

Cao DY, Ji YP, Tang B, et al., 2012. Estrogen receptor β activation is antinociceptive in a model of visceral pain in the rat. *J Pain*, 13(7):685-694. https://doi.org/10.1016/j.jpain.2012.04.010

Cao DY, Bai G, Ji YP, et al., 2015. Epigenetic upregulation of metabotropic glutamate receptor 2 in the spinal cord attenuates oestrogen-induced visceral hypersensitivity. *Gut*, 64(12):1913-1920. https://doi.org/10.1136/gutjnl-2014-307748

Cepeda MS, Carr DB, 2003. Women experience more pain and require more morphine than men to achieve a similar degree of analgesia. *Anesth Analg*, 97(5):1464-1468.

Cervero PF, Laird JMA, 1999. Visceral pain. *Lancet*, 353(9170): 2145-2148. https://doi.org/10.1016/S0140-6736(99)01306-9

Chaban V, 2012. Estrogen and visceral nociception at the level of primary sensory neurons. *Pain Res Treat*, 2012: 960780. https://doi.org/10.1155/2012/960780

Chaban V, 2015. Visceral pain modulation in female primary afferent sensory neurons. *Curr Trends Neurol*, 9:111-114.

Chaban VV, Mayer EA, Ennes HS, et al., 2003. Estradiol inhibits ATP-induced intracellular calcium concentration increase in dorsal root ganglia neurons. *Neuroscience*, 118(4):941-948. https://doi.org/10.1016/S0306-4522(02)00915-6

Chaloner A, Greenwood-van Meerveld B, 2013. Sexually dimorphic effects of unpredictable early life adversity on visceral pain behavior in a rodent model. *J Pain*, 14(3): 270-280. https://doi.org/10.1016/j.jpain.2012.11.008

Chen Y, Chen AQ, Luo XQ, et al., 2014. Hippocampal NR2B-containing NMDA receptors enhance long-term potentiation in rats with chronic visceral pain. *Brain Res*, 1570: 43-53. https://doi.org/10.1016/j.brainres.2014.05.001

Daniel JM, Dohanich GP, 2001. Acetylcholine mediates the estrogen-induced increase in NMDA receptor binding in CA1 of the hippocampus and the associated improvement in working memory. *J Neurosci*, 21(17):6949-6956. https://doi.org/10.1523/JNEUROSCI.21-17-06949.2001

Dunn PM, Zhong Y, Burnstock G, 2001. P2X receptors in peripheral neurons. *Prog Neurobiol*, 65(2):107-134. https://doi.org/10.1016/S0301-0082(01)00005-3

Eyster KM, 2016. The estrogen receptors: an overview from different perspectives. *Methods Mol Biol*, 1366:1-10. https://doi.org/10.1007/978-1-4939-3127-9_1

Gao P, Ding XW, Dong L, et al., 2017. Expression of aromatase in the rostral ventromedial medulla and its role in the regulation of visceral pain. *CNS Neurosci Ther*, 23(12): 980-989. https://doi.org/10.1111/cns.12769

García-Ovejero D, Veiga S, García-Segura LM, et al., 2002. Glial expression of estrogen and androgen receptors after rat brain injury. *J Comp Neurol*, 450(3):256-271.

https://doi.org/10.1002/cne.10325

Garcia Rodriguez LA, Ruigómez A, Wallander MA, et al., 2000. Detection of colorectal tumor and inflammatory bowel disease during follow-up of patients with initial diagnosis of irritable bowel syndrome. *Scand J Gastroenterol*, 35(3):306-311. https://doi.org/10.1080/003655200750024191

Gaumond I, Arsenault P, Marchand S, 2002. The role of sex hormones on formalin-induced nociceptive responses. *Brain Res*, 958(1):139-145. https://doi.org/10.1016/S0006-8993(02)03661-2

Gaumond I, Arsenault P, Marchand S, 2005. Specificity of female and male sex hormones on excitatory and inhibitory phases of formalin-induced nociceptive responses. *Brain Res*, 1052(1):105-111. https://doi.org/10.1016/j.brainres.2005.06.011

Hardingham GE, Bading H, 2010. Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. *Nat Rev Neurosci*, 11(10):682-696. https://doi.org/10.1038/nrn2911

Heitkemper MM, Jarrett M, 2001. Gender differences and hormonal modulation in visceral pain. *Curr Pain Headache Rep*, 5(1):35-43. https://doi.org/10.1007/s11916-001-0008-z

Hubbard CS, Karpowicz JM, Furman AJ, et al., 2016. Estrogen-dependent visceral hypersensitivity following stress in rats: an fMRI study. *Mol Pain*, 12:1744806916654145. https://doi.org/10.1177/1744806916654145

Ji YP, Murphy AZ, Traub RJ, 2006. Sex differences in morphine-induced analgesia of visceral pain are supraspinally and peripherally mediated. *Am J Physiol Regul Integr Comp Physiol*, 291(2):R307-R314. https://doi.org/10.1152/ajpregu.00824.2005

Ji YP, Murphy AZ, Traub RJ, 2007. Estrogen modulation of morphine analgesia of visceral pain in female rats is supraspinally and peripherally mediated. *J Pain*, 8(6):494-502. https://doi.org/10.1016/j.jpain.2007.01.006

Ji YP, Tang B, Traub RJ, 2008. The visceromotor response to colorectal distention fluctuates with the estrous cycle in rats. *Neuroscience*, 154(4):1562-1567. https://doi.org/10.1016/j.neuroscience.2008.04.070

Ji YP, Tang B, Traub RJ, 2011. Spinal estrogen receptor alpha mediates estradiol-induced pronociception in a visceral pain model in the rat. *Pain*, 152(5):1182-1191. https://doi.org/10.1016/j.pain.2011.01.046

Ji YP, Bai G, Cao DY, et al., 2015. Estradiol modulates visceral hyperalgesia by increasing thoracolumbar spinal GluN2B subunit activity in female rats. *Neurogastroenterol Motil*, 27(6):775-786. https://doi.org/10.1111/nmo.12549

Kalyuzhny AE, Arvidsson U, Wu W, et al., 1996. μ-Opioid and δ-opioid receptors are expressed in brainstem antinociceptive circuits: studies using immunocytochemistry and retrograde tract-tracing. *J Neurosci*, 16(20):6490-6503. https://doi.org/10.1523/JNEUROSCI.16-20-06490.1996

Labus JS, Gupta A, Coveleskie K, et al., 2013. Sex differences in emotion-related cognitive processes in irritable bowel syndrome and healthy control subjects. *Pain*, 154(10):2088-2099. https://doi.org/10.1016/j.pain.2013.06.024

Lefebvre RA, 1995. Nitric oxide in the peripheral nervous system. *Ann Med*, 27(3):379-388. https://doi.org/10.3109/07853899509002591

Li Y, Xu J, Jiang F, et al., 2016. G protein-coupled estrogen receptor is involved in modulating colonic motor function via nitric oxide release in C57BL/6 female mice. *Neurogastroenterol Motil*, 28(3):432-442. https://doi.org/10.1111/nmo.12743

Liu LM, Tsuruoka M, Maeda M, et al., 2007. Coeruleospinal inhibition of visceral nociceptive processing in the rat spinal cord. *Neurosci Lett*, 426(3):139-144. https://doi.org/10.1016/j.neulet.2007.06.030

Magnusson JE, Martin RV, 2002. Additional evidence for the involvement of the basal ganglia in formalin-induced nociception: the role of the nucleus accumbens. *Brain Res*, 942(1-2):128-132. https://doi.org/10.1016/S0006-8993(02)02489-7

Malykhina AP, 2007. Neural mechanisms of pelvic organ cross-sensitization. *Neuroscience*, 149(3):660-672. https://doi.org/10.1016/j.neuroscience.2007.07.053

Marino M, Galluzzo P, Ascenzi P, 2006. Estrogen signaling multiple pathways to impact gene transcription. *Curr Genomics*, 7(8):497-508. https://doi.org/10.2174/138920206779315737

Meleine M, Matricon J, 2014. Gender-related differences in irritable bowel syndrome: potential mechanisms of sex hormones. *World J Gastroenterol*, 20(22):6725-6743. https://doi.org/10.3748/wjg.v20.i22.6725

Micevych PE, Chaban V, Ogi J, et al., 2007. Estradiol stimulates progesterone synthesis in hypothalamic astrocyte cultures. *Endocrinology*, 148(2):782-789. https://doi.org/10.1210/en.2006-0774

Moriyoshi K, Masu M, Ishii T, et al., 1991. Molecular cloning and characterization of the rat NMDA receptor. *Nature*, 354(6348):31-37. https://doi.org/10.1038/354031a0

Myers B, Schulkin J, Greenwood-van Meerveld B, 2011. Sex steroids localized to the amygdala increase pain responses to visceral stimulation in rats. *J Pain*, 12(4):486-494. https://doi.org/10.1016/j.jpain.2010.10.007

Nilsen J, Chen SH, Brinton RD, 2002. Dual action of estrogen on glutamate-induced calcium signaling: mechanisms requiring interaction between estrogen receptors and Src/mitogen activated protein kinase pathway. *Brain Res*, 930(1-2):216-234. https://doi.org/10.1016/S0006-8993(02)02254-0

Pan YW, Chen FG, Huang S, et al., 2016. TRPA1 and TRPM8

receptors may promote local vasodilation that aggravates oxaliplatin-induced peripheral neuropathy amenable to 17β-estradiol treatment. *Curr Neurovasc Res*, 13(4):309-317.
https://doi.org/10.2174/1567202613666160601144254

Papka RE, Storey-Workley M, 2002. Estrogen receptor-α and -β coexist in a subpopulation of sensory neurons of female rat dorsal root ganglia. *Neurosci Lett*, 319(2):71-74.
https://doi.org/10.1016/S0304-3940(01)02562-9

Pawlak J, Brito V, Küppers E, et al., 2005. Regulation of glutamate transporter GLAST and GLT-1 expression in astrocytes by estrogen. *Mol Brain Res*, 138(1):1-7.
https://doi.org/10.1016/j.molbrainres.2004.10.043

Pfaffl MW, Lange IG, Meyer HHD, 2003. The gastrointestinal tract as target of steroid hormone action: quantification of steroid receptor mRNA expression (AR, ERα, ERβ and PR) in 10 bovine gastrointestinal tract compartments by kinetic RT-PCR. *J Steroid Biochem Mol Biol*, 84(2-3):159-166.
https://doi.org/10.1016/S0960-0760(03)00025-6

Qiu J, Bosch MA, Tobias SC, et al., 2003. Rapid signaling of estrogen in hypothalamic neurons involves a novel G-protein-coupled estrogen receptor that activates protein kinase C. *J Neurosci*, 23(29):9529-9540.
https://doi.org/10.1523/JNEUROSCI.23-29-09529.2003

Ratka A, Simpkins JW, 1991. Effects of estradiol and progesterone on the sensitivity to pain and on morphine-induced antinociception in female rats. *Horm Behav*, 25(2):217-228.
https://doi.org/10.1016/0018-506X(91)90052-J

Reinders CI, Herulf M, Ljung T, et al., 2005. Rectal mucosal nitric oxide in differentiation of inflammatory bowel disease and irritable bowel syndrome. *Clin Gastroenterol Hepatol*, 3(8):777-783.
https://doi.org/10.1016/S1542-3565(05)00182-5

Riley JL III, Robinson ME, Wise EA, et al., 1998. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. *Pain*, 74(2-3):181-187.
https://doi.org/10.1016/S0304-3959(97)00199-1

Romeo RD, McCarthy JB, Wang A, et al., 2005. Sex differences in hippocampal estradiol-induced *N*-methyl-D-aspartic acid binding and ultrastructural localization of estrogen receptor-alpha. *Neuroendocrinology*, 81(6):391-399.
https://doi.org/10.1159/000089557

Rowan MP, Berg KA, Roberts JL, et al., 2014. Activation of estrogen receptor α enhances bradykinin signaling in peripheral sensory neurons of female rats. *J Pharmacol Exp Ther*, 349(3):526-532.
https://doi.org/10.1124/jpet.114.212977

Rudolph LM, Cornil CA, Mittelman-Smith MA, et al., 2016. Actions of steroids: new neurotransmitters. *J Neurosci*, 36(45):11449-11458.
https://doi.org/10.1523/JNEUROSCI.2473-16.2016

Sandner-Kiesling A, Eisenach JC, 2002. Estrogen reduces efficacy of μ- but not κ-opioid agonist inhibition in response to uterine cervical distension. *Anesthesiology*, 96(2):375-380.

Sherman JJ, LeResche L, 2006. Does experimental pain response vary across the menstrual cycle? A methodological review. *Am J Physiol Regul Integr Comp Physiol*, 291(2):R245-R256.
https://doi.org/10.1152/ajpregu.00920.2005

Shibuya K, Takata N, Hojo Y, et al., 2003. Hippocampal cytochrome P450s synthesize brain neurosteroids which are paracrine neuromodulators of synaptic signal transduction. *Biochim Biophys Acta Gen Subj*, 1619(3):301-316.
https://doi.org/10.1016/S0304-4165(02)00489-0

Sinchak K, Wagner EJ, 2012. Estradiol signaling in the regulation of reproduction and energy balance. *Front Neuroendocrinol*, 33(4):342-363.
https://doi.org/10.1016/j.yfrne.2012.08.004

Tang B, Ji YP, Traub RJ, 2008. Estrogen alters spinal NMDA receptor activity via a PKA signaling pathway in a visceral pain model in the rat. *Pain*, 137(3):540-549.
https://doi.org/10.1016/j.pain.2007.10.017

Ter Horst GJ, Wichmann R, Gerrits M, et al., 2009. Sex differences in stress responses: focus on ovarian hormones. *Physiol Behav*, 97(2):239-249.
https://doi.org/10.1016/j.physbeh.2009.02.036

Thomas GM, Huganir RL, 2004. MAPK cascade signalling and synaptic plasticity. *Nat Rev Neurosci*, 5(3):173-183.
https://doi.org/10.1038/nrn1346

Traub RJ, Cao DY, Karpowicz J, et al., 2014. A clinically relevant animal model of temporomandibular disorder and irritable bowel syndrome comorbidity. *J Pain*, 15(9):956-966.
https://doi.org/10.1016/j.jpain.2014.06.008

Vanderhorst VGJM, Terasawa E, Ralston HJ III, 2002. Estrogen receptor-alpha immunoreactive neurons in the ventrolateral periaqueductal gray receive monosynaptic input from the lumbosacral cord in the rhesus monkey. *J Comp Neurol*, 443(1):27-42.
https://doi.org/10.1002/cne.10098

Vodo S, Arcelli D, Fiorenzani P, et al., 2013. Gonadal ERα/β, AR and TRPV1 gene expression: modulation by pain and morphine treatment in male and female rats. *Physiol Behav*, 110-111:80-86.
https://doi.org/10.1016/j.physbeh.2012.12.014

Zhou HY, Chen SR, Pan HL, 2011. Targeting *N*-methyl-D-aspartate receptors for treatment of neuropathic pain. *Expert Rev Clin Pharmacol*, 4(3):379-388.
https://doi.org/10.1586/ecp.11.17

Zielińska M, Fichna J, Bashashati M, et al., 2017. G protein-coupled estrogen receptor and estrogen receptor ligands regulate colonic motility and visceral pain. *Neurogastroenterol Motil*, 29(7):e13025.
https://doi.org/10.1111/nmo.13025

中文概要

题　目：雌激素调节内脏痛的研究进展

概　要：女性和男性的疼痛感受不同，疼痛的患病率和严重程度也存在性别差异，这在临床研究和动物实验中均得到证实。性激素参与疼痛传播并调节内脏疼痛敏感性。有研究发现血清雌激素水平与内脏疼痛敏感性密切相关。本综述旨在总结雌激素在调节内脏痛中的作用及其相关的中枢和外周机制。

关键词：雌激素；内脏痛；痛觉过敏；去卵巢