Mechanisms of Estrogen and Its Receptors in Pathological Pain: Postprint

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Abstract

Pathological pain is a serious chronic disease that includes inflammatory pain, neuropathic pain, and cancer pain. Extensive research has confirmed a close relationship between estrogen and its receptors and pathological pain, which plays a non-negligible role in its occurrence and development, thereby attracting significant attention from numerous researchers worldwide. By reviewing relevant domestic and international literature from recent years, this article elaborates on the research progress regarding the mechanisms of estrogen and its receptors in pathological pain, aiming to provide a theoretical basis for the prevention and treatment of pathological pain and to guide future research directions.

Full Text

Mechanism of Estrogen and Estrogen Receptors in Pathologic Pain

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Abstract

Pathologic pain is a serious chronic disease encompassing inflammatory pain, neuropathic pain, and cancer pain. Extensive research has confirmed that estrogen and its receptors are closely associated with pathologic pain and play a significant role in its initiation and progression, attracting considerable attention from researchers worldwide. By synthesizing relevant domestic and international literature from recent years, this review elucidates the research progress

on the mechanisms of estrogen and its receptors in pathologic pain, aiming to provide a theoretical basis for the prevention and treatment of pathologic pain and to guide future research directions.

Keywords: Estrogens; Estrogen receptor; Inflammatory pain; Neuropathic pain; Cancer pain

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In 2020, the International Association for the Study of Pain revised its definition of pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [1]. Pain signals are detected by nociceptors, generate excitation, and are transmitted via nerve fibers to the dorsal root ganglia (DRG), which then relay these signals to the central nervous system to produce pain sensation. Pathologic pain represents one of the most common clinical pain types, categorized into inflammatory pain, neuropathic pain, and cancer pain. Due to the complex mechanisms underlying its development and progression, identifying valuable targets for pain modulation holds significant importance for future research.

Previous animal model studies have found that female rats often exhibit hyperalgesia compared to male rats, and estrogen supplementation can reverse this symptom [2]. Meanwhile, inhibiting or knocking out estrogen receptors can reduce pain thresholds [3]. In clinical research, sex differences in pain are well-documented, with epidemiological surveys indicating that women demonstrate higher pain sensitivity, lower tolerance, and lower pain thresholds compared to men [4-5]. These differences in pain perception may be related to sex hormones, with estrogen considered an important factor affecting sensory processing and transduction. As research on pathologic pain deepens, estrogen-related pain has garnered increasing attention, though the underlying mechanisms remain incompletely understood. Investigating the mechanisms of estrogen in pathologic pain may provide a basis for developing sex-specific clinical diagnosis and treatment protocols to improve therapeutic efficacy and quality of life for pain patients. Therefore, this review aims to present the latest understanding of estrogen and its receptors in pathologic pain and summarize their regulatory mechanisms in the initiation and maintenance of pathologic pain, providing a reference for further research.

1. Overview of Estrogen and Its Receptors

Estrogen is a steroid hormone primarily comprising estrone (E1), 17β-estradiol (E2), and estriol (E3). E1 is present in the smallest amount and is mainly synthesized by ovarian granulosa cells. E2 is abundant and most potent, exerting regulatory effects on peripheral cells and tissues, and is primarily produced by ovarian granulosa cells. After menopause, when ovarian E2 production ceases, extragonadal sites can produce E2, such as mesenchymal cells in breast tissue, osteoblasts, and chondrocytes. Testosterone and androstenedione catalyzed by aromatase represent an important source of E1 and E2, and neurons and as-

trocytes can also produce estrogen through aromatase expression [6]. E3 is a metabolite of E2 found in urine, primarily produced in the placenta of pregnant women. Estrogen also regulates other physiological functions, including modulation of the immune system (e.g., neutrophils, macrophages, mast cells) and nervous system (e.g., microglia, astrocytes), as well as regulation of sensory, cognitive, and emotional processes [7].

Estrogen exerts its functions by binding to specific estrogen receptors (ER), which are classified based on location into nuclear receptors (nER) and membrane receptors (mER). nER mainly includes ERα and ERβ, encoded by different genes and expressed in various tissues. ERα levels are highest in the uterus and pituitary, while ERβ levels are highest in the ovary (specifically granulosa cells), lung, and prostate, suggesting potential functional differences due to distinct tissue distribution patterns. However, both participate in pain transmission and inhibition in brain tissue [8]. The G-protein coupled estrogen receptor (GPER) belongs to the mER family. Compared to other estrogen receptors, GPER exhibits lower binding affinity for E2, which may be related to its rapid response to estrogen and activation of second messenger-mediated intracellular signaling cascades [9]. GPER can participate in both peripheral sensitization mediated by inflammatory pain and neuronal sensitization and neuroinflammatory responses in neuropathic pain [10].

2. Regulatory Effects of Estrogen and Its Receptors on Inflammatory Pain

2.1 Mechanism Overview of Inflammatory Pain

Inflammatory pain is primarily caused by activation of peripheral nociceptors by toxic chemicals and mechanical or thermal stimuli, manifesting mainly as hyperalgesia and allodynia. Peripheral tissue injury triggers inflammatory responses by stimulating immune cells to release a series of inflammatory mediators. These mediators bind to receptors expressed on nociceptive neurons, causing neuronal hyperexcitability and further transmission of nociceptive signals to the DRG, spinal dorsal horn, and brain, contributing to pain perception induction and maintenance. Additionally, inflammatory mediators induce sensitization of transient voltage-gated ion channels, leading to peripheral sensitization. Estrogen can regulate the formation, generation, and maintenance of inflammatory pain through ER-mediated modulation of inflammatory mediators (e.g., trophic factors, cytokines, chemokines) and related ion channel expression.

Nerve growth factor (NGF) is a neurotrophic factor produced in peripheral tissues and an important inflammatory mediator involved in inflammatory pain. E2 significantly reduces NGF expression and release through the MEK/ERK1/2 signaling pathway, regulating hyperalgesia formation even under stimulation by transforming growth factor-$ 1 or IL-1 $ [11]. Arachidonic acid is metabolized by cyclooxygenase-2 (COX-2) into prostaglandin E2 (PGE2) to promote inflammatory cell activation and migration, directly triggering nociceptors through its

receptors. E2 can increase PGE2 conversion by upregulating COX-2 expression to maintain inflammatory pain generation [12]. Estrogen deficiency can activate the NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome, promoting inflammatory factor production and enhancing pain sensation [13].

Chemokines (CCL) participate in inflammatory pain initiation and maintenance by directly activating nociceptive sensory neurons. In knockout mouse models of ER or aromatase, disruption of estrogen transduction pathways reduces CXCL13/CXCR5 expression, attenuates p38 phosphorylation, and decreases Nav1.8 current density, thereby preventing inflammatory pain maintenance [14-15]. Estrogen exerts anti-inflammatory and anti-hyperalgesic effects by downregulating substance P and proinflammatory cytokines (IL-1β, TNF-α, and IL-6) expression in intervertebral discs [16]. Estrogen acts on ER to attenuate IL-23-induced p38 phosphorylation in DRG of female mice, thereby inhibiting inflammatory factor cascades and alleviating pain [17-18].

2.2 Estrogen Regulates Inflammatory Pain Through ER-Mediated Ion Channel Expression

Transient receptor potential vanilloid subfamily 1 (TRPV1) is a cation channel expressed on sensory neurons that plays an important role in inflammatory pain pathogenesis. E2 participates in inflammatory pain generation by upregulating TRPV1 expression in a dose-dependent manner [19]. Peripheral serotonin (5-hydroxytryptamine, 5-HT) can increase inflammatory responses and exert nociceptive effects. 5-HT receptors can act on sensory neurons expressing TRPV1 channels, promoting channel phosphorylation to enhance peripheral sensitization [20]. Studies have found that E2 reduces 5-HT reuptake by downregulating plasma membrane monoamine transporter gene expression through ERβ and the MAPK/ERK signaling pathway, thereby alleviating pain [21]. Additionally, PGE2 can enhance TRPV1 expression, cell surface trafficking, and axonal transport, thereby increasing receptor activity [22].

3. Estrogen and Its Receptors in Neuropathic Pain

3.1 Mechanism Overview of Neuropathic Pain

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory system [23]. Its mechanisms involve both peripheral and central aspects. The peripheral mechanism involves changes in nerve fiber density after nerve fiber terminals are affected by injury, toxins, drugs, or inflammatory mediators, leading to neuronal excitation that stimulates neuropathic pain occurrence and induces changes in synaptic receptor channel expression and composition, resulting in abnormal signal transmission to maintain pain sensation. Additionally, some cells (glial cells and autonomic neurons) can induce hyperalgesia by altering their numbers and channel expression. The central mechanism involves increased expression of nociceptor ion channels in the central nervous

system under intense or sustained stimulation, which lowers pain thresholds and increases pain sensitivity. Furthermore, microglia and astrocytes activated by excitatory neurotransmitters released from nearby neurons release trophic factors and proinflammatory cytokines, participating in neuropathic pain formation and maintenance [24]. Estrogen regulates neuropathic pain through both peripheral and central mechanisms.

3.2 Estrogen Regulates Neuropathic Pain by Acting on Peripheral Nerves

Previous studies have utilized various rodent models to investigate peripheral mechanisms of initiation and maintenance, such as the spared nerve injury (SNI), chronic constriction injury (CCI), and spinal nerve ligation (SNL) models [25-27]. E2 attenuates SNI-induced neuronal excitability by upregulating voltage-gated chloride channel-3 expression in DRG of ovariectomized rats and significantly improves cold pain thresholds [25]. E2 can significantly reduce mechanical and thermal pain thresholds in CCI model rats, and this sensitivity-enhancing mechanism may be related to upregulated N-methyl-D-aspartate receptor 1 (NMDAR1) expression in dorsal root ganglia, suggesting that estrogen may participate in hyperalgesia and allodynia generation and maintenance in peripheral nerve pain by regulating NMDAR1 expression [26]. Studies have confirmed that ERβ selective agonists exhibit anti-allodynic effects in the SNL model of neuropathic pain and also alleviate chemotherapy-induced (paclitaxel, oxaliplatin, and vincristine) neuropathic pain abnormalities [27].

3.3 Estrogen Regulates Neuropathic Pain by Acting on Central Nervous System

Neuropathological changes in the central nervous system, including neuroinflammation and increased neuronal excitability, are driven by altered neuron-glia transmission. Glutamate levels increase significantly after spinal cord injury, accompanied by allodynia and hyperalgesia. E2 administration reduces glutamate levels in the ipsilateral ventral posterolateral thalamic nucleus and significantly increases mechanical allodynia and thermal hyperalgesia thresholds to alleviate pain [28]. After nerve injury, spinal neuron properties are altered, changing their ion channel expression levels. For example, 5-HT receptors participate in pain facilitation after tissue damage and nerve lesions [29], and E2 exacerbates nociceptive pain behavior and pain signal transmission by regulating 5-HT2A receptor and TRPV1 co-expression through ERα [30]. Brain-derived neurotrophic factor (BDNF) is a key neuromodulator in peripheral and central pain transmission, and estrogen increases BDNF protein levels, enhancing BDNF/TrkB signaling to participate in pain responses [31].

E2 reduces GABAA receptors, decreases presynaptic inhibition, and causes spontaneous neuronal activity [32]. In rat SNL models, similar disinhibition effects occur with weakened postsynaptic inhibitory currents and reduced expression of G protein-gated inwardly rectifying potassium channels [33-34]. E2

enhances depolarizing responses to GABA and AMPA synaptic conductances in arcuate kisspeptin neurons by diminishing voltage-gated potassium currents [35]. Inflammatory mediators mediated by injured neurons and activated glial cells can affect central nervous system pathological changes in neuropathic pain. For example, dorsal horn neurons show elevated CCL13/CCR5 expression in rat CCI models; interferon-γ can activate microglia; in rat SNL models, astrocytes and CD4+ T cells secrete large amounts of IL-17. E2 can promote neuropathic pain formation and maintenance by regulating CCL, proinflammatory factors, and glial cell participation in central nervous system pain transmission [36-39].

4. Estrogen and Its Receptors in Cancer Pain

4.1 Mechanism Overview of Cancer Pain

Cancer pain is defined as pain caused by primary cancer itself or tumor metastasis. Bone cancer pain is a complex pain state with both inflammatory and neuropathic components. The most commonly studied animal model is the bone cancer pain model. Bone cancer pain is one of the most common clinical pain types, with approximately 60%-84% of advanced cancer patients experiencing varying degrees of bone pain. The pain mechanisms experienced by patients after cancer cells metastasize to bone are complex, involving interactions between inflammatory cells, tumor cells, bone cells, stromal cells, and neurons [40].

4.2 Estrogen Regulates Bone Cancer Pain Through ER Action on Cells and Ion Channels

Osteoclasts and tumor cells release H+ into the extracellular space to create an acidic environment that activates acid-sensitive ion channels (e.g., TRPV1), stimulating stromal cells to produce and release growth factors (NGF, BDNF) and proinflammatory mediators (IL-1β, IL-6) [41-42], and stimulating macrophages to produce proinflammatory cytokines (IL-1β, IL-6, TNFα) and prostaglandins [43], thereby inducing pain by binding to receptors on sensory neurons [44]. Studies have confirmed that increased insulin-like growth factor-1 release from tumor cells in bone cancer pain models correlates with TRPV1 channel expression and activation in DRG neurons [45]. Combined with the aforementioned mechanisms, estrogen can participate in bone cancer pain formation and development by regulating TRPV1 channel activation.

E2 and the GPER-selective ligand G-1 trigger the GPER/EGFR/ERK/c-fos signaling pathway, increasing vascular endothelial growth factor (VEGF) through upregulation of hypoxia-inducible factor [46], thereby exacerbating bone cancer pain via this signaling pathway [47]. ERα can promote cancer cell migration and recruit immunosuppressive cells to the tumor microenvironment through the CCL2/CCR2 signaling pathway, while also activating astrocytes and increasing aromatase expression via the CXCL12/CXCR4 signaling pathway, contributing to bone cancer pain development and maintenance [48-51]. GPER promotes excitatory transmission by functionally upregulating calcium/calmodulin-

dependent protein kinase IIα in glutamatergic neurons and increasing glutamate receptor-1 subunit clustering at excitatory synapses, while reducing inhibitory transmission in the spinal cord by upregulating $ $1 subunits and downregulating $ $2 subunits, thereby promoting bone cancer pain development [52].

Estrogen receptor-related receptor α (ERRα) promotes tumor cell local growth by upregulating the osteoclastogenesis inhibitor osteoprotegerin and VEGF, but inhibits breast cancer cell proliferation in bone and osteoclast differentiation and activity, thereby limiting bone tumor occurrence [53]. Further studies have found that ERRα may activate immune responses in the bone microenvironment through ERRα-mediated induction of chemokines (CCL17 and CCL20) and reduction of TGF-$ 3, $inhibitingbreastcancercellgrowthaftertumorcellanchoringinbone$[54]. $However, studiesoncastration-resistantprostatecancerhavefoundthatERR$ $ overexpression significantly increases prostate cancer progression and metastasis in bone. Mechanistic studies show that this receptor enhances bone remodeling by increasing expression of metastatic factors (e.g., VEGF-A, WNT5A, TGF-$ 1)$andcreatingatumorgrowth-favorableenvironment$[55]. $Therefore, ERR$ $ function appears inconsistent or even opposite across different cancer types or bone metastasis stages, representing a key question for future exploration.

5. Summary and Outlook

With the increasing aging population, the prevalence of degenerative diseases and corresponding chronic conditions has risen concurrently, leading to increasing incidence of pathologic pain and gradually becoming a major clinical challenge. Commonly used opioid analgesics only temporarily relieve patient pain and carry adverse effects such as addiction and tolerance. Therefore, developing novel analgesic drugs is urgently needed. In recent years, numerous researchers have continued to explore specific mechanisms. Clinical studies and epidemiological surveys have demonstrated that pathologic pain occurrence and development are closely associated with estrogen and its receptors, which have attracted widespread attention as potential novel analgesic targets. However, research has revealed numerous and sometimes contradictory mechanisms of estrogen in pathologic pain. Therefore, further clarification of estrogen-regulated pain signaling pathways to identify key targets for treating and preventing pathologic pain, along with developing corresponding analgesic drugs, is crucial in pathologic pain research. This review summarized the pain regulatory mechanisms of estrogen and its receptors in inflammatory pain, neuropathic pain, and cancer pain, providing a reference for continued in-depth research on pathologic pain.

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Note: Figure translations are in progress. See original paper for figures.