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Receptors Associated with Sexual Dimorphism in Pain Expression in Rodents

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Abstract

Pain is the body's alarm system for potentially harmful stimuli in the environment. The nociceptive process allows us to detect these stimuli through specific neurons called nociceptors. However, pain can become a pathological condition. Chronic pain affects approximately 20% of the world's population. The pathophysiology of chronic pain involves central and peripheral sensitization mechanisms. In this context, sexual dimorphism is a determining factor in the perception and modulation of pain. These differences are mainly explained by hormonal and neuroimmune differences. Consequently, preclinical research provides a fundamental basis for understanding sex-dependent variations in nociception. Animal pain models allow the study of these pathophysiological mechanisms. These models are classified according to the type of pain they reproduce: nociceptive, inflammatory, neuropathic, or nociplastic. Therefore, scientific evidence supports the need to develop therapeutic strategies with a sex-dependent approach in pain conditions.

Keywords

Allodynia, Nociplastic Pain, Rodents, Drug Therapy

1. Introduction

Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [1]. From a biological perspective, pain is an essential protective mechanism against noxious stimuli, as it helps

prevent further injury and promotes tissue repair processes [2]. Pathological pain results from cellular, molecular, and structural modifications of the networks that modulate pain perception and response, altering their function under different conditions. Consequently, pain loses its adaptive-protective character, becoming chronic, debilitating, and sometimes disabling [3] [4]. Chronic pain affects approximately 20% of the world's population, according to the U.S. Centers for Disease Control and Prevention [5]-[7]. In México, the number of people suffering from chronic pain is unknown. However, in 2010, it was estimated that approximately 28 million Mexicans suffered from this type of pain, out of a population of 112 million at that time [8]. Pain perception begins with the detection of noxious stimuli by nociceptors [9] [10]. These neurons possess a high activation threshold for distinguishing between innocuous and noxious stimuli [9] [11] and express specialized receptors and ion channels for various stimuli [12] [13]. Nociceptors are classified into three fiber types according to their characteristics: C fibers, which are slow and unmyelinated; Aδ fibers, which are faster and lightly myelinated; and a subgroup of Aβ fibers, which conduct noxious stimuli at high speed [14]-[16]. Nociceptors transduce stimuli into action potentials that propagate to the dorsal horn of the spinal cord [12] [17]. The arrival of the action potential at the central terminal then induces the release of neuromodulators such as glutamate and substance P [12]. In this way, nociceptive information ascends to the thalamus and brainstem via specific tracts [18] [19]. These projections integrate nociceptive activity with homeostatic processes [19]. Finally, third-order neurons project to various brain areas to generate the sensory, emotional, and cognitive components of pain [20].

2. Pain Classification

Pain can be classified according to its duration, function, and neurobiological mechanism. Based on its duration, acute pain has a limited course, generally less than three months, and tends to resolve once the underlying cause is treated. In contrast, chronic pain persists for extended periods, exceeding three months, and can continue even after the initial damage has been resolved, often requiring continuous and multidisciplinary therapeutic management [2]. Based on its function, pain is classified as adaptive and maladaptive. Adaptive pain is defined as a physiological and protective response of the nervous system to a real or potential noxious stimulus, whose purpose is to preserve bodily integrity and promote tissue recovery. It warns of damage, promotes avoidance behaviors, and facilitates reparative processes. It originates from the transient activation of peripheral nociceptors and the transmission of the pain impulse to the central nervous system via Aδ and C fibers, without altering pain modulation mechanisms. Its duration is limited and proportional to the magnitude of the injury or inflammation [21]. Maladaptive pain is defined as pain that loses its original protective function and persists in the absence of an active noxious or inflammatory stimulus, becoming a pathological condition. It is associated with phenomena of peripheral and central sensitization,

abnormal synaptic plasticity, persistent microglial activation, and dysfunction of descending inhibitory systems. As a result, non-noxious or low-intensity stimuli can produce allodynia or hyperalgesia, generating a disproportionate pain perception independent of the initial tissue injury [22].

According to itr neurobiological mechanism, it is classified as: nociceptive pain, inflammatory pain and neuropatic pain.

2.1. Nociceptive Pain

Nociceptive pain is defined as a protective sensory and emotional response originating from the activation of peripheral nociceptors to potentially harmful mechanical, thermal, or chemical stimuli, which trigger the transmission of the pain impulse to the central nervous system [23]. This type of pain serves as an adaptive physiological function, alerting the body to possible tissue damage and generating withdrawal reflexes or avoidance behaviors that prevent harm and facilitate recovery [3]. The primary afferent fibers involved in this process are mainly: Aδ fibers, myelinated and fast-conducting, responsible for acute, well-localized, and short-lived pain; and C fibers, unmyelinated and slow-conducting, which transmit dull, diffuse, and persistent pain. And, to a lesser extent, Aβ fibers conduct tactile stimuli, but can participate in pain transmission under conditions of peripheral or central sensitization [23].

2.2. Inflammatory Pain

Inflammatory pain is defined as pain that arises because of the activation and sensitization of peripheral nociceptors by chemical mediators released during the inflammatory process, in response to tissue injury, infection, or cell damage [24]. It is characterized by an increased nociceptive response secondary to the release of proinflammatory mediators such as prostaglandins, bradykinin, histamine, serotonin, IL-1β, IL-6, and TNF-α at the site of tissue injury [25] [26]. Clinically, it manifests as primary and secondary hyperalgesia, with localized pain that is usually accompanied by redness, heat, swelling, and functional loss in the affected area. From a pathophysiological perspective, this type of pain involves both peripheral sensitizations, due to a decrease in the activation threshold of nociceptors (mainly C and Aδ fibers), and central sensitization, resulting from the release of cytokines and glial activation in the spinal cord [27]. Among the receptors involved are TRPV1, P2X3, ASICs, and prostanoid receptors (EP), whose activation promotes neuronal depolarization and synaptic potentiation. Inflammatory pain represents an adaptive response that facilitates the protection of the injured tissue, although its persistence can induce plastic changes and contribute to the chronicity of the pain [9] [28].

2.3. Neuropathic Pain

Neuropathic pain originates because of direct injury to or dysfunction of the central or peripheral nervous system [29]-[31]. It is characterized by the presence of

neuronal sensitization mechanisms and alterations in endogenous inhibitory modulation [32]. Neuropathic pain presents characteristics such as hyperalgesia, an increased pain response.

3. Pathophysiological Mechanism of Chronic Pain

Chronic pain involves mechanisms that include central sensitization, peripheral sensitization, and GABAergic disinhibition. The IASP defines central sensitization as an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input [33]-[35]. The main causes of central neuropathic pain include spinal cord injuries, Multiple Sclerosis (MS), chemotherapy [36], traumatic brain injuries, and strokes [37]. Central sensitization involves an alteration in the synaptic plasticity of neurons in the dorsal horn of the spinal cord and supraspinal structures such as the thalamus and somatosensory cortex. This process is characterized by sustained neuronal hyperexcitability caused by the excessive release of glutamate and the activation of NMDA, AMPA, and kainate receptors, which promote calcium influx into neurons and trigger intracellular signaling cascades dependent on Protein Kinase C (PKC) and MAPK/ERK [38]. These pathways activate the phosphorylation of ion channels and modify gene expression, promoting synaptic potentiation and the persistence of the nociceptive signal. Furthermore, the activation of microglia and astrocytes releases proinflammatory mediators such as IL-1β, TNF-α, and BDNF, which reduce GABAergic inhibition and exacerbate hypersensitivity [39]. As a result, clinical phenomena such as allodynia, secondary hyperalgesia, and persistent pain in the absence of peripheral stimuli occur. Peripheral sensitization refers to the increased responsiveness and reduced threshold of nociceptive neurons in the periphery to stimulation of their receptive fields [35] [40] [41]. Some causes of peripheral neuropathic pain include diabetic neuropathy [42], postherpetic neuralgia [43], trigeminal neuralgia [44], phantom limb pain [45], and spinal nerve compression neuropathy [46]. Mediators such as prostaglandins, bradykinin, histamine, serotonin, ATP, Interleukins (IL-1β, IL-6), and Tumor Necrosis Factor alpha (TNF-α) induce a decrease in the activation threshold of nociceptors and an increase in discharge frequency, promoting peripheral sensitization [47].

This process results from the release of inflammatory and neurogenic mediators such as prostaglandins, bradykinin, histamine, serotonin, ATP, Interleukins (IL-1β, IL-6), and TUMOR necrosis Factor alpha (TNF-α), which interact with G protein-coupled receptors (EP, B2, 5-HT, P2Y) and ion channels such as TRPV1, TRPA1, ASICs, and P2X3. Its activation causes phosphorylation and sensitization of sodium (Nav1.7, Nav1.8) and calcium (Cav2.2) channels, generating spontaneous ectopic discharges and an increased firing rate in C and Aδ fibers [9] [47]. These increased afferent signals reinforce central excitability, creating a feedback loop that perpetuates pain.

GABAergic disinhibition is another crucial mechanism in the pathophysiology of chronic pain. Under physiological conditions, inhibitory interneurons that re-

lease GABA and glycine regulate nociceptive transmission in the dorsal horn of the spinal cord, preventing excessive propagation of the pain signal. However, in chronic pain, there is a functional loss of these interneurons or a decrease in GABAergic synaptic efficacy, caused by reduced GABA synthesis, alteration of the chloride ion gradient, or internalization of GABA_A receptors [48] [49]. Increased Brain-Derived Neurotrophic Factor (BDNF) released by microglia alters the expression of the KCC2 chloride cotransporter, reversing the anion gradient and transforming the inhibitory action of GABA into an excitatory response [50]. This phenomenon amplifies central sensitization and contributes to the maintenance of persistent pain.

4. Animal Models of Pain

Research in animal models is fundamental to understanding the neurobiological basis of pain, from its sensory processing to the sexual dimorphism that influences its regulation [51] [52]. Pain models are classified according to their underlying pathophysiological mechanism, the affected tissue, or the temporal course of the pain [53].

Nociceptive Pain: Animal models of nociceptive pain are primarily based on spinal reflexes, and the behavioral responses used for their assessment include tail flicking, paw withdrawal or elevation, trembling, licking, nipping, cowering, or decreased weight-bearing [54]. On the other hand, nociceptive pain can also be assessed by measuring the frequency of withdrawal of the injected limb, vertical activity (rearing), or horizontal locomotion, indicators of the degree of discomfort or hypersensitivity [53].

Inflammatory pain: Most models of inflammatory pain are based on the induction of an immune response or the administration of inflammatory mediators. Among the irritant chemical agents used to reproduce this type of pain in rodents are carrageenan, capsaicin, and Freund's complete adjuvant (CFA), which induce local or systemic inflammation [55].

Neuropathic pain: Nociplastic pain arises from altered nociception despite no clear evidence of actual or potential tissue damage causing peripheral nociceptor activation or evidence of disease or injury to the somatosensory system causing pain [56]. One of the most widely used models for its study is Spinal Nerve Ligation (SNL), which consists of ligating the L5 or L6 roots of the spinal nerve [57]. The contralateral, uninjured leg serves as a control, and the animals are evaluated using mechanical hyperalgesia and allodynia tests, analyzing behavioral changes in response to tactile, thermal, or cold stimuli applied to the affected limb [53]. To determine the mechanical threshold of response, von Frey filaments are used, applied with progressively increasing force until the withdrawal reflex is elicited. These models reproduce with high accuracy the neuropathic abnormalities detected in human neuropathic pain, making them widely used in the exploration of new therapeutic strategies [58].

Nociplastic pain: Due to its functional nature, nociplastic pain presents an ex-

perimental challenge, as its pathophysiology involves central mechanisms of sensitization, synaptic dysfunction, and neuroimmune alterations. Among the preclinical models used for its study, several approaches stand out that reproduce processes of central sensitization and emotional dysregulation associated with this type of pain. The Chronic Mild Stress model seeks to simulate the effects of persistent emotional and physiological stress, capable of inducing generalized hyperalgesia and central sensitization [59]. The Reserpine-Induced Pain Model is based on the repeated administration of reserpine, an irreversible inhibitor of the Vesicular Monoamine Transporter 2 (VMAT2), which causes sustained monoamine depletion and dysfunction of descending pain inhibitory pathways. As a result, animals develop diffuse hypersensitivity, mechanical and thermal hyperalgesia, anhedonia, and decreased locomotor activity, along with glial activation and increased proinflammatory cytokines [60]. Another relevant model is sleeping deprivation-induced central hypersensitivity. Partial sleep restriction for several days increases spontaneous activity of nociceptive neurons in the dorsal horn, reduces spinal serotonin concentration, and generates diffuse allodynia, reproducing the sensory alterations typical of fibromyalgia [61]. Finally, the Repeated Acid Injection Model involves the repeated administration of intramuscular injections of an acidic solution (pH 4.0 - 4.5) into the gastrocnemius or masseter muscle. After two to three weeks, the animals develop diffuse mechanical and thermal hypersensitivity [62]. These models reproduce the phenomena of central sensitization, monoaminergic dysfunction, and neuroinflammation that characterize nociplastic pain, constituting fundamental tools for exploring sex-dependent differences in pain modulation and expression.

Taken together, animal models of pain allow us to understand the pathophysiological mechanisms underlying different pain modalities and offer a solid experimental basis for studying sex-dependent variations in nociceptive perception and modulation. Accumulated evidence suggests that such differences are not solely due to factors ot only genetic or neuroanatomical factors, but also the modulating influence of sex hormones on the neuronal circuits and glial cells involved in pain transmission and regulation. In this context, the interaction between estrogen, testosterone, and progesterone with their respective receptors plays a crucial role, modulating both nociceptive sensitivity and the associated inflammatory and emotional response. Therefore, it is essential to delve deeper into the analysis of the sex hormones involved in the pain process to fully understand sexual dimorphism in its expression and treatment.

Various studies have demonstrated that biological sex is a determining factor in the perception, modulation, and response to pain, influenced by hormonal, neuroendocrine, immunological, and genetic differences. In this context, experimental models in rodents represent a fundamental tool for studying sexual dimorphism in nociception. This is because they allow the control of biological and environmental variables, the reproduction of different types of pain (nociceptive, neuropathic, inflammatory or nociplastic) and the evaluation of changes in the expres-

sion of receptors associated with the transmission and modulation of pain.

5. Sexual Dimorphism in Chronic Pain

Sexual dimorphism refers to the differences between individuals of the same species [63]. Several factors are involved in this phenomenon; some of the differences are attributed to the influence of sex hormones and their receptors, which modulate sensitivity and response to pain [63] [64].

In addition to hormonal factors, the neuroimmunological mechanisms involved in pain modulation have been identified as differing between males and females, reflecting a qualitative divergence in how the nervous system processes nociceptive stimuli [65] [66]. In male rodents, spinal microglial activation plays a fundamental role in the generation and maintenance of central sensitization. Activation of Toll-Like Receptor 4 (TLR4) in microglia induces the release of proinflammatory cytokines (IL-1β, TNF-α, IL-6) and Brain-Derived Neurotrophic Factor (BDNF), as well as activation of the p38 MAPK pathway, resulting in GABAergic disinhibition and increased neuronal excitability [67] [68]. In contrast, in female rodents, pain sensitization does not depend on microglia, but rather on the activation of $CD4^+$ T lymphocytes that infiltrate the spinal cord and release proinflammatory cytokines and growth factors, indirectly modulating nociceptive transmission [69] [70]. In experimental models, T-cell depletion induces the use of microglial pathways in females, pathways typically observed in males, confirming the existence of alternative, sex-dependent cellular mechanisms in pain modulation [69].

In general, sexual dimorphism in the pathophysiology of pain reflects differences in neuroimmune interactions: Males: TLR4-mediated microglial activation → BDNF release → decreased GABAergic inhibition → central sensitization. Females: $CD4^+$ T-cell activation → cytokine release → indirect modulation of neuronal excitability. These differences not only underscore the influence of biological sex on pain mechanisms, but also have therapeutic relevance, given that microglial inhibitors such as minocycline show analgesic efficacy in males, while their effect in females is limited, highlighting the need to develop analgesic strategies with a sex-specific approach [69].

6. The Role of Sex Hormones in Pain

Sex hormones play an important role in pain modulation, acting on peripheral and central mechanisms of the nervous system [71]. Fluctuations in circulating levels of estradiol and progesterone in females, and testosterone and dehydroepiandrosterone (DHEA) in males, influence pain perception, tolerance, and analgesic response, determining not only pain intensity but also the efficacy of pharmacological treatments [63] [72]. The dual function of sex hormones depends on factors such as hormone concentration, physiological context, tissue type, and the activated molecular signaling pathway [73]. For example, hormonal fluctuations of the estrous cycle are known to modulate these actions, increasing susceptibility

to chronic painful diseases such as migraine, fibromyalgia, or neuropathic pain in women [74] [75].

6.1. Female Hormones

17β-Estradiol is the most potent and physiologically relevant form of estrogen in females. It acts by activating the estrogen receptors ERα, ERβ, and GPER1, which are in sensory neurons, glial cells, the spinal cord, and the periaqueductal gray matter—regions involved in nociceptive processing [76] [77].

In the genomic pathway, the ERα and ERβ receptors act as nuclear transcription factors. After estradiol binding, the hormone-receptor complex translocates to the nucleus and binds to specific DNA regions called Estrogen Response Elements (EREs), modulating the transcription of genes involved in synaptic plasticity, inflammation, and pain perception [78]. On the other hand, the non-genomic pathway comprises rapid actions mediated by membrane receptors such as GPER1 (G protein-coupled estrogen receptor 1) and, to a lesser extent, by plasma membrane-associated estrogen receptors. In specific contexts, estradiol can exert a pronociceptive effect, promoting a state of sensitization of the nervous system. This effect involves the activation of G Protein-Coupled Receptors (GPER1) and classical nuclear receptors (ERα/ERβ), which stimulate the Phospholipase C (PLC) and Protein Kinase C (PKC) signaling cascades, increasing neuronal excitability in sensory neurons. Furthermore, the activation of MAPKs (p38 and ERK) increases the expression of ion channels and pro-inflammatory receptors in the dorsal horn of the spinal cord. Estradiol also upregulates the expression of the bradykinin B2 receptor, a key mediator of inflammatory pain [74] [79] [80].

However, multiple lines of evidence indicate that estradiol exerts antinociceptive effects under certain physiological and experimental conditions. Activation of ERβ and GPER1 receptors in the periaqueductal gray and spinal cord increases the release of endorphins and enkephalins, enhancing the descending inhibition of pain [74] [76]. Furthermore, estradiol can inhibit the expression of TRPV1 channels in dorsal root ganglion neurons, reducing thermal and mechanical sensitivity [81]. In neuropathic pain models, treatment with 17β-estradiol decreases microglial activation and the release of IL-1β and TNF-α, contributing to an anti-inflammatory and neuroprotective profile [82] [83].

Overall, the genomic and non-genomic actions of estradiol can be both pro- and antinociceptive, depending on the dose, the physiological context, the phase of the estrous cycle, and the predominance of activated receptor subtypes. This dynamic balance explains its dual role as a facilitator or inhibitory modulator of pain, contributing to the sexual dimorphism in pain expression and suppression [64].

Progesterone modulates nociception through its PR-A and PR-B receptors and via its neuroactive metabolites such as allopregnanolone, which acts as a positive modulator of $GABA_A$ receptors and reduces neuronal excitability. These effects are primarily exerted on sensory neurons and glial cells [84]. Furthermore, progesterone can interact directly with sigma-1 receptors (σ_1R), intracellular chaper-

one proteins that regulate neuronal excitability. Unlike its metabolites, progesterone itself functions as an endogenous direct antagonist of σ_1R. Normal activation of σ_1R potentiates ion channels and NMDA receptors, facilitating nociceptive transmission and central sensitization; therefore, progesterone-mediated σ_1R antagonism contributes to reduced neuronal hyperexcitability [85]. In spinal cord injury models, progesterone administration has been shown to decrease microglial activation, reduce the release of IL-1β and TNF-α, and attenuate the overexpression of NMDA receptors, demonstrating its neuroprotective and analgesic effects [85] [86].

6.2. Male Hormones

Testosterone is the most potent and physiologically relevant form of androgen in males. Testosterone limits the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) [73] [87]. Furthermore, one study demonstrated that serum testosterone levels correlate with higher mechanical pain thresholds in normal male mice compared to castrated males and females, highlighting a key contribution of androgens to the regulation of pain sensitivity [88]. In this study, Androgen Receptor (AR) expression in primary sensory neurons—especially in CGRP neurons of the Dorsal Root Ganglion (DRG)—was unique to normal males, absent in castrated males or females, and its conditional deletion in sensory neurons reduced the mechanical pain threshold, with increased excitability of spinal dorsal horn neurons [88]. In animal models of neuropathic pain from sciatic nerve ligation, orchiectomy exacerbates hyperalgesia, which is reversed by exogenous testosterone administration, demonstrating the protective effect of androgen signaling [88].

Dehydroepiandrosterone (DHEA) and its sulfated form (DHEA-S) exert dual effects on nociception, which are determined by the pathophysiological context. Experimentally, it has been shown that intrathecal administration of DHEA-S under baseline or acute stress conditions increases glutamate release and decreases GABAergic inhibition in the dorsal horn of the spinal cord, thereby facilitating nociceptive transmission through activation of the σ_1 receptor and phosphorylation of the NR1 subunit of the NMDA receptor [89]. However, this pro-nociceptive effect is context-dependent. In states of hormonal dysregulation characterized by hypocortisolism or androgen deficiency, DHEA appears to play a predominant neuroprotective and anti-inflammatory role. Under these conditions, it acts by modulating the activity of Kv7 channels to stabilize the neuronal membrane and reduce microglial activation, thereby counteracting central sensitization and pain.

7. Receptors Involved in Pain Expression According to Sex

Among the main receptors involved in pain are hormonal (ER, AR and GPER1), neuronal (opioid, serotonergic, glutamatergic and cannabinoid), immunological (TLR4, macrophages, T cells, B cells, neutrophils, natural killers) and those belonging to the tyrosine kinase family (TrkB) and neurotrophin receptor (p75), whose

interactions support the sex-dependent differences in the perception and modulation of pain [63] [66] [69] [76].

7.1 Hormone Receptors

The Androgen Receptor (AR) in the spinal cord, amygdala, and dorsal root ganglia has antinociceptive effects by suppressing microglial activation and reducing the release of proinflammatory cytokines such as IL-1β and TNF-α [90]. Estrogen receptors (ERα, ERβ, and GPER1) modulate neuronal excitability through genomic and non-genomic mechanisms. Stimulation of ERα induces glutamate release in the dorsal horn of the spinal cord, intensifying central sensitization. Conversely, ERβ and GPER1 have antinociceptive effects, inhibiting the expression of proinflammatory mediators and promoting the release of inhibitory neurotransmitters [70]. Progesterone receptors participate in the inhibitory modulation of pain through the synthesis of neurosteroids such as allopregnanolone, which enhances GABAergic neurotransmission and reduces neuronal excitability [91].

7.2. Opioids

Opioid receptors, particularly the μ-Opioid Receptor (MOR) and the κ-Opioid Receptor (KOR), play a central role in endogenous and pharmacological analgesia. In rodent models, MOR expression has been observed to show sex-dependent differences: recent studies with transgenic mice show distinct and sex-specific expression of mu opioid receptors, with a lower proportion of neurons expressing MOR in certain cortical areas of females. Furthermore, literature reviews indicate that females may require higher doses of μ-opioid agonists to achieve effects similar to those seen in males [92]. Regarding the KOR system, it has been documented that females exhibit greater sensitivity to KOR agonists in neuropathic pain models, which suggests a specific sexual regulation of this pathway [93]. These functional differences could originate from variations in intracellular docking, receptor dimerization (e.g., MOR/KOR), and modulation by gonadal hormones [94] [95].

7.3. Glutamatergic (NMDA/AMPA) Receptors

Glutamate receptors, especially NMDA receptors, are very important for synaptic plasticity, long-term strengthening, and central sensitization in chronic pain research. In rodents, dorsal horn neurons have been observed to have sex differences in NMDA receptor activation following nerve injury [96]. These observations indicate that females may exhibit greater NMDA activation, which could contribute to the chronicity of pain. This occurs due to increased calcium influx, greater neuronal excitability, and decreased GABAergic inhibition [97].

7.4. Serotonergic

The serotonergic system also shows implications in pain modulation with sex differences. A review study suggests that the mechanisms that reduce pain signaling,

involving 5-HT1A and 5-HT3 receptors, may function differently in men and women. This may influence how pain signaling is controlled [98]. However, specific data on serotonergic subtype density in rodents by sex are still scarce.

7.5. Endocannabinoids

The endocannabinoid system (CB1 and CB2 receptors) helps regulate the release of glutamate and other signals that stimulate neurons, as well as influencing glial cell inflammation. Although research focusing on the sexual dimorphism of this system is still emerging, some clinical and preclinical reports suggest that the efficacy of cannabinoid agonists may vary by sex, possibly due to differences in CB1/CB2 expression or coupling [99].

7.6. Immunological

Immune cells, such as macrophages, CD4 T lymphocytes, and neutrophils, exhibit both pro-nociceptive and anti-nociceptive effects. Immune cells release cytokines and mediators that directly influence the excitability of nociceptors. While proinflammatory cytokines promote pain, anti-inflammatory cytokines such as IL-10, IL-4, and TGF-β can reduce pain perception. For example, IL-10 acts directly on nociceptors to generate analgesic effects, and the absence of the IL-10 receptor in nociceptors increases pain [100]. IL-4 inhibits nociceptor sensitization and promotes the production of endogenous opioids by macrophages [101].

7.7. Neurotrophic Receptors

Neurotrophic receptors, especially TrkB (tropomyosin receptor kinase B) and p75NTR (p75 neurotrophin receptor), are fundamental for synaptic plasticity, neuronal survival, and the control of chronic pain. Both mediate the actions of Brain-Derived Neurotrophic Factor (BDNF), which is an important modulator of neuronal excitability and central sensitization that occurs after inflammatory or neuropathic injuries [102].

The TrkB receptor, which has a high affinity for BDNF, activates intracellular signaling pathways such as PI3K/Akt, MAPK/ERK, and PLCγ, which promote synaptic potentiation and nociceptive transmission. In rodent models of neuropathic pain, BDNF-TrkB overexpression in the dorsal horn of the spinal cord contributes to GABAergic disinhibition and hyperexcitability. Neuronal mechanisms that facilitate the chronicity of pain [103]. Recent studies indicate that this pathway shows sex differences [104]. In males, BDNF released by microglia is a key activator of the TrkB pathway, which directly leads to GABAergic disinhibition [105]. Under pathological conditions, p75NTR enhances the release of proinflammatory cytokines (TNF-α, IL-1β) and microglial activation, contributing to persistent pain [106] [107]. The interaction between TrkB and p75NTR determines the balance between neuroprotection and sensitization. Hormonal factors directly affect its expression: estrogens increase the production of the Ntrk2 gene (which encodes TrkB) and enhance receptor activation, while testosterone decreases p75NTR

expression, helping to control neuroinflammation [106]. This neurotrophic-hormonal coupling explains the sex dimorphism in synaptic plasticity and the chronicity of pain.

8. Therapeutic Routes

Historically, opiates have largely been the cornerstone of pain treatment, whether acute or chronic, due to their availability and effectiveness. However, with increased use, associated risks have been revealed: tolerance, dependence, and overdose [108]. Their mechanism involves binding to the same opioid receptors in the central nervous system, producing similar analgesic and euphoric effects [109]. Multiple studies have shown that morphine is more effective in males than in females, demonstrating that this variability is due to differences in the location or binding to opiate receptors and to physiological mechanisms or anatomical differences between the sexes, rather than to its pharmacokinetics [110].

Regarding estrogens, estrogen receptors are present throughout the Central Nervous System (CNS): amygdala, thalamus, nociceptive areas, and Anterior Cingulate Cortex (ACC). Previous studies demonstrate that estrogen can regulate the sensory system and pain. Studies in mice have shown that the lack or absence of estrogen triggered by ovariectomy produces hyperalgesia, while its administration eliminates it [76]. In rats exposed to a continuous increase in estrogen as hormone replacement therapy, the analgesic effect of estrogen was suppressed in the early phase of ovariectomy, resulting in an increase in ERα and a decrease in ERβ. On the other hand, in rats whose estrogen levels gradually decreased, both receptors were slightly increased. The results show that a slight increase in both receptors restores the nociceptive threshold, compared to when only one of the receptors remains elevated. In other words, the analgesic effects of estrogens depend on the exposure time and the balance between the different types of receptors that are activated or increased, and their interaction with each other [111].

On the other hand, testosterone has an inhibitory modulatory effect on pain. Preclinical research has shown that the Transient Receptor Potential Vanilloid 1 (TRPV1) receptor is overexpressed in orchiectomized male rats and female rats. When testosterone levels are low or decrease, TRPV1 receptor expression increases, causing increased pain sensitivity. However, in mice treated with testosterone replacement therapy, this receptor decreases, as does musculoskeletal pain [86]. Regarding the TRPV1 receptor, agonists are generally used as a therapeutic measure for pain. One of them is capsaicin, which is the prototype TRPV1 agonist. When the agonist stimulates the receptor, after an initial excitation period, a refractory period of desensitization follows, meaning the neuron stops responding to new stimuli. If this stimulus is applied in high doses, a reversible degeneration of the peripheral nerve terminals occurs, resulting in a decrease in local sensitivity for a time [112].

9. Conclusions

Consideration of biological sex and hormonal context is crucial in the perception

of pain. Preclinical research confirms sexual dimorphism in pain perception. Hormonal and immunological differences explain this variability. Animal pain models validate this sexual difference and suggest possible molecular mechanisms involved. Therefore, preclinical research provides a paradigm for the development of more effective analgesics for pain specific to men and women.

Conflicts of Interest

There is no conflict of interest in carrying out this study.

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