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Review article

Sex differences in pain and opioid mediated antinociception: Modulatory role of gonadal hormones

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ABSTRACT

Sex-related differences in pain and opioids has been the focus of many researches. It is demonstrated that women experience greater clinical pain, lower pain threshold and tolerance, more sensitivity and distress to experimentally induced pain compared to men. Sex differences in response to opioid treatment revealed inconsistent results. However, the etiology of these disparities is not fully elucidated. It is, therefore, conceivable now that this literature merits to be revisited comprehensively. Possible multifaceted factors seem to be associated. These include neuroanatomical, hormonal, neuroimmunological, psychological, social and cultural aspects and comorbidities. This review aims at providing an overview of the substantial literature documenting the sex differences in pain and analgesic response to opioids from animal and human studies within the context of the modulatory effects of the aforementioned factors. A detailed and critical discussion of the cellular and molecular signaling pathways underlying the modulatory actions of gonadal hormones in the sexual dimorphism in pain processing and opioid analgesia is extensively presented. It is indicated that sexual dimorphic activation of certain brain regions contributes to differential pain sensitivity between females and males. Plausible crosstalk between sex hormones and neuroimmunological signaling pertinent to toll-like and purinergic receptors is uncovered as causal cues underlying sexually dimorphic pain and opioid analgesia. Conceivably, a thorough understanding of these factors may aid in sex-related advancement in pain therapeutic management.

1. Introduction

Pain is defined as an unpleasant sensory and emotional sensation associated with physical damage [1]. It is the most common debilitating disorder, which can negatively affect the patient's quality of life [2]. Clinically, pain assessment is problematic as different emotional responses are evoked in patients having comparable injuries. Pain is classified into different types namely; acute, chronic, somatic, visceral and neuropathic pain [3]. The prevalence of pain complains is very high in clinical centers [4]. A systematic review and meta-analysis has reported the prevalence of different types of pain in general adult populations of low- and middle-income countries as follows: headache (42%), temporomandibular disorder (35%), unspecified chronic pain (34%), low back pain (21%), joint pain (14%), chronic migraine (12%), chronic tension type headache (8%), and chronic pelvic/prostatitis pain (4%) [5]. Pain management is a complex challenge for most primary care physicians [6]. For decades, opioids have been regarded worldwide as the mainstay for treatment of moderate to severe pain. However, its use is often faced with plethora of side effects-related clinical challenges including tolerance, dependence and likehood of abuse [7,8].

Recently, many epidemiological studies demonstrated greater pain spreading and sensitivity among women relative to men [9]. Consequently, specifying sex differences in pain is critical for clinical pain management. Multiple published reviews discussed the factors contributing to sex differences in response to analgesia [10–14] namely, neural, hormonal, pathological, psychological, neuroimmunological and sociocultural factors. However, articles addressing how signaling pathways of sex hormones mediate pain sensation and opioid actions are relatively scarce [4,15,16]. Therefore, the aim of this article is to generally present an overview of these factors in modulating pain sensation and to specifically highlight the differential role of sex hormones and their signaling pathways in mediating pain perception as well as opioid-induced analgesia.

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2. Sex-based epidemiology of pain and responses to opioid analgesics

Many studies provide evidence that women are at greater risk than men for many clinical pain conditions, such as fibromyalgia, chronic fatigue syndrome and interstitial cystitis [17]. Consistent with these observations are the clinical findings related to sex differences in experimentally induced pain. In this sense, it has been shown that, in comparison with men, healthy women have significantly lower pain threshold and tolerance for electrical [18–21], pressure [22–26] and thermal stimuli [27–32]. Moreover, females experience greater sensitivity to temporal summation of pain [33–35], as well as to muscle pain induced by intramuscular injections of glutamate and hypertonic saline [36–40].

Sex differences in response to treatment with opioids revealed inconsistent results [41–43]. Females have been shown to consume 30% more morphine than males to attain the same extent of analgesia [42]. In other studies, greater morphine analgesia has been reported among females than males [41] and no sex difference has been found in response to morphine-induced analgesia [43]. However, given that the morphine-associated adverse effects, including headache, nausea and dysphoria, are more pronounced in women compared to men, the quantitative consumption of opioids may not be a key indicator of pain relief [43]. A similar profile of contradictory results has been also shown in different animal pain models. In this context, male rats show more sensitivity to the analgesic effects of morphine than females in the hot-plate, abdominal-constriction and tail-flick tests [44]. On the other hand, in the CBA/J strain, females exhibit a 5-fold increase in sensitivity to morphine compared to males [45].

Sex differences in response to μ-opioid agonists other than morphine have also been addressed. Women consume significantly more tramadol than men after cholecystectomy [46]. Likewise, animal studies in mice showed that the value of ED_{50} of tramadol antinociception is significantly lower in males than in females, indicating that males are more sensitive to the drug [47]. To extend observations, researchers have investigated the antinociceptive responses to partial opioid agonists in women compared to men [48–52]. In management of post-dental surgery pain, women show enduring analgesic responses compared to men treated with pentazocine, nalbuphine and butorphanol [48,49]. On the other hand, men have shown a hyperalgesic response to low dose nalbuphine that can be ameliorated with a subanalgesic dose of morphine [50]. Women also show greater pain relief using pentazocine/naloxone combination therapy following endodontic surgery compared with men [51]. Contrary to dental pain, patients treated in the emergency room for trauma-related pain showed no sex-related differences using butorphanol [52]. These clinical findings suggest more boosting antinociceptive responses to partial opioid agonists among women experiencing dental pain relative to the inconsistent sex-related differences in the analgesic response to pure μ-opioid drugs.

3. Factors contributing to sex differences in pain and analgesia

Various factors contribute to the sex differences in pain and analgesia observed in the clinical and the experimental settings. These factors include 1) neuroanatomical factors; 2) hormonal aspects; 3) neuroimmunological, 4) psychological factors; 5) social and cultural aspects as well as 6) comorbidities (Fig. 1).

3.1. Neuroanatomical factors

The periaqueductal gray (PAG), present in the midbrain, projects descending neurons to the noradrenergic pontine and the rostral ventromedial medulla (RVM). PAG is one of the main anatomical structures

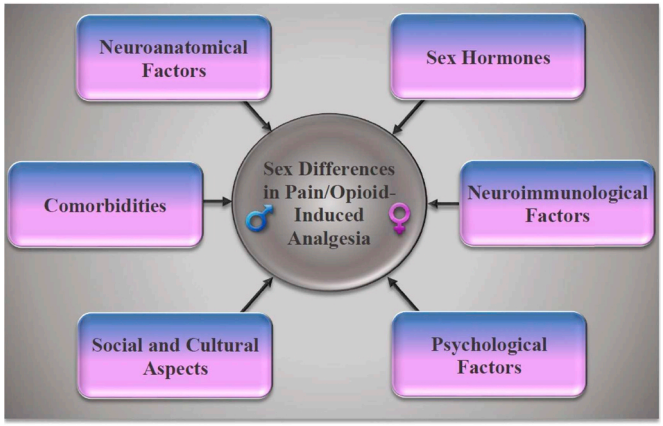

Fig. 1. Different factors involved in sexual dimorphism in response to pain and opioid analgesia.

mediating inhibition of nociceptive inputs at the level of the spinal cord via noradrenaline and serotonin release [53]. Activation of these descending modulatory circuits is induced by inflammatory pain and contributes to opioid-induced antinociception [54]. Quantitative and qualitative aspects regarding the PAG-RVM neural projections are sexually dimorphic. In comparison to males, female rats have been found to have significantly more PAG-RVM neural projections. However, much less PAG-RVM output neurons are activated by persistent inflammatory pain in females than in males [55]. In addition, brain imaging studies show sexually dimorphic activation of certain brain regions, such as the anterior cingulate cortex (ACC), the insular cortex (IC) and the medial prefrontal cortex (MPC), known to play a key role in the sensory, cognitive and emotional aspects of pain [56]. For example, women show greater activation in MPC, IC and ACC in response to thermal and electrical stimuli [56]. Sex difference in other brain areas activated by visceral stimulus has also been documented. For instance, while female patients with irritable bowel syndrome exhibit much greater activation in the ventromedial prefrontal cortex, ACC and left amygdala, male patients display greater activation of the PAG, right dorsolateral prefrontal cortex and insula [57].

In published epidemiological studies, the receptor intensity present in the central nervous system greatly influences the differences in opioid-induced antinociception between men and women [58]. The ventrolateral region of the caudal PAG, including the dorsal raphe nucleus, is the most sensitive site to μ opioid receptor-mediated antinociception [59]. The PAG represents an essential structure for the systemic opioid-mediated antinociception, since opioid specific antagonism of the PAG abolishes this antinociception [60]. The μ opioid receptors expressed in PAG are higher in male than in female rats, the fact that positively correlates with the sex difference in morphine-induced analgesia, suggesting that males require less morphine than females [55].

Central administration of opioids into the PAG in different species, including rats [61–63], cats [64], in addition to electrically-stimulated PAG in humans [65], induces antinociception with sex related-difference. This antinociception is diminished by central [66] or systemic [67] administration of the opioid antagonist, naloxone, indicating that the opioid receptor mechanism mediates the antinociception originated from the PAG. In spite of the observation that supraspinal opioid administration to the PAG [63] and RVM [68] produce more antinociception in males, other studies have reported greater antinociception in females [63] or no observed sex difference [69,70]. These contradictory results may be attributed to the nature of the nociceptive stimulus, the relative potency of the μ agonists, the use of conscious

versus anesthetized rats, the hormonal stage of the estrous cycle of females, and the animal species or strain [71], in addition to the structural or functional difference of the midbrain PAG in the descending pain pathway in males and females.

3.2. Hormonal effects

3.2.1. Hormonal effect on pain

Sex hormones are believed to be involved in sex-dependent pain. The influence of sex hormones on nociception can be both organizational, of long-term developmental influences, and activational, which is associated with transient effects in adulthood [72]. One approach to investigate the role of gonadal hormones in pain perception is via gonadal steroid manipulations such as gonadectomy and hormone replacement therapy either at birth or at adulthood to determine organizational effects or activational effects, respectively. Published data concerning the organizational effects of the hormones reveal that the early presence of testosterone and its metabolites during male rat development exerts an antinociceptive effect in inflammation-induced mechanical allodynia [73]. Furthermore, the administration of testosterone reverses the inflammation-induced sensitivity in males gonadectomized in adulthood, but not in males gonadectomized neonatally. These findings indicate that testosterone in early life is essential for the long-life integrity of the endogenous antinociceptive mechanisms against mechanical stimuli following inflammation [73].

Results of studies that addressed the activational effects of gonadal hormones are inconsistent. Interestingly, male rats required a higher dose of capsaicin to induce hyperalgesia, compared to female rats. The potency of capsaicin is significantly increased in males and decreased in female rats when gonadectomized [74]. Likewise, male rats have less nociceptive responses to formalin injection than females. This difference is abolished when both sexes are gonadectomized [75]. Similarly, it has been demonstrated that, in comparison to intact female rats, the induction of hyperalgesia following alcohol ingestion is less rapid and severe in ovariectomized rats and that the alcohol-induced neuropathy is reproduced by estrogen replacement in the female rats [76]. Moreover, estradiol has been shown to mediate a greater sensitivity to thermal and mechanical nociceptive stimuli in female than male mice and that this phenomenon is attenuated following estrogen receptor gene ablation [77].

In contrast, estrogens have been demonstrated to exert antinociceptive action in visceral pain-related [78] and formalin-induced behavior [79]. Nonetheless, the bimodal actions of estrogens are far much complicated and influenced by the phases of the menstrual cycle. In this sense, results of meta-analytic study have revealed that whereas higher pain threshold and tolerance to ischemic muscle, thermal and pressure pain are associated with the follicular phase, lower pain thresholds to electrical pain are noticed in the luteal phase [80]. Table 1 summaries the correlation between gonadal hormones and sexual dimorphism in different pain models in clinical and animal studies.

The implication of gonadal hormones in the sex-correlated difference in pain is further proven by different brain imaging techniques, which reveal an interaction of gonadal hormones with pain-processing brain regions [81] as well as with the endogenous opioid system [82,83]. For example, the activity in the pain inhibitory brain region, RVM, in response to thermal noxious stimuli, significantly increases with increasing testosterone in women using combined oral contraceptive pills [81]. On the other hand, in an experimentally induced sustained pain setting, women treated with micronized estradiol show an increased μ-opioid neurotransmission tone in the thalamus, nucleus accumbens, and amygdala [83]. Findings of animal studies using different assay techniques have illustrated also a direct interaction between gonadal hormones and the endogenous opioid system. In one study, testosterone replacement therapy following gonadectomy has been found to elicit a significant increase in beta-endorphin concentration in many hypothalamic brain areas and in plasma in female rats, but not in male rats [84]. Furthermore, a functional association between the estrogen receptors alpha and the endogenous δ and κ opioid receptors has been shown in the spinal cord, where the content and secretion of methionine-enkephalin and β-endorphin is directly regulated by estrogen receptors [85]. In contrast, a genetic study using trigeminal formalin model mice knockout for aromatase, the enzyme responsible for the conversion of testosterone to 17β-estradiol, has displayed an increased nociceptive behavior, which is reversed by estradiol treatment [86].

Multiple studies have been carried out in an attempt to explore the cellular and molecular mechanisms underlying the modulatory actions of gonadal hormones in the sexual dimorphism in pain processing. The nociceptive actions of estradiol may contribute to the sexual dimorphism of temporomandibular disorders pain sensitivity through upregulation of the hippocampal expression of transient receptor potential vanilloid 1, which is known to play a key role in central pain processing [87,88]. On the other hand, 17β-estradiol administration significantly increases sensitivity to mechanical and thermal pain stimuli via the upregulation of N-methyl-D-aspartate (NMDA) receptor 1 expression in dorsal root ganglia [89]. Similarly, estradiol has been found to increase the spinal expression of NMDA receptor NR1 subunit in the visceral pain model [90]. Interestingly, the antinociceptive

Table 1
Studies showing correlation between gonadal hormones and sexual dimorphism in pain.

Type of studies		Type of pain	Findings	Reference
Clinical Experimental Studies	Ischemic muscle, thermal and pressure	Higher pain thresholds in follicular phase	[80]	
	Electrical	Higher pain thresholds in luteal phase	[80]	
	Thermal	Testosterone increases RVM activity	[81]	
	Sustained deep somatic	Greater μ-opioid system activation in men than women during follicular phase	[82,83]	
Animal Studies	Inflammation-induced mechanical allodynia	Antinociceptive effects of testosterone	[73]	
	Chemical (capsaicin)	Antinociceptive effects of testosterone	[74]	
	Chemical (formalin)	Antinociceptive effects of testosterone	[75]	
	Alcohol-induced neuropathy	Nociceptive effects of estrogen	[76]	
	Thermal and mechanical nociceptive stimuli	Nociceptive effects of estrogen	[77]	
	Visceral	Antinociceptive effects of estrogen	[78]	
	Chemical (formalin)	Antinociceptive effects of estrogen	[79]	
	———	Increase in plasma and hypothalamic β-endorphin concentration in females than males with testosterone replacement therapy following gonadectomy	[84]	
	———	Estrogen-mediated regulation of content and secretion of methionine-enkephalin and β-endorphin	[85]	
	Trigeminal formalin induced pain	Lack of estrogen increases pain	[86]	

Table 2
Animal studies showing the influence of gonadal hormones on opioid-induced analgesia.

Opioid drug	Type of pain test	Animal Species	Findings	Reference
Etorphine Buprenorphine Dezocine Butorphanol Nalbuphine	Thermal	F344 and Sprague Dawley rats	Decreased and increased antinociception in male and female rats, respectively, following gonadectomy	[101]
Morphine	Thermal	Sprague Dawley Rats	Decreased antinociception in male rats following gonadectomy	[97]
	Thermal	Swiss-Webster mice	Decreased antinociception in male mice following gonadectomy	[98]
	Thermal	Sprague Dawley rats	Decreased and increased antinociception in male and female rats, respectively, following gonadectomy	[103,111]
	Thermal	F344 & Sprague Dawley rats	Decreased antinociception in male rats following gonadectomy	[101]
	Thermal & mechanical	Rats	Unaltered antinociception in male rats following gonadectomy	[44]
	Thermal & mechanical	Rats & mice	Varied age-related changes in morphine's dose-response as a function of sex, with decreases in ED_{50} for sham males and increases in ED_{50} for sham females	[99]
	Thermal	Sprague Dawley Rats	Reduced morphine-induced analgesia during both proestrus and estrus in comparison to diestrus	[58]
	Thermal/ jump test	Sprague Dawley Rats	Abrogation of sex-related differences in morphine-induced antinociception after castration or testosterone administration to female rats in neonatal but not in adult rats	[100,105]
	Thermal	Charles Foster Strain Rats	Attenuated morphine-induced analgesia following ovariectomy	[106]
	Thermal	Sprague-Dawley rats	Reduced morphine-induced analgesia in the estrus in comparison to the diestrus or proestrus phase	[69,103]
	Thermal	CD-1 mice	Comparable morphine-induced analgesia across all phases of the estrus cycle	[107]
	Thermal	Swiss–Webster mice	More profound morphine-induced analgesia during diestrus compared to proestrus phase	[107]
SNC 80 (δ receptor-selective opioid)	Thermal	Sprague-Dawley rats	Unaltered and decreased antinociception in male and female rats, respectively, in the tail withdrawal test following gonadectomy	[111]
Hydromorphone	Thermal	Sprague-Dawley rats	Unaltered and increased antinociception in male and female rats, respectively, in the tail withdrawal test foloowing gonadectomy	[111]
U50,488 (κ receptor-selective opioid)	Thermal	Sprague-Dawley rats	Unaltered and decreased antinociception in the tail withdrawal and hot plate test, respectively, in both male and female rats following gonadectomy	[111]

Table 3
Clinical studies showing the influence of gonadal hormones on opioid-induced analgesia.

Opioid drug	Type of pain	Findings	Reference
Morphine	Ischemic pain	Increased sensitivity to pain among women during the follicular compared to the luteal phase	[108]
	Labor pain	Profoung analgesia in non-pregnant women, but absent in painful uterine contraction during the first stage of parturition	[109]
	Total abdominal hysterectomy	Comparable post-operative analgesic needs between women in luteal and follicular phases	[110]
Pethidine	Labor pain	Profound analgesia in non-pregnant women, but absent in painful uterine contraction during the first stage of parturition	[109]
Tramadol	Total abdominal hysterectomy	Comparable post-operative analgesic needs between women in luteal and follicular phases	[110]

actions of 17β-estradiol injected in the intra-locus coeruleus region in response to formalin-induced pain has been shown to be facilitated by activation of NMDA receptors [91]. Likewise, the analgesic effect of intra-nucleus paragigantocellularis lateralis injection of 17β-estradiol on the formalin-induced inflammatory pain has been reported to be mediated via activation of membrane-bound $GABA_A$ receptors [92]. An interaction between estrogen and serotonin has been detected by the study of Chauvel et al. [93], which shows that the intraperitoneal injection of serotonin decreases the occurrence of cortical spreading depression, the likely cause of the migraine aura, during the estrous phase of cycling rats, but not in males. As for the testosterone interactions accountable for sexual dimorphism in pain, findings point out to the ability of testosterone, but not estradiol, to upregulate cannabinoid receptor [94] and μ-opioid receptor [95] in trigeminal ganglia under inflammatory conditions in male, but not female rats. Testosterone antihyperalgesic effects are also suggestive of its potential to suppress the transcription of inflammatory pain mediators, such as interleukin (IL)-4 and γ-interferon [96].

3.2.2. Hormonal effect on opioid antinociception

The contributory role of sex hormones in the differences in opioid-induced antinociception is evident in many studies [97–102]. The antinociceptive effects of high-efficacy opioids (etorphine and morphine) and the low-efficacy opioids (buprenorphine and dezocine), as well as the mixed-action opioids (butorphanol and nalbuphine), are more potent in gonadally intact male rats compared to female rats. Moreover, the magnitude of the observed antinociception is profoundly decreased and increased by gonadectomy in male and female rats, respectively [101]. This suggests an antinociceptive role of testosterone and pronociceptive role of estrogen. The decrease in the sensitivity to morphine following castration in male rats is a coherent finding of other studies [97,98,103]. Moreover, the attenuated responses to morphine in castrated rats are blunted by testosterone replacement [97,103]. However, other studies have shown that the potency of morphine following castration is either increased [99] or unaltered [44]. Besides many experimental variables such as subject age, opioid dose [104], rodent strain and opioid efficacy [101], the inconsistency of results is attributed to the timed gonadectomy methodology. Whereas sex-related differences in opioid antinociception observed in adult rats are abrogated via castration of male pups or testosterone administration to female neonates, they are still noticeable when castration or testosterone administration is performed in adult rats, suggestive of an organizational, rather than activational, effect of gonadal hormones [100,105]. Similar pattern of discrepancy is noticeable in female rats eliciting an increased [99,101], decreased [106], or unchanged [44,100] opioid induce-antinociception following gonadectomy.

The extent of opioid analgesia seems to be greatly influenced by the hormonal level in different phases of the estrus cycle. For instance, during the estrus phase, the antinociceptive effect of systemically [103] or intracerebroventrically [69] administered morphine is significantly less than that noted during the diestrus (when estrogen and progesterone are lowest) or proestrus (when estrogen level is high). On the other hand, a contradictory observation has been reported by Loyd et al. [58], showing that morphine-induced analgesia is reduced during both proestrus and estrus in comparison to diestrus. Interestingly, the impact of the estrus cycle-related hormonal fluctuation on morphine analgesia seems to be interrelated with genotype of the animal used. Whereas the antinociceptive effect of morphine is comparable across all phases of the estrus cycle in CD-1 mice, it is more profound in Swiss–Webster mice during diestrus compared to proestrus phase [107]. The association between the hormonal menstrual cycle phases and the opioid analgesic responses has also been reported in clinical studies. In one study, it has been shown that normally cycling women are more sensitive to morphine analgesia for ischemic pain during the follicular compared to the luteal phase [108]. Moreover, Olofsson et al. [109] reported that morphine and pethidine produce analgesia in non-pregnant women, whereas these opioids show no analgesic potency over painful uterine contraction during the first stage of parturition. In contrast, no significant difference in the overall tramadol or morphine consumption has been observed between women in luteal and follicular phases following total abdominal hysterectomy [110].

The effects of gonadal hormones are also agonist-specific. Barring the exception that testosterone decreases the antinociception mediated by the δ receptor–selective agonist, SNC 80 [111], it increases the sensitivity of male mature rats to μ and κ receptor–selective agonists [97,98,101,103,111].

On the other hand, the impact of the female sex hormones, estrogen and progesterone, on modulation of opioid antinociception has been revealed to be dependent on the selectivity of opioid agonist. Ovariectomy of female rats increases, decreases, or has no effect on receptor antinociception following administration of morphine and hydromorphone (high efficacy μ opioid receptor agonist), SNC 80 (δ opioid receptor agonist) or U50,488 (κ opioid receptor agonist), respectively, in the tail withdrawal test [111]. However, different antinociceptive responses to these opioids have been demonstrated upon employing other nociceptive tests [111], indicating a further interrelation between the modulatory effects of gonadal hormones on opioid analgesia and the type of the nociceptive stimuli. Tables 2 and 3 present studies describing the effect of gonadal hormones on opioid analgesia in animal and clinical studies, respectively.

Based on the common secondary messenger pathways and co-expression of opioid receptors and gonadal steroid hormone receptors in the PAG [112] and spinal cord [113], it is postulated that a signaling crosstalk among estrogen and opioid receptors contribute to the sex differences in opioid mediated analgesia [114]. The overlapping signaling cascades include the mitogen-activated protein kinases (MAPK), protein kinase A (PKA), B (PKB), C (PKC), phospholipase C, inositol triphosphate, ERK and tyrosine kinases [114,115]. Although not directly linked to sex-related differences in opioid analgesia, the interactions between gonadal steroid hormone receptors and opioid receptors, described in previous physiological and pharmacological studies, may underlie the molecular mechanisms of the regulatory actions of gonadal hormones on opioid-harnessed analgesia. For example, estradiol has been shown to rapidly attenuate the ability of the selective μ-opioid agonist, DAMGO, to hyperpolarize guinea pig hypothalamic neurons via binding to a specific receptor, which activates PKA to uncouple μ opioid receptors from its inwardly rectifying K^+ channels [116]. Moreover, estradiol has also been revealed to provoke μ opioid

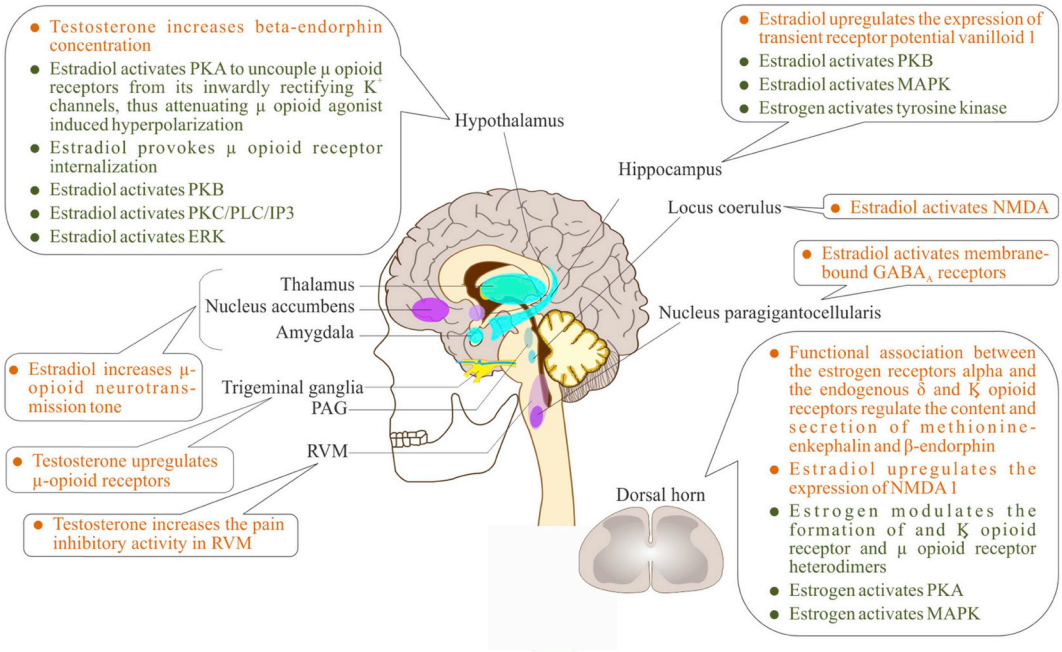

Fig. 2. Interactions of gonadal hormones in pain-processing brain regions and opioid-induced antinociception.
Footnote: Orange and green writings showing the effect of gonadal hormones on pain and opioid-induced antinociception, respectively.

receptor internalization [117], thus, decreasing opioid binding sites availability on the cell membrane. Finally, the spinal synthesis of estrogen has been found essential for the formation of κ and μ opioid receptor heterodimers [113], which are 4-fold greater in the spinal cord of proestrus female versus male rats [118]. These heterodimers are prerequisite for eliciting the sexually dimorphic spinal morphine antinociception [118]. Studies aimed at exploring the cellular and molecular mechanisms underlying testosterone modulatory effects on opioid analgesia are scarce. However, it has been demonstrated that androgen receptors activate the transcriptional machinery of the μ opioid receptor gene under inflammatory conditions in the trigeminal sensory neurons [119]. Nevertheless, future studies are warranted to determine the antihyperalgesic role of testosterone in the sexual dimorphism of opioid-mediated analgesia. A model of the interaction of gonadal hormones with different pain-processing brain regions and opioid-induced antinociception is depicted in Fig. 2.

3.3. Neuroimmunological factors

The concept of pain-evoked modulation of immune function has been previously published [120–123]. More recently, the involvement of the immune system in pain processing has been suggested to be sex-dependent, accounting for the sexual dimorphism in inflammatory and neuropathic pain [124]. Notably, immune and immune-like glial cells have been reported to exert both pro- and antinociceptive effects following injury via the release of pro- and anti-inflammatory mediators [125].

Developing evidence suggest that females manifest greater proinflammatory immune responses to tissue damage than males [125–127]. The enhanced proinflammatory cytokine release accounts for the development of more inflammation and pain [125]. This may partially explain the increased prevalence of autoimmune diseases and associated inflammatory pain in females [125,127,128]. Adding another point of complexity, sex hormones serve as potential mechanistic underpinnings of the immunity-related sex difference in pain processing [14,124,125]. Therefore, in this section, a special attention is directed to the sex hormones-immune system interactions as potentially causal factors contributing to the observed sex differences in pain.

3.3.1. Impact of sex differences in the activity of immunocompetent cells and their secretion of inflammatory mediators

Sexual dimorphism in pain can be attributed to qualitatively different immunity cell population dictated by sex hormones. For instance, higher testosterone level in males evokes an anti-inflammatory $CD4^+$ Th2-dominant immune population, whereas higher baseline estrogen and progesterone levels in females generate an inflammatory $CD4^+$ Th1-dominant immune population [125].

Sex differences in pain signaling also seem to be dependent on sex hormone-based differential activation of immunocompetent cells. Whereas pain hypersensitivity following either nerve injury or inflammation is mediated by activation of the spinal microglia in male mice, spinal cord T cells infiltration facilitates pain sensation in female mice [14]. In support of this observation, Taves et al. [129] showed that, following induction of neuropathic pain, only male mice have enhanced microglial activity of p38 MAPKs. Of note, intracellular kinases are activated by cellular stress as well as in response to inflammatory cytokines [130]. Testosterone preferentially activates the immune systems in both sexes, as castration elicited a response similar to that observed in females and as testosterone administration to castrated males, or to females, switched the pain pathway to a microglia-dependent one [14].

Sex hormones have been also implicated in shifting the activity of the immune system cells (Fig. 3). With that said, testosterone has been demonstrated to exert an anti-inflammatory effect via suppression of the release of the pro-inflammatory mediators, INFγ [131], IL-5 [96] and nitric oxide (NO) [132] by Th1, T cells and macrophages, respectively. This is accompanied by concomitant induction of anti-inflammatory cytokine production, IL-10, by Th2 cells [133] and by macrophages [132]. Given the aforementioned data, it is not surprising that men are at lower risk for autoimmune disease driven by these immune cells [134]. On the other hand, testosterone has been shown to elicit a pro-inflammatory response mediated by the release of proinflammatory cytokines, tumor necrosis factor (TNF-α), IL-6 and IL-1β, from astrocytes treated with lipopolysaccharide (LPS) [135].

Likewise, estradiol modulates the immune cell system in a dose-, time- and sex-dependent manner (Fig. 3). Whereas low doses of estradiol enhanced proinflammatory cytokines TNF-α release from T cells

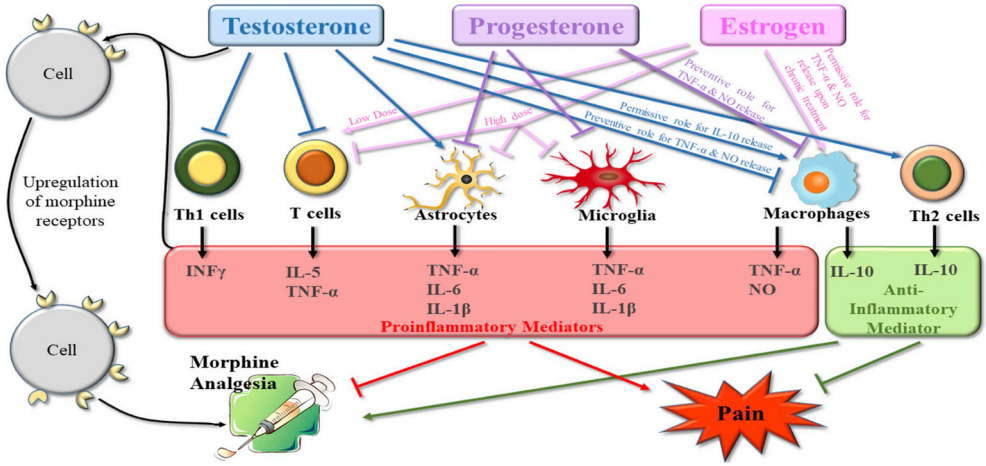

Fig. 3. Sex hormone-dependent release of inflammatory mediators from neuroimmune cells and its implication in pain and opioid analgesia.

Footnote: A schematic presentation for the interaction between sex hormones and inflammatory mediators in nociception and in opioid-induced analgesia. *Arrowheads indicate activation and perpendicular lines signify inhibition. Testosterone elicits the anti-inflammatory response by inhibiting the release of INFγ, IL-5 and NO by Th1, T cells and macrophages, respectively (Blue perpendicular lines) and by inducing the production of IL-10 by Th2 cells and by macrophage (Blue arrowheads), whereas it elicits a proinflammatory response by inducing the release of cytokines, TNF-α, IL-6 and IL-1β, from astrocytes (Blue arrowheads). Estrogen (low dose) enhances proinflammatory cytokines TNF-α, IL-5 release from T cells (pink arrowheads) and decreases (high dose) proinflammatory cytokine production in microglia, astrocytes and T cells (pink perpendicular line). Chronic estrogen triggers the proinflammatory mediators production in macrophages (pink arrowheads). Progesterone exerts anti-inflammatory effects by inhibiting activation of astrocyte, microglia and macrophage and by repressing the production of proinflammatory cytokines (IL-1β, IL-6 and TNF-α) and NO (purple perpendicular line). Typically, in contrast to the anti-inflammatory mediators, proinflammatory mediators antagonize morphine analgesia and promote nociception. The proinflammatory cytokines upregulates μ-opioid receptor expression in a testosterone-dependent manner. INFγ: γ-interferon; IL: interleukin; NO: nitric oxide; TNF-α: tumor necrosis factor-α.*

[136], high levels of estradiol decrease proinflammatory cytokine production in microglia [137], astrocytes [138] and T cells [136] in response to LPS exposure. Chronic but not acute estradiol administration in female mice stimulates the pro-inflammatory mediators production in macrophages [139]. Finally, estradiol supplementation downregulates LPS-induced IL-1β mRNA in female but not male hippocampal microglia [140].

With regards to progesterone, studies have shown that it exerts anti-inflammatory effects by inhibiting activation and proliferation of astrocyte and microglia/macrophage and by repressing the production of proinflammatory cytokines (IL-1β and TNF-α) and NO [141–143] (Fig. 3).

Interestingly, the sex differences in the analgesic effects of morphine seem to be linked to the sex hormone-imposed sexual dimorphism in innate immunity. The elegant study of Zhang et al. [95] has showed that the inflammatory cytokines such as TNFα, IL-1β and IL-6 upregulate μ-opioid receptor expression only in the trigeminal ganglia cultures from male rats. The cytokine-induced upregulation of μ-opioid receptor mRNA expression, suggestive of higher morphine analgesia, is abrogated in trigeminal ganglia from castrated male rats, and was restored with testosterone replacement [95]. On the other hand, no significant change in μ-opioid receptor mRNA expression has been observed in trigeminal ganglia cultures prepared from ovariectomized female rats [95]. Taken together, these observations provide an implicit reasoning for the reduced morphine-induced analgesia in females observed in several studies [144–146]. Nevertheless, given that uterine TNF, IL-1β, and IL-6 expressions increase during proestrus and estrus stages in rats [147,148], it is tempting to speculate that the lower morphine efficacy during the proestrus reported in another study [58] is due to the increased expression of inflammatory cytokines in this phase.

3.3.2. Impact of sex differences in the activity of immunocompetent cells receptors

The immune system's response to injury is initiated by the activation of pattern recognition receptors (PRRs), such as toll-like receptors (TLRs), through binding to noxious endogenous ligands [149]. The stimulation of TLRs activates downstream signaling pathways leading to the robust production and release of proinflammatory mediators [150], followed by upregulation of TLRs culminating in pain hypersensitivity [151]. TLRs are expressed on a wide variety of mammalian cell types including non-neuronal (e.g., microglia, astrocytes, oligodendrocytes) and sensory neuronal cells [151]. TLR2-5, TLR7 and TLR9 are implicated in pain processing with TLR4 being most studied [149]. Recently, sex differences in TLR-mediated pain has been suggested. Whereas stimulation of macrophages TLR4 initiates pain in male mice, stimulation of sensory neurons TLR4 evokes pain in female mice [152]. Not surprisingly, the TLR-mediated pain has been shown by other researchers to be sex hormone-dependent. For instance, the intrathecal administration of TLR agonist, LPS, causes allodynia in male but not female mice in a testosterone-dependent manner [153]. Moreover, the regulation of TLR expression seems to be under the influence of sex hormones in an age-dependent manner [140]. Although TLR4 mRNA expression is not significantly altered by estradiol supplementation to neonatal microglia and astrocytes, it is significantly upregulated only in female adult microglia. Interestingly, estradiol administration in vivo upregulates TLR4 mRNA expression in response to LPS, in both sexes [140].

Recent studies have revealed the engagement of TLR4 signaling in the sexually dimorphic effects of morphine [154,155]. LPS activation of ventrolateral PAG TLR4 results in a rightward shift in the morphine dose–response curve in females compared with males. The observed sex difference in morphine analgesia is reversed by blockade of ventrolateral PAG TLR4 [154,155]. As mentioned earlier, TLR4 activation induces the release of proinflammatory mediators, thus reducing morphine-induced analgesia [156]. Interestingly, morphine is reported to activate glial TLR4 by binding to TLR4 co-receptor, myeloid differentiation factor 2 [157], thereby initiating a neuroinflammatory response and paradoxical hyperalgesia [11]. Nevertheless, given the crosstalk between estradiol and TLR4 [140], it is reasonable to hypothesize that estradiol may augment TLR4 activation in response to opioid administration, implicating the contribution of sex hormones in the sex differences in the TLR4 modulation of morphine analgesia.

3.3.3. Impact of sex differences in the activity of purinergic signaling

Following nerve injury, activated microglia also respond with upregulation of purinergic receptors [134]. Stimulation of purinergic receptors by extracellular ATP leads to the production of proinflammatory mediators, thus evoking and maintaining neuropathic pain [158]. Many studies have succeeded in illustrating sexual dimorphism

in the expression of microglial purinergic receptors (P2R), namely, ionotropic (P2X) and metabotropic (P2Y) receptors. For example, basal expressions of P2X1, P2X4, P2X7, P2Y12, and P2Y13 are found lower in females than males, whereas mRNA levels of P2X3, P2X5, and P2Y4 are higher in microglia from females compared to males [159,160]. However, nerve injury precipitates an increased cell surface expression and function of P2X4Rs in spinal microglia from male rats only, which is attenuated by the intrathecally administered P2X4R antagonist [161].

The influence of sex hormones on P2R expression has been proven by many studies. For instance, estrogen increases P2X1 and P2X7 mRNA levels in microglia isolated from castrated males, but not from ovariectomized females, whereas it preserves P2X4 expression in microglia isolated from either sex [162]. On the other hand, P2X3 receptor is upregulated in dorsal root ganglia of pregnant [163] and ovariectomized [164] rats but remains unchanged following castration [164]. Furthermore, the increased P2X3 expression is reversed by estrogen replacement [164].

In addition to the established role of microglial P2R in mediating pain, spinal glial P1Rs (adenosine receptors), including A_1, A_{2A}, A_{2B} and A_3R, have been implicated in regulating pain [165]. Additionally, sex hormone modulation of P1R expression in the context of pain has been recently proposed by Fried et al. [166]. It is known that activation of A_1 and A_{2A} receptor induces antinociception and nociception, respectively [167]. Given that estradiol increases A_1 receptor expression in breast cancer cell line [168] and ovariectomy decreases A_{2A} receptors expression [169], the occurrence of menstrual migraine at the start of the menses, during which estrogen and progesterone levels suddenly decrease [166], suggests a plausible crosstalk between sex hormones and adenosine signaling, underlying sexually dimorphic pain.

3.4. Psychological aspects

Many psychological and affective aspects have been reported to influence the coping, interpretation and reporting of pain as well as treatment outcomes in both sexes. For example, men manage their pain by self-distraction and problem-focused tackles, whereas females tend to resort to emotion-focused tactics, catastrophizing, positive self-statements and social support [9]. In addition, some psychological disorders, such as anxiety and depression, are associated with the experience and report of certain types of pain. For instance, depressive symptoms have been found to predict future musculoskeletal disorders, including lower back pain [170,171]. Interestingly, positive emotions, such as positive mood, are associated with a reduction of reported pain in women but not in men [172]. Are women more emotional than men? A question that greatly reflects sex difference on pain expression. In a meta-analysis of sex differences in the feeling of motions [173], women tend to experience more negative emotions, such as more guilt, shame and embarrassment than men do and, consequently, report more painful sensation than men do. Furthermore, many researchers have documented a positive correlation between the current experience of pain and the pain history in females rather than males [174]. For example, childhood sexual abuse is associated with increased adult pain complains, such as migraine, abdominal pain and back pain [175], poorer self-reported health, and exacerbated negative impact in healthy adults [176].

The impact of psychological aspects on the analgesic responses to and the consumption of opioids by both sexes can be dictated by the following observations. Given that sex-specific effects, such as erectile dysfunction, have been reported in patients receiving opioids [177], it can be inferred that men have decreased inclination for requesting opioids to avoid such unwanted effects. However, a population-based cohort study has showed that age-matched men prescribed opioids for chronic non-cancer pain are at higher risk than women for escalation to high-dose therapy and death of opioid overdose. Although the link between sex differences and the risk of dose escalation or opioid-induced mortality is not determined, it could be partly due to greater propensity of men to high risk behaviors surrounding opioids than their women counterparts [178]. On the other hand, lower opioid consumption among women is probably impelled by the increased susceptibility to the associated adverse effects, namely nausea and vomiting [179].

3.5. Social and cultural aspects

Sex-specific sociocultural norms greatly contribute to sex difference in pain perception. Generally, expression of pain is socially more acceptable among women, who tend to experience pain with greater emotion and display more worries about the consequences of pain [180]. In contrast, men tend to show more increased pain tolerance and greater resistance in reporting pain [34]. Gender role expectations seem to be another contextual factor contributing to sex differences in performance on the experimental pain task [181]. In this sense, women exhibit reduced pain threshold, enhanced pain unpleasantness and less pain tolerance in the cold pressor task pain, compared with men [182]. On the other hand, an opposite opinion may be raised, suggesting women as profound candidates for endorsing themselves with greater pain severity in an effort to maintain their role in the family [183]. Nevertheless, the examiner sex greatly influences the pain threshold of both males and females. While men can tolerate more pain in the presence of a female nurse or physician [184], pain threshold of women drops dramatically in presence of an attractive male examiner, and hence they report higher pain levels [185]. A similar profile is reported by Kállai et al. [186], who found that cold pain tolerance is higher for both females and males when examined by a laboratory personnel of the opposite sex. Aging has been negatively correlated with pain threshold by many researchers [187,188], and it tends to blunt the difference between men and women regarding pain threshold [189].

Social and cultural aspects seem to differentially influence opioid consumption among men and women to achieve pain relief using different opioid administration settings. Whereas self-administration of opioids using patient-controlled analgesia is associated with lower postoperative opioid consumption among women than men [190], provider-administering morphine is associated with lower opioid consumption among men than women [191], suggesting that men are reluctant to confess pain or request analgesic from the provider. Sex-difference in response to opioids has been found to change as a function of age. It has been shown that sex difference in opioid relief of postoperative pain is more pronounced in younger participants, with women requiring higher doses of morphine. This difference is not observed in elderly subjects [191]. In another study, Zheng et al. [192] demonstrated that older women received more opioids compared to older men and that such sex difference in opioid consumption is absent in younger groups. Discrepancies between these studies might be attributed to other confounders, such as psychological variables and physical impairment [192].

3.6. Comorbidities

Comorbidities frequently occur with pain and tend to substantially augment illness severity, which may consequently influence treatment outcomes [193]. Comorbid mood disorders are more commonly associated with pain in women than men [192]. For example, several lines of evidence reveal that depression and pain are highly comorbid and that women have higher prevalence of depression than men [10]. Moreover, in comparison to men, women tend to experience higher levels of anxiety, which has been associated with increased clinical pain and amplified experimental pain sensitivity [10]. However, men have been shown to exhibit more anxiety-associated pain than women [194]. Comorbid eating-related disorders, as well as metabolic-related disorders, are more prevalent in men than women [195]. In addition, physical-related comorbidities, such as cancer and non-cancer pain, are more common in females than males [196]. Similarly, a significant positive association between pain and medical comorbidities, like

hypertension, diabetes, asthma, osteoarthritis, osteoporosis, cardiac and respiratory problems, are significantly more profound in females than males [197]. Notably, these comorbidities have been documented as significant predictors of poor opioid treatment outcomes [197,198]. Taken together, it is not surprising that females need to consume 30% more morphine than males to attain the same extent of analgesia [190], especially that they anecdotally report that pain relief for one disorder provides analgesia for another [199].

4. Conclusions

An increasing amount of evidence indicates that there are significant sex differences in clinical and experimental pain sensitivity in men and women. The factors underlying sex differences in the experience of pain are multifactorial and complex. Psychological and sociocultural factors such as pain-related catastrophizing may explain sex-based differences in reporting certain types of pain and opioid consumption. Gonadal hormones also have a substantial impact on perception of different types of pain, as well as on the analgesic response to opioids. Additionally, the existence of differences in endogenous pain inhibitory circuitry may contribute to the sex difference in pain sensation. Neuroimmunological aspects are additional factors that require attention in future studies examining sexual dimorphism in pain and opioid analgesia. Further and in-depth exploration of these contributing factors is warranted for sex-based tailoring of pain management.

Declaration of competing interest

The authors have declared no conflicts of interest.

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List of abbreviations

A: Adenosine
ACC: Anterior cingulate cortex
DH: Dorsal horn
IC: Insular cortex
IL: Interleukin
INFγ: γ-Interferon
LPS: Lipopolysaccharide
MAPK: Mitogen-activated protein kinases
MPC: Medial prefrontal cortex
NMDA: N-methyl-D-aspartate
NO: Nitric oxide
P2R: Purinergic receptor
PAG: Periaqueductal gray
PKA, PKB, PKC: Protein kinase A, Protein kinase B, Protein kinase C
PRRs: Pattern recognition receptors
RVM: Rostral ventromedial medulla
TLR: Toll-like receptor
TNF-α: Tumor necrosis factor-α
δ: delta
κ: kappa
μ: mu