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# ThermoTRP channels in pain sexual dimorphism: new insights for drug intervention

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ABSTRACT

Chronic pain is a major burden for the society and remains more prevalent and severe in females. The presence of chronic pain is linked to persistent alterations in the peripheral and the central nervous system. One of the main types of peripheral pain transducers are the transient receptor potential channels (TRP), also known as thermoTRP channels, which intervene in the perception of hot and cold external stimuli. These channels, and especially TRPV1, TRPA1 and TRPM8, have been subjected to profound investigation because of their role as thermosensors and also because of their implication in acute and chronic pain. Surprisingly, their sensitivity to endogenous signaling has been far less studied. Cumulative evidence suggests that the function of these channels may be differently modulated in males and females, in part through sexual hormones, and this could constitute a significant contributor to the sex differences in chronic pain. Here, we review the exciting advances in thermoTRP pharmacology for males and females in two paradigmatic types of chronic pain with a strong peripheral component: chronic migraine and chemotherapy-induced peripheral neuropathy (CIPN). The possibilities of peripheral druggability offered by these channels and the differential exploitation for men and women represent a development opportunity that will lead to a significant increment of the armamentarium of analgesic medicines for personalized chronic pain treatment.


**Contents**



*Abbreviations:* 5-HTF1, 5-hydroxytryptamine 1F; ASCO, American Society of Clinical Oncology; CGRP, calcitonin gene related peptide; CIPN, chemotherapy induced peripheral neuropathy; CLR/RAMP1, calcitonin receptor-like receptor/receptor activity modifying protein-1; DRG, dorsal root ganglion; eGFP, enhanced green fluorescent protein; ER, estrogen receptor; FDA, Food and Drug Administration; IB4, Isolectin B4; iPSC, induced pluripotent stem cells; NGF, nerve growth factor; NO, nitric oxide; NSAIDs, Nonsteroidal anti-inflammatory drugs; PACAP, pituitary adenylate cyclase-activating polypeptide; PAG, periaqueductal gray; PKCε, protein kinase C-epsilon; ROS, reactive oxygen species; RVM, rostral ventromedial medulla; S1PR1, sphingosine-1-phosphate receptor; σ-1R, sigma-1 receptor; SD, spreading depression; SNP, single-nucleotide polymorphisms; TLR, Toll-like receptor; TNC, trigeminal nucleus caudalis; TrkA, tropomyosin-related kinase A; TRP, transient receptor potential; TRPA1, transient receptor potential ankyrin 1; TRPM3, transient receptor potential melastatin 3; TRPM8, transient receptor potential melastatin 8; TRPV1, transient receptor potential vanilloid type 1; TRPV2, transient receptor potential vanilloid type 2; TRPV3, transient receptor potential vanilloid type 3; TRPV4, transient receptor potential vanilloid type 4.

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## 1. Introduction

Chronic pain is a major health challenge of our society affecting up to 20% of the population that suffer pain daily. The high prevalence and the disabling condition of pain has a notable social and economic impact. A seminal study estimated an annual yearly cost of 635 billion$ for USA. This estimate includes the main costs associated to the syndrome, namely cost of medical care and treatment and productivity loss (Gaskin & Richard, 2012). Similar values could be estimated for the rest of the world suggesting an overall economic impact of 3–10% GDP (Breivik, Eisenberg, & O'Brien, 2013). Despite this enormous societal burden, the therapeutics for treating chronic pain continue to be surprisingly limited, being still concentrated mainly in nonsteroidal anti-inflammatory drugs (NSAIDs) alone or combined with acetaminophen along with anti-convulsant and anti-epileptic pharmacotherapy for pain types resistant to current analgesics.

Several reasons may be considered for the poor efficacy of the pharmacological armamentarium available to alleviate chronic pain: (i) traditionally, pain has been considered an associated symptom to a disease rather than an illness itself. Fortunately, chronic pain is currently treated as a malady, which is resulting in a better medical and pharmaceutical attention of patients; (ii) chronic pain is a complex, multifactorial disease involving nociceptive, affective and/or cognitive aspects (Raja et al., 2020), which require an integrated and coordinated interdisciplinary collaboration of preclinic and clinic researchers; (iii) the genetic/epigenetic factors driving predisposition to develop chronic pain constitutes still a major gap of our knowledge; (iv) pre-clinical animal models partially mimic the pathophysiology of chronic pain, and for some types of pain such as migraine, back pain and fibromyalgia we do not have yet compelling models; (v) opiates, the cornerstone for the management of acute moderate to severe pain, show poor efficacy in chronic pain and represent a source of adverse events that can threaten the safety of the chronic patients; (vi) pre-clinical testing to evaluate the anti-hyperalgesic and anti-allodynic potency and efficacy of drug candidates has been performed in cohorts of young males, resulting in a plethora of analgesic candidates that failed in clinical trials that use heterogeneous cohorts of patients; and, (vii) chronic pain exhibits a strong sex dimorphism with an overall higher prevalence in women than in men that has been largely overlooked by the preclinical research community until 2014 (Clayton & Collins, 2014). Noteworthy, the pain community has started to consider sex as a significant variable, resulting in the use of females in preclinical studies, including when testing drug candidates. Taken together, a notable endeavor in the right direction has been undertaken, although additional efforts are still required to fully comprehend the underlying mechanisms contributing to the sexual dimorphism of chronic pain.

Transient receptor potential (TRP) channels are sensory proteins that include more than 50 cation channels with widely varying functions and ubiquitous distribution in various cells and tissues. Some members of the TRP channel family, such as ankyrin 1 (TRPA1), vanilloid subtypes 1, 2 and 4 (TRPV1, 2 and 4), and melastatin 3 and 8 (TRPM3 and TRPM8), are sensors of thermal, mechanical and chemical stimuli (Huang, Li, Dhaka, Story, & Cao, 2012; Sousa-Valente, Andreou, Urban, & Nagy, 2014). The physiological relevance of TRP channels was recently acknowledged after the award of the Nobel Prize of Medicine to Prof. David Julius and Ardem Patapoutian, for their discoveries on these thermal and mechanical transducers (Ledford & Callaway, 2021). These channels are abundantly expressed in primary sensory neurons mainly in dorsal root and trigeminal ganglia (Huang et al., 2012; Sousa-Valente et al., 2014). Other less-studied thermosensory channel are TRPV3, primarily expressed in keratinocytes (Peier et al., 2002) and TRPV4, found in primary afferents and skin cells including keratinocytes, macrophages and mast cells (Zhang, Henry, & Chen, 2021). These channels are members of the so-called thermoTRP channel family and encode neuronal responses from noxious cold to harmful heat (Fig. 1). Notably, simultaneous knockout of TRPV1, TRPA1 and TRPM3 eliminated acute noxious heat responses in mice (Vandewauw et al., 2018), while deletion of TRPM8 affected cold sensing (Peier et al., 2002). Complementary, thermoTRPs are also gated by chemical agents such as capsaicin (TRPV1), menthol (TRPM8), allicin (TRPA1) and pregnenolone sulfate (TRPM3) (Silverman, Chen, Kravatz, Chavan, & Chang, 2020; Vriens et al., 2011), and the activity of some members may be notably enhanced by pro-inflammatory and/or pro-algesic agents (Silverman et al., 2020). Because of their $Ca^{2+}$ permeability, stimulation of most thermoTRP channels promotes the release of pro-inflammatory peptides such as αCGRP that contribute to peripheral sensory sensitization (Alarcón-Alarcón et al., 2022; Bautista et al., 2005; Citak et al., 2022; Devesa et al., 2014; Kichko, Neuhuber, Kobal, & Reeh, 2018; Meng et al., 2009; Ponsati et al., 2012), as well as to trigger pain episodes such as those in migraine (Meng et al., 2009). An important progress has been attained understanding some of the physiological roles of these channels, unveiling a contribution to body temperature homeostasis (Señarís, Ordás, Reimúndez, & Viana, 2018), which appears important to prevent the thermal dysfunction produced by potent and selective channel antagonists (Koivisto, Belvisi, Gaudet, & Szallasi, 2022). Structurally, thermoTRP channels exhibit an overall similar structure of four identical subunits, assembled around a central aqueous pore that organizes the permeation pathway (Fig. 1), and includes a selectivity ionic filter and the channel gates (Latorre, Zaelzer, & Brauchi, 2009). Cryo-electron microscopy has significantly contributed to unveil the structure-function correlates of thermoTRPs and paved the way for a rational design of drugs that control dysfunctional channels in pathological states, such as chronic inflammatory pain, chemotherapy-induced peripheral neuropathy (CIPN) and migraine (Artero-Morales, González-Rodríguez, & Ferrer-Montiel, 2018; Schumacher, 2010; Villalba-Riquelme, de la Torre-Martínez, Fernández-Carvajal, & Ferrer-Montiel, 2022).

Noteworthy, a growing body of research suggests the functional modulation of these receptors by sex hormones that may contribute to the different sex prevalence observed in conditions of chronic pain, as exemplified by migraine that exhibits a 3 times higher prevalence in women than in men (Artero-Morales et al., 2018; Stewart, Shechter, & Rasmussen, 1994). For instance, TRPM8 appears to be activated by testosterone (Asuthkar et al., 2015), and to a lower extent also by progesterone and estradiol (Mohandass et al., 2020). Indeed, TRPM8 has shown roles in pain, migraine, CIPN, and dimorphic sexual behavior (Alarcón-Alarcón et al., 2022; Chasman et al., 2011; Liu et al., 2013; Mohandass et al., 2020; Villalba-Riquelme et al., 2022; Wei, Kim, & McKemy, 2022). TRPM3 is gated by pregnenolone sulfate (Vriens et al., 2011), and TRPV1 and TRPA1 appear to interact with the progesterone receptor Sig-1a receptor (Cortés-Montero, Sánchez-Blázquez, Onetti, Merlos, & Garzón, 2019; Marcotti et al., 2022). Thus, modulation of thermoTRPs by sex hormones open new venues for understanding the sex dimorphism in chronic pain, as well as to develop more personalized analgesic drugs.

Sex differences in pain prevalence and severity are quite evident and excellent reviews have been published on sex dimorphism in chronic pain, including both preclinical and clinical studies, and the reader is referred to these reviews for further information (Gregus, Levine,

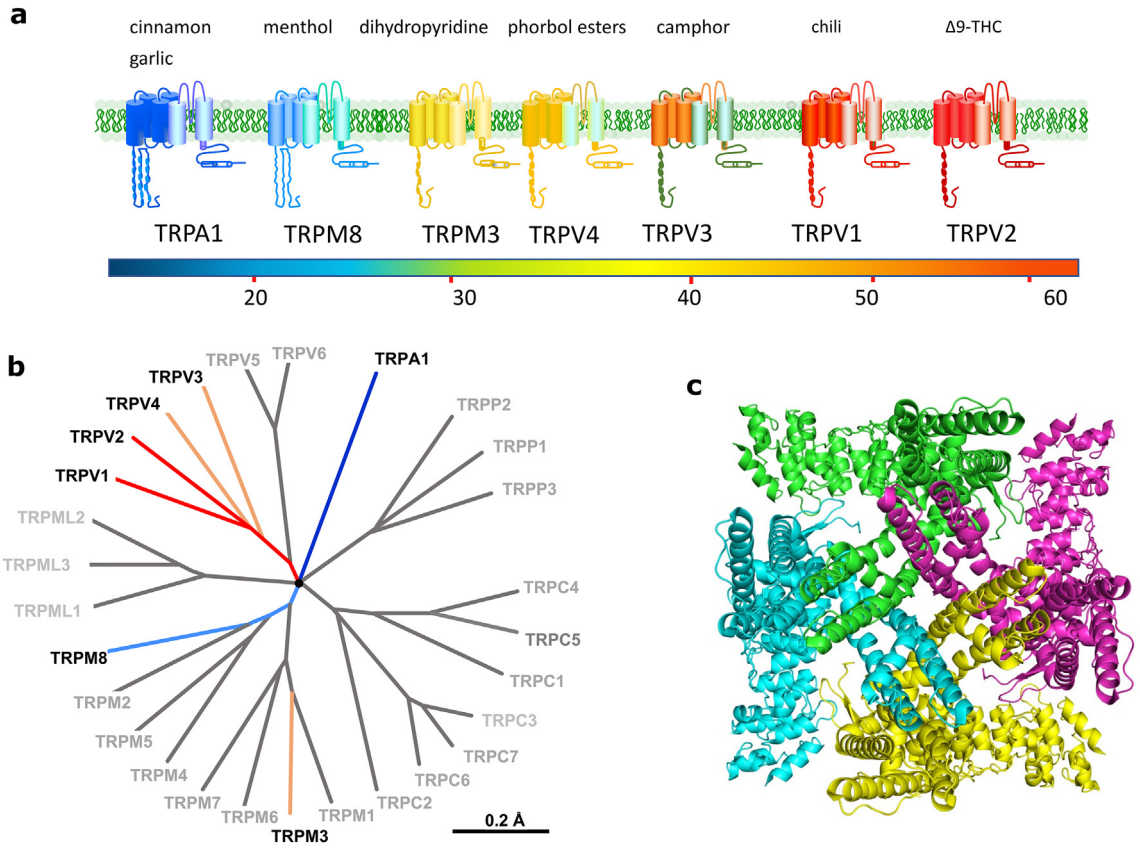


**Fig. 1. ThermoTRP Channels. a.** Schematic representation of the six mammalian thermoTRP channels. Each subunit consists of six transmembrane domains (S1–S6), a hydrophilic pore loop linking transmembrane segments five (S5) and six (S6), and large cytoplasmic N- and C- terminals (NB: not drawn to scale). All thermoTRPs have a variable number of ankyrin repeat domains in the N-terminus (except TRPM8 which has none). ThermoTRPs display distinct thermal thresholds from noxious hot (TRPV2) to cold (TRPA1). Each thermoTRP is also activated by specific natural compounds and by synthetic substances, which are also known to induce relevant thermal and pain sensations in humans. **b.** Phylogenic tree of human TRP channels. Based on sequence homology, all TRP channels fall into seven subfamilies that comprise proteins with distinct channel properties. The thermoTRP are represented by colors based on their temperature activation range, in deep red appear those channels activated by noxious heat (TRPV2 ≥52°C; TRPV1 ≥43°C), in orange those activated by warm temperatures (TRPV3 ≥36°C; TRPM3 ≥30°C and TRPV4 ≥34°C) in light blue channel activated by cold (TRPM8 ≤28°C), and the one activated by noxious cold (TRPA1 ≤17°C) is represented by deep blue. The bar (0.2) indicates point accepted mutation units, which is the evolutionary distance between two amino acids (1 point accepted mutation unit = 1 point mutation event per 100 amino acids, which is accepted and is passed to progeny). **c.** Upper view of the ribbon structural model of a typical tetramer arrangement of TRP channels. These channels may form homomeric or, within a subfamily, heteromeric channel complexes.

Eddinger, Yaksh, & Buczynski, 2021; Mogil, 2020; Presto, Mazzitelli, Junell, Griffin, & Neugebauer, 2022). These differences appear to have a strong hormonal component, although the precise details and impact are yet under intense investigation. A paradigmatic example of chronic pain syndrome with a significant sex dimorphism is chronic migraine that is up to 3 times more common in women than in men (Lagman-Bartolome & Lay, 2019; Safiri et al., 2022). In addition, chronic migraine also exhibits a strong hormonal influence as the higher prevalence is centered during the women fertile period (Stovner et al. 2018). Similarly, CIPN is a neuropathic type of pain produced due to the nerve damage caused by chemotherapeutic agents that has been also shown to exhibit sex dimorphism (Schmetzer & Flörcken, 2012). For tumors with a similar incidence for women and men, sex differences in CIPN prevalence depends on the chemotherapeutic regime used. Here, we review the information available for the contribution of thermoTRP channels to chronic migraine and CIPN, as these are two paradigmatic chronic pain syndromes that exhibit a demonstrated sex dimorphism. Interestingly, although the molecular mechanisms that cause both pathologies are radically different, they share as a common factor the functional alteration of some TRP channels, the so-called thermoTRP, whose activity is also differently modulated depending on sex. Although still quite in its infancy, the role of sex and gender in chronic pain and its influence in pain therapeutics has become a hot topic in pain transduction and pharmacology research. In this context, thermoTRP receptors have emerged as druggable targets for customized pain control in individuals of any sex.

## 2. Sexual dimorphism of chronic migraine

Migraine is a recurrent primary head pain of moderate to severe intensity, usually manifested by episodes of disabling unilateral headache with pulsatile characteristics (Ferrari et al., 2022). This clinical condition affects 1 in 7 people, which makes around 1 billion people worldwide (Safiri et al., 2022). Several factors are associated with increased migraine risk, including female sex, being of middle age or overexposure to stressful conditions. Point prevalence of migraine is similar in boys and girls before puberty (~5%) but during adolescence it begins to increase at a higher rate in females, reaching peak levels at around the 40 years of age, when it affects 35% of women and 15% of men. Then, prevalence starts to decrease gradually to become again similar in men and women after the 50 years of age (~5%) (Stovner et al. 2018). Overall, around 2 in 3 migraine patients are females, and compared to men, women also report stronger migraine-related symptoms and disability (Lagman-Bartolome & Lay, 2019). Migraine has a strong polygenetic component (Hautakangas et al., 2022), being highly heritable (34–57%, (Mulder et al., 2003)) and more common in individuals with European ancestors (Key et al., 2018). It has intermediate prevalence in Asian countries located at intermediate latitudes and is less frequent in African populations (Key et al., 2018). The striking higher prevalence of migraine in females has been attributed to genetic factors, to the sexual hormone milieu and to differences in pain and stress responsiveness (Safiri et al., 2022), but the precise mechanisms involved are still poorly understood.

Migraines typically start with prodromal symptoms that last between hours and days and can include fatigue, drowsiness, nausea and vomiting, yawning, mental slowness, impaired concentration, or photophobia (Stovner et al. 2018). This long-lasting premonition is occasionally followed by a minutes-to-hour phase of aura that involves positive visual manifestations such as flashing lights (scintillation) and signs of loss of function like darkening of the visual field (scotoma), paresthesia or motor/speech impairments. Afterwards, the headache crisis begins, and a disabling, generally unilateral and throbbing head pain is presented during 4 to 72 hours, accompanied by photophobia, phonophobia, hypersensitivity to touch and/or nausea and vomiting. The painful and invalidating crisis can be followed by postdromal symptoms which last from hours to days after the resolution of the headache, mainly tiredness, hyperesthesia or allodynia, somnolence, and certain degree of cognitive dysfunction (Ferrari et al., 2022; Louter et al., 2013). In addition, psychiatric and non-psychiatric comorbidities such as anxiety and depression, epilepsy or myocardial infarction can coexist (Ferrari et al., 2022) and the quality of life of the patients is certainly impaired.

NSAIDs or paracetamol constitute the first-line pharmacological treatment for migraine, followed by triptans as second-line medications, alone or combined with fast-acting NSAIDs (Eigenbrodt et al., 2021). Third-line drugs include gepants, which are calcitonin gene related peptide receptor (αCGRP) antagonists and diptans, which are agonists of serotonin 5-HT1F receptors. When required, adjunct prokinetic/antiemetic medications like domperidone or metoclopramide are administered to inhibit nausea and vomiting. Among novel therapies that have been tested to mitigate highly frequent migraine crisis (>15 episodes month) stands up botulinum neurotoxin A (Botox), the first therapeutic specifically approved for chronic migraine by the US Food and Drug Administration (FDA) (Chen et al., 2021), useful for very resistant and disabling migraines. Furthermore, a monoclonal antibody, Erenumab (Aimovig®, Amgen & Novartis), that targets the calcitonin-gen related peptide (αCGRP) receptor, along with Fremanezumab (Ajovy™, TEVA Pharmaceuticals), galcanezumab (Emgality, Eli Lilly) and eptinezumab (Vyepti, Lundbeck), monoclonal antibodies raised against CGRP peptides, were approved as preventive therapy for episodic migraines in 2018 and there is moderate-to-high quality evidence of efficacy for chronic and episodic migraine (Sacco et al., 2022). Note that these therapeutics are targeting the αCGRP signalling pathway, as the "gepant" family of compounds, indicating that this pathway is pivotal in migraine. Noteworthy, αCGRP is released from peptidergic trigeminal nociceptors by activation of thermoTRP channels such as TRPV1 and TRPA1 (Alarcón-Alarcón et al., 2022; Bautista et al., 2005; Devesa et al., 2014; Meng et al., 2009; Ponsati et al., 2012), and modulated by TRPM8 (Citak et al., 2022; Kichko et al., 2018). These channels configurate an interesting therapeutic axis of the αCGRP signalling pathway and may be also involved in the sex dimorphism of the disease.

The period lived with disability in individuals suffering of migraine has kept similar along the years despite the available pharmacotherapy, and the pronounced sexual dimorphism is still patent (Safiri et al., 2022). Thus, the precise causes of the pronounced sexual dimorphism need to be clarified, particularly which pathophysiological differences between males and females are involved and also whether these differences contribute to a divergence in the response to current or potential pharmacological treatments (Paige et al., 2022). In this sense, thermoTRP receptors that have been closely involved in migraine pathophysiology, are abundantly expressed in the trigeminal system innervating the meninges, and, importantly, have shown differential modulation by male and female sexual hormones, thereby they are postulated in this review as potential modulators of chronic migraine amenable for adaptation to men and women.

The pathogenesis of migraine, i.e. the mechanisms explaining why and how migraine crisis are triggered or happen spontaneously, remains poorly understood probably because of the relative unpredictability of migraine attacks (Ferrari et al., 2022). Exposures to environmental irritants or to stressful events are known to trigger migraine-related pain in experimental models and in sensitive individuals, involving the stimulation of primary afferents and the participation of the hypothalamus, a brain region crucial in homeostatic and hormonal control (Iyengar, Johnson, Ossipov, & Aurora, 2019). The aura phase, found in certain individuals, is associated with spreading depression (SD), a slowly-propagating wave of intense depolarization that happens all at once in most neurons and glia of a given gray matter brain region (Ferrari et al., 2022). Such depolarization is followed by suppression of all spontaneous o evoked electrical activity in the same area (depression), generating a wave that spreads at a speed of ~3 mm/s, generally from the occipital area towards more rostral regions (Ferrari et al., 2022). The SD event lasts around 1 minute and is followed by arterial dilation and hyperoxygenation (Ayata & Lauritzen, 2015). At this point, increases in the production/release of Nitric Oxide (NO) and ROS are detected experimentally around trigeminal axons innervating meningeal vasculature (Garthwaite, Charles, & Chess-Williams, 1988; Pradhan, Bertels, & Akerman, 2018; Read, Smith, Hunter, & Parsons, 1997). NO has vasodilatory effects and stimulates neurotransmitter release, especially of αCGRP, a pivotal contributor to migraine pain (Ashina et al., 2019). Other mediators are also released and contribute to neurogenic inflammation and mastocyte degranulation, including substance P, pituitary adenylate cyclase-activating polypeptide (PACAP), bradykinin, neurokinin A, Nerve Growth Factor (NGF), prostaglandin or eicosanoids (Sarchielli et al., 2006; Spekker, Tanaka, Szabó, & Vécsei, 2021). These primary afferent neurons innervating the meninges extend their central terminals to the trigeminal nucleus caudalis (TNC) of the cervical spinal cord, where they synapse with high-threshold and wide dynamic range neurons that receive also input from primary afferents innervating the periorbital skin and pericranial muscles (Ferrari et al., 2022; Iyengar et al., 2019). TNC neurons connect with the thalamus, the first and main relay center of nociceptive information in the brain. There, thalamic neurons integrate peripheral nociceptive information through projections to the somatosensory cortex, which processes information on somatotopic localization, and to limbic regions of the brain such as the amygdala or the striatum, which evoke the affective-motivational components of pain (Bushnell, Ceko, & Low, 2013). TNC neurons also send inputs to the hypothalamus via the thalamus, thereby affecting autonomic responses such as the wake/sleep cycle, the nausea or the vomiting. At the same time there is a hypothalamic/thalamic top-down modulation of the periaqueductal gray (PAG), a brain area crucial in the descending modulation of pain. The PAG conveys affective-motivational, hormonal and circadian/homeostatic information and exerts its modulatory activity through is connections with On and Off cells of the rostral ventromedial medulla (RVM), which facilitate (On) or inhibit (Off) nociceptive transmission in the TNC synapses of the cervical spinal cord (Fields, 2004; Holland, 2009). Indeed, progressive failures in descending inhibitory control of the trigeminal system have been described to favor migraine-related pain in laboratory animals (Boyer, Dallel, Artola, & Monconduit, 2014). Thus, the trigeminal system reacts to peripheral stimulation and to central descending modulation, constituting the cornerstone of migraine pain and offering at the same time the possibility of pharmacological control through peripheral targeting.

### 2.1. TRP channels in the pathophysiology of migraine

During recent years, a growing body of research has elucidated an important participation of TRP channels in the pathophysiology of migraine, mainly involving TRPA1, TRPV1 and TRPM8 channels, all three receptors prominently involved in thermosensation and expressed in primary afferent neurons of trigeminal and dorsal root ganglia. The presence of these receptors in the meningeal circuitry, normally kept at homeothermic temperature, suggests additional functions other than thermosensation, and offers exceptional possibilities for the control of migraine-related pain in a sex-dependent fashion.

### 2.2. TRPA1 and TRPV1

The relevance of TRPA1 in pain sensation in humans was evidenced with the finding of a gain-of-function mutation in the TRPA1 gene that causes episodes of debilitating pain after fasting or physical stress (Kremeyer et al., 2010). In the same line, several single-nucleotide polymorphisms (SNP) in the TRPV1 gene have been associated with the presence of migraine (Carreño et al., 2012; Yakubova et al., 2021). TRPA1 and TRPV1 are expressed in ~6–20% and 50% of trigeminal afferents, respectively, and virtually all TRPA1 fibers co-express TRPV1 (Fig. 2, diagram in **b**) (Bautista et al., 2005; Huang et al., 2012). Many of these TRPA1/TRPV1 fibers contain the migraine-inducing neuropeptide αCGRP. In these neurons, stimulation of TRPA1/TRPV1 elicits vesicular release of αCGRP, a process that induces migraine-related pain in preclinical models (Iannone, De Logu, Geppetti, & De Cesaris, 2022) and can be inhibited through specific TRP antagonists or by using exocytosis inhibitors (Alarcón-Alarcón et al., 2022; Bautista et al., 2005; Devesa et al., 2014; Meng et al., 2009; Ponsati et al., 2012).The promiscuity of TRPA1 and TRPV1 renders trigeminal neurons innervating the skin, the tongue or the olfactory system receptive to environmental physical stimuli (extreme cold and heat), and to external agents such as mustard oil, capsaicin, allyl isothiocyanate, acrolein, formaldehyde, cigarette smoke, umbellunone, all stimuli reportedly capable of inducing migraine-related pain in sensitive individuals, experimentally and in real life (Fig. 2, mechanisms in **d**) (Andrè et al., 2008; Bautista et al., 2006; Leishman et al., 2017; Nassini et al., 2012). However, TRPA1 and TRPV1 are also sensitive to physiologically relevant endogenous compounds. For instance, TRPV1 is a receptor of endovanilloids like anandamide (N-arachidonoylethanolamine) one of the main endogenous cannabinoids (Fig. 2, mechanisms in **a**) (Ross, 2003), and TRPA1 is targeted by reactive species of oxidative, nitrative or carbonylic stress (Fig. 2, mechanisms in **a**) (Iannone, Nassini, Patacchini, Geppetti, & De Logu, 2022; Marone et al., 2018; Miyake et al., 2016; Miyamoto, Dubin, Petrus, & Patapoutian, 2009; Sullivan et al., 2015).

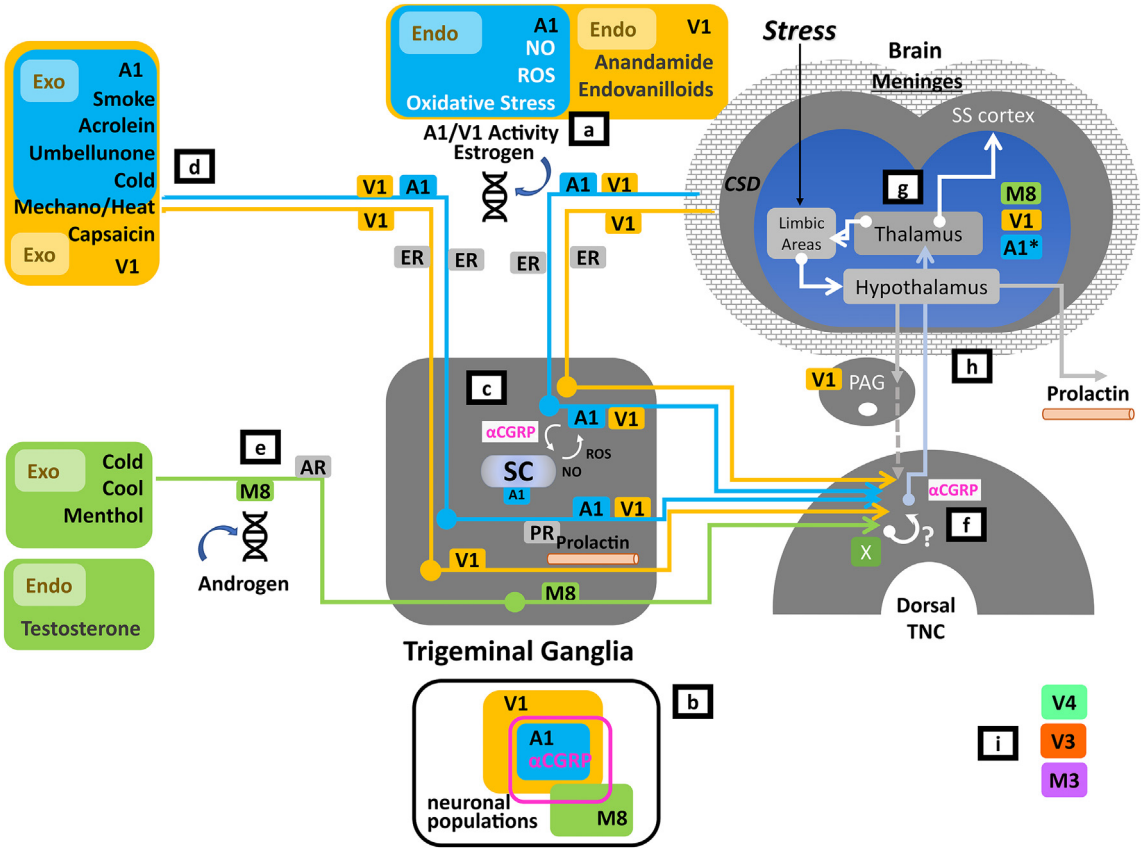


**Fig. 2. ThermoTRP channels in migraine and its sexual dimorphism. a.** After cortical spreading depression (CSD, Brain) or oxidative stress, endogenous agonists (Endo) of TRPA1 receptor such as Nitric Oxide (NO) or Reactive Oxygen Species (ROS) activate TRPA1 of primary afferents innervating the meninges and promote pain. Endogenous TRPV1 agonists such anandamide or other endovanilloids can also exert pronociceptive effects in the periphery. Stimulation of TRPA1/TRPV1 or estrogenic signaling through the estrogen receptor (ER) facilitates TRPV1 and TRPA1 overexpression. **b.** In the trigeminal ganglia, 97% of TRPA1 and 60–70% of TRPV1 neurons co-express the migraine-inducing neurotransmitter αCGRP, and almost all TRPA1 neurons express also TRPV1. TRPM8 neurons constitute around 10% of trigeminal population of which 26% co-express αCGRP. **c.** TRPA1 / TRPV1 stimulation promotes αCGRP release from trigeminal neurons. αCGRP stimulates receptors in Schwann cells (SC), which in turn release nitric oxide (NO) that activates Schwann cell TRPA1 and promotes generation of reactive oxygen species (ROS). ROS further enhance TRPA1 neuronal activation. Stimulation of prolactin receptor (PR) sensitizes TRPA1/TRPV1 neurons. **d.** Exogenous environmental irritants (Exo) can stimulate peripheral TRPA1/TRPV1 fibers involved in smell, taste, touch, heat, cold or noise detection and facilitate αCGRP release. **e.** Exogenous stimuli (Exo) such as cold/cool temperatures or menthol and the endogenous male hormone testosterone (Endo) can promote TRPM8 activity. Testosterone facilitates TRPM8 expression through stimulation of androgen receptor (AR). TRPM8 stimulation decreases TRPA1/TRPV1-associated pain. **f.** TRPA1/TRPV1 neurons release αCGRP in the dorsal trigeminal nucleus caudalis (TNC) and stimulate 2$^{nd}$ order neurons that send projections to the thalamus. This neurotransmission could be repressed through descending modulation from supraspinal areas or by TRPM8 peripheral activity, either directly through presynaptic glutamate receptors or through interneuron recruitment. **g.** TNC neurons synapse with thalamic neurons that send projections to the somatosensory cortex (SS cortex) which provides information of intensity, quality and duration of pain. Thalamic neurons also project to limbic areas such as the amygdala, which provide the emotional value of pain. TRPV1 and TRPM8 have been described in neurons of multiple brain areas and central TRPA1 expression has been described in glial cells. The central role of these receptors in migraine-related pain is mostly unknown. **h.** Stressful stimuli stimulate brain regions related with affective processing and also modify the activity of the hypothalamus. Female hypothalamic neurons activated after stress release more prolactin than male ones, and prolactin released to the bloodstream can sensitize TRPA1/TRPV1 neurons through prolactin receptor. TRPV1 stimulation in the PAG promotes descending inhibition of pain by modulating TNC neurotransmission through the rostral ventromedial medulla. **i.** TRPV4, TRPV3 and TRPM3 have been related to the pathophysiology of migraine and to sexually dimorphic behaviors but their role in migraine is largely unexplored.

TRPA1 has been proven essential for the pro-nociceptive effects of ROS and NO donors also in preclinical models of acute and chronic migraine (Alarcón-Alarcón et al., 2022; De Logu et al., 2022; Marone et al., 2018) and plays a crucial role on NO-induced vasodilation (Sullivan et al., 2015), two fundamental aspects of migraine pathophysiology. In the periphery TRPA1 is expressed in neurons, but has also been described in fibroblasts, inner ear hair cells, Satellite glial cells and in Schwann cells (SC, Fig. 2, mechanism in **c** (Iannone, Nassini, et al., 2022)). Stimulation of CLR/RAMP1 (calcitonin receptor-like receptor/receptor activity modifying protein-1) in Schwann cells promotes cAMP-dependent NO production, which in turn activates Schwann cell TRPA1 and allows the release of ROS that sustain peripheral pain sensitization through the stimulation of neuronal TRPA1 (De Logu et al., 2022). This mechanism implies possible sensitization of neighboring cells within trigeminal structures, not necessarily affected by the primary sensitization. Thus, the induction of TRPA1/TRPV1-mediated pain through external stimulation of gustatory/olfactory/auditory/skin-innervating primary afferents could trigger sensitization of meningeal neurons through feed-forward stimulation between peripheral glial cells and neurons. Although, the synaptic confluence of first order neurons in common high-threshold or wide-dynamic range 2$^{nd}$ order neurons that may extend their receptive field in the TNC was also described as a central mechanism for this cross-sensory sensitization (Fig. 2, pathway in **f**), (Burstein, Yamamura, Malick, & Strassman, 1998).

Spatial transcriptomics in human primary afferents has recently revealed that women express higher number of differentially-regulated genes in TRPA1-containing fibers than men (Tavares-Ferreira et al., 2022), suggesting basal differences in sensitivity to external and internal stimuli activating TRPA1. This is consistent with the higher peripheral expression of neuronal αCGRP also described in women (Tavares-Ferreira et al., 2022) and endorsed by the high degree of co-localization between TRPA1 and αCGRP in rodents (~97%) (Story et al., 2003). These cellular differences between males and females may be exacerbated after repeated or strong stimulation of peripheral TRPA1 which promote activity-dependent TRPA1 overexpression in preclinical models of pain including migraine (Fig. 2, mechanism in **a** (Alarcón-Alarcón et al., 2022; Martínez-Rojas et al., 2018; McNamara et al., 2007)). While TRPA1 expression or intrinsic functioning seems similar between males and females and its deletion equally abrogates migraine-related pain in both sexes in mice (Alarcón-Alarcón et al., 2022), several basic research studies have described sexual-dimorphic mechanisms that converge on TRPA1-expressing neurons. A recent study has revealed that repeated stressful stimuli induces a specific release of prolactin from hypothalamic arcuate nucleus neurons in females. The subsequent increase in circulating prolactin is able of sensitizing trigeminal TRPA1-expressing neurons through their prolactin receptors, and this priming leads to exaggerated trigeminal painful responses to otherwise innocuous concentrations of the TRPA1 agonist umbellunone (Fig. 2, mechanism in **h**) (Watanabe et al., 2022). Thus, stress-related prolactin release could favor TRPA1-associated migraines preferentially in females through this mechanism. While prolactin is a female hormone particularly abundant during pregnancy and breastfeeding, and both periods are known by having less frequency of migraine (David, Kling, & Starling, 2014), the role of prolactin promoting pain specifically in females has also been described in preclinical migraine models by several groups (Avona et al., 2021; Ikegami et al., 2022) and may involve a sex-biased TRPA1 or TRPV1 signaling (Fig. 2, mechanism in **c**) (Patil, Ruparel, Henry, & Akopian, 2013).

Additional relevant findings potentially contributing to a sexual dimorphism include possible TRPA1 estrogen-dependent expression and stimulation through estrogen metabolites, which promote primary afferent sensitization and pain-like behaviors specifically in females through TRPA1 (Xie et al., 2022). Interestingly, also the use of aromatase inhibitors that prevent the transformation of testosterone to 17-β-estradiol promoted an exacerbated pain sensation (Fusi et al., 2014). Such strong pain sensitization was found to be associated to the direct stimulation of TRPA1 by this type of electrophilic compounds. Their structural similarities with estrogen-related molecules further support the notion that interactions of female steroids with TRPA1 could be a source of sexual dimorphism and may have an impact on the presentation of menstrual migraines. TRPA1 expression has also been described in brain astrocytes, where its activation reduced the activity of inhibitory synapses (Fig. 2, mechanism in **g**) (Shigetomi, Tong, Kwan, Corey, & Khakh, 2011), however, this finding was controversial and several studies failed to report TRPA1 transcripts within the brain (Duque et al., 2022; Zhang et al., 2014). Nonetheless, the absence of TRPA1 in brain neurons seems clear and suggests a reduced possibility of adverse psychotomimetic events. Hence, TRPA1 inhibition or desensitization represents a potential therapeutic strategy for the prevention and relief of migraine-associated pain (Iannone, Nassini, et al., 2022) that should also cover neuroplasticity events idiosyncratic to the female sex. In this regard, clinical trials have been designed to assess the efficacy of selective TRPA1 antagonists inhibiting heat perception (clinicaltrials.gov, NCT05275751) or alleviating neuropathic or acute post-surgical pain (reviewed in Iannone, Nassini, et al., 2022; Souza Monteiro de Araujo et al., 2020). Despite the accumulating preclinical evidence, no studies have been published yet assessing the efficacy of TRPA1 antagonism or desensitization against migraine, and none of them explicitly address a possible sex bias.

TRPV1 has also been closely involved in the pathophysiology of migraine and its targeting through botulinum toxins (Burstein, Blumenfeld, Silberstein, Manack Adams, & Brin, 2020; Pasierski & Szulczyk, 2022) or its peripheral desensitization through specific agonists have shown certain efficacy in alleviating migraine (Fernández-Carvajal, González-Muñiz, Fernández-Ballester, & Ferrer-Montiel, 2020; Saper et al., 2002). In the case of the TRPV1 agonists, adverse effects such as transient hypothermia limited their use. Around 60–70% of TRPV1+ trigeminal neurons co-express αCGRP in male rats (Fig. 2, diagram in **b**) (Price & Flores, 2007) and similar to TRPA1, TRPV1 inhibition decreases αCGRP release from primary afferents (Meng et al., 2009). However, TRPV1 is also found in neurons from brain structures related with pain processing including thalamus, hypothalamus, hippocampus, amygdala or periaqueductal gray (Fig. 2, mechanism in **g**) (Kauer & Gibson, 2009). In these areas, endocannabinoid signaling through TRPV1 can induce pronociceptive (Wu et al., 2010; Xiao et al., 2016) or antinociceptive effects (Barrière et al., 2020; Palazzo, Rossi, & Maione, 2008). For instance, TRPV1 stimulation in the PAG was proven antinociceptive and has been proposed as one of the antinociceptive mechanisms of acetaminophen (Barrière et al., 2020). Furthermore, the reduced fear, anxiety-like behavior or stress-induced sensitization of TRPV1 knockout mice suggests also a role in brain areas implicated in affective-emotional behavior (Kauer & Gibson, 2009). This heterogenous activity indicates a complex role of this receptor at central level, which is in contrast with the clear pronociceptive and vasodilatory actions of peripheral TRPV1 agonism (Caterina et al., 2000; Zygmunt et al., 1999).

Women show stronger trigeminal sensitization than men in response to intradermal application of the TRPV1 agonist capsaicin (Gazerani, Andersen, & Arendt-Nielsen, 2005). This TRPV1-induced sensitization is more intense during the menstrual phase, which also suggests an interplay between female sexual hormones and TRPV1. In addition, estrogen-dependent responses of TRPV1 have been replicated in rodents and cellular models, where female hormones generally favor pain sensitization through TRPV1 (Fig. 2, mechanism in **a,** reviewed in Artero-Morales et al. (2018)). Thus, estrogens have been proposed to modulate TRPV1 activity mainly in three different ways by: (i) genomic regulation where estrogen receptors increase TRPV1 expression through tropomyosin-related kinase A (TrkA) receptors (Artero-Morales et al., 2018; Payrits et al., 2017); (ii) sensitization through intracellular signaling involving PKCε phosphorylation or TrkA receptor activity (Goswami et al., 2011; Gu, Li, & Huang, 2018; Payrits et al., 2017); or, (iii) direct stereospecific interaction where

17-β-estradiol increases open probability of the channel and could have neuroprotective effects (Artero-Morales et al., 2018; Ramírez-Barrantes et al., 2020). Indeed, although the involvement of TRPV1 was not thoroughly explored, the endogenous TRPV1 agonist anandamide produced increased αCGRP release in mesenteric arteries of females but not in males, and this was dependent on 17-β-estradiol that was absent in ovariectomized rats but recovered after supplementation of the hormone (Peroni et al., 2007). Hence, the αCGRP release and vasodilatory effect of anandamide was more prominent in females suggesting a predisposition to vasodilatory effects mediated through TRPV1.

In the same line, anandamide induced central effects selectively in females, impairing fear extinction through signaling at TRPV1 (Morena et al., 2021). Interestingly, modulation of TRPV1 activity has also been observed after exposure to environmental compounds that mimic estrogenic molecules such as bisphenol A (Rossi et al., 2020). This finding is compatible with the exacerbated migraine-like behavior observed after bisphenol-A exposure in a rat model of migraine (Vermeer, Gregory, Winter, McCarson, & Berman, 2014). The sexual dimorphism involving TRPV1 activity in migraine may go beyond its interaction with estrogenic compounds in neurons. For instance, ethanol reduces the activation threshold of TRPV1 and favors its activity at body temperature. In addition, it produces TRPV1 sensitization against the endogenous cannabinoid anandamide (Trevisani et al., 2002). In this scenario, differences in ethanol metabolism or pharmacokinetics between males and females could favor migraine preferentially in women after the intake of alcoholic beverages (Erol & Karpyak, 2015). Another source of migraine modulation specific for women could come from the female hormone progesterone, which binds the endogenous chaperone sigma 1 receptor (σ1R). Since σ1R favors the insertion of functional TRPV1 into the neuronal plasma membrane and progesterone inhibits this process (Ortíz-Rentería et al., 2018), this mechanism could be particularly relevant during pregnancy, a period particularly associated with less incidence of migraines (David et al., 2014). However, none of these latter assumptions have been formally investigated.

The accumulated evidence on the involvement of TRPV1 in migraine yielded a clinical trial assessing the efficacy of the TRPV1 antagonist SB-705498 for the treatment of acute migraine (www.clinicaltrialsregister.eu; EudraCT Number: 2005-004480-37). While there was a lack of benefit when compared to placebo, the brain penetrance described for the antagonist (Lambert et al., 2009) could have promoted mixed antinociceptive and pronociceptive effects. Unfortunately, a clinical trial assessing the efficacy of a peripherally-restricted TRPV1 antagonist for migraine has not been announced yet. The use of topical or peripherally-restricted antagonists or the development of novel photoswitchable agents to modulate TRPV1 and TRPA1 activity through optical stimulation (Frank et al., 2015; Lam et al., 2020; Qiao et al., 2021) may offer new therapeutic opportunities for the inhibition of migraine pain and the disruption of their sexual dimorphic signaling during chronic migraine.

### 2.3. TRPM8

Multiple genetic studies in humans associate the presence of SNPs affecting the TRPM8 gene with migraine susceptibility (Chasman et al., 2011; Chen et al., 2018; Ling, Chen, Fann, Wang, & Wang, 2019; Siokas et al., 2022). Some of these polymorphisms are linked also with increased allodynia, anxiety and depression in migraine, highlighting the relevance of TRPM8 in its pathophysiology. In this regard, rs10166942 appears associated to an increased risk having the T allele vs the C, (Chasman et al., 2011) or with increased cold sensitivity elicited by the cold pressor test (3–5°C); and, rs7577262 appears associated to an increased risk having the G vs. the A allele (Chasman et al., 2014). Of these polymorphisms, rs10166942 is the most studied one, with carriers of the rs10166942[T] allele having increased risk for migraine and carriers of the rs10166942[C] allele showing protection. Given that the SNP is located upstream to the TRPM8 gene in putative regulatory regions (Key et al., 2018), it could be expected normal functioning of the channel and increased or decreased expression of the protein. In this regard, one report predicted reduced TRPM8 expression in carriers of rs10166942[C] allele and higher TRPM8 levels in rs17862920[T] carriers (Gavva et al., 2019), which also associated with increased cold pain in the cold pressor test. Thus, while the evidence is still weak, increased TRPM8 expression has been interpreted as a possible pain-inducing mechanism absent in rs10166942[C] carriers (Gavva et al., 2019; Wei et al., 2022). Interestingly, the rs17862920[T] allele was also suggested as an evolutionary adaptation to cold temperatures after the observation of a population distribution largely dependent on temperature, higher latitudes and European ancestry (Key et al., 2018), whereas the rs10166942[C] migraine-free allele was found to be more primitive and common in lower and warmer latitudes. Since the SNP affects a genetic region with affinity for a transcription factor, it could be inferred from this study that the reduced cold sensitivity of rs17862920[T] allele carriers could be associated with decreased TRPM8 expression, an evolutive advantage protective against cold that also facilitated migraine (Key et al., 2018). However, it has not been considered whether an overexpressed TRPM8 in individuals with the rs17862920[T] allele could also be an adaptative protective mechanism inherently present in certain migraine populations. In this line, promoting TRPM8 activity through cooling or with canonical TRPM8 agonists such as menthol is a pain-relieving strategy commonly used by migraineurs that has also been used successfully to alleviate migraine pain in clinical studies (Fig. 1, mechanism in **e**) (Borhani Haghighi et al., 2010; Shah et al., 2021; St Cyr et al., 2015).

TRPM8 stimulation has been shown to inhibit TRPA1 and TRPV1-related pain in animal models of migraine (Alarcón-Alarcón et al., 2022; Andersen, Gazerani, & Arendt-Nielsen, 2016; Kayama et al., 2018; Liu et al., 2013; Ren, Dhaka, & Cao, 2015). TRPM8 is expressed in a ~10–13% of trigeminal neurons, a subset of neurons mostly void of TRPA1/TRPV1 channels in laboratory animals and humans (Dhaka, Earley, Watson, & Patapoutian, 2008; Huang et al., 2012; Kobayashi et al., 2005; Story et al., 2003; Tavares-Ferreira et al., 2022) (Fig. 1, diagram in **b**). Although studies using TRPM8 eGFP mice found TRPV1 expression in ~5–20% of TRPM8 fibers (Dhaka et al., 2008; Kobayashi et al., 2005), it is described that dural afferents express TRPM8 receptors in very low proportion (~3–4%, (Huang et al., 2012; Ren et al., 2018)). Of $TRPM8^{+}$ trigeminal neurons, up to 26% were found to express αCGRP (Kim et al., 2014) (Fig. 1, diagram in **b**). The main interactions between TRPM8 and TRPA1/TRPV1 meningeal fibers transmitting migraine-related pain could be expected to occur either at the TNC in the cervical spinal cord or indirectly through higher supraspinal circuitry. This latter possibility builds on the recent description of TRPM8-expressing neurons also in central brain areas, where its function has been scarcely explored (Mohandass et al., 2020; Ordás et al., 2021). Several mechanisms have been proposed to explain the pain-relieving effects of peripheral TRPM8 activity (Fig. 1, mechanism in **f**). It has been described that spinal glutamate release from TRPM8 fibers exerts an inhibitory function through metabotropic glutamatergic receptors expressed either presynaptically in adjacent fibers or post-synaptically (Proudfoot et al., 2006). A cross-inhibitory intracellular effect of TRPM8 over TRPV1-induced c-Jun N-terminal kinase phosphorylation has also been reported (Kayama et al., 2018). In addition, it has been proposed that TRPM8 activation could facilitate recruitment of inhibitory interneurons that silence TRPA1/TRPV1-expressing nociceptors (Dussor & Cao, 2016), although this circuit has not been characterized thus far. Accordingly, TRPM8 activity may occlude signaling of TRPA1/TRPV1-expressing nociceptors and their subsequent αCGRP release.

On the other hand, pronociceptive actions of TRPM8 activity have also been proposed during chronic migraine based on the lower cold pain threshold manifested by a proportion of migraine patients (Nahman-Averbuch et al., 2018) and after the pronociceptive effects observed upon meningeal application of the TRPM8 agonist icilin in rodents (Burgos-Vega et al., 2016). However, sensitivity to extreme cold has been associated also with TRPA1 stimulation and additional

transducers, and icilin is too a known TRPA1 agonist (Buijs & McNaughton, 2020; Paricio-Montesinos et al., 2020; Story et al., 2003; Winter, Gruschwitz, Eger, Touska, & Zimmermann, 2017). Nevertheless, a recent group with extended experience on the pronociceptive actions of TRPM8 has described a pronociceptive function of this receptor also in a model of chronic migraine induced by repeated treatment with the NO donor nitroglycerin containing a percentage of propylene glycol (Wei et al., 2022). According to the authors, TRPA1 could initiate its pronociceptive actions upstream of the TRPM8 fibers (Yamaki, Chau, Gonzales, & McKemy, 2021). Thus, TRPA1-expressing cells would release pronociceptive mediators to sensitize TRPM8 fibers that promote cold sensitivity in migraine. Regardless of the validity of all these assumptions, the accumulating preclinical and clinical evidence underlines the relevance of the TRPM8 receptor in migraine pathophysiology.

An additional effort will be needed to clarify the pronociceptive and/or antinociceptive actions of TRPM8 in preclinical models of migraine and also in the clinics. Available clinical data only describe at most significant pain-relieving efficacy for canonical TRPM8 agonists (Borhani Haghighi et al., 2010; Lopresti, Smith, & Drummond, 2020; St Cyr et al., 2015), however it must be recognized that these agonists lack specificity and can produce desensitization of the channel. Hence, it is unclear whether the obtained outcomes in these studies in humans are due to activation or desensitization. The use of novel specific agonists or additional validation through different types of compounds is still needed to clarify the contribution of TRPM8 to migraine in humans.

TRPM8 expression shows a clear sexual dimorphism in humans, being prominently expressed in male tissues such as the prostate or the testicles (Uhlén et al., 2015). Different genetic studies have revealed trends for increased risk of migraine in female carriers of the TRPM8 SNP rs17862920[T] (Chasman et al., 2011; Ling et al., 2019), although this is in contrast with other studies finding similar prevalence in males and females (Siokas et al., 2022) and with the remarkable sexual dimorphism of general migraine where females represent at least 2 of each 3 patients and develop also more pronounced symptomatology Lagman-Bartolome & Lay, 2019; Stovner et al. (2018). Indeed, one of the genetic studies on the same SNP shows significant association of migraine with the T allele only in males (Kaur, Ali, Ahmad, Pandey, & Singh, 2019), supporting the possibility of TRPM8 being particularly relevant in males. In this line, we have found in our laboratory a dimorphic function of TRPM8 in a mouse model of chronic migraine. The model displays a sexual dimorphic phenotype in which repeated nitroglycerin administration induces persistent hypersensitivity solely in females, whereas males readily recover from the migraine crisis (Alarcón-Alarcón et al., 2022). Using TRPM8 knockout mice, we have found that TRPM8 is essential for the reinstatement of normal sensitivity in males, whereas female mice do not alter their migraine-like behavior (Alarcón-Alarcón et al., 2022). After observing several previous studies suggesting that TRPM8 could act as a testosterone receptor (Asuthkar et al., 2015; Kondrats'kyĭ, Kondrats'ka, Skryma, Prevars'ka, & Shuba Ia, 2009), we tested the hypothesis that testosterone could actually provide protection through TRPM8. In agreement, downregulation of this protective mechanism in males led to persistent mechanical hypersensitivity, whereas acute testosterone favored recovery in females (Alarcón-Alarcón et al., 2022). This pain relief was markedly reduced in TRPM8 knockout mice and was sensitive to the specific antagonist AMTB, although additional TRPM8 antagonists were not assessed. The agonistic activity of physiological picomolar concentrations of testosterone (Yoo & Napoli, 2019) over TRPM8 was corroborated through calcium imaging in cellular models expressing rat and human TRPM8 (Alarcón-Alarcón et al., 2022). Since progesterone and 17-β-estradiol also bind to TRPM8, although with lower affinity than testosterone, their menstrual drop might partially contribute to trigger migraine episodes during menstruation.

Although a previous study suggested that the androgen receptor could exert a tonic inhibition of TRPM8 activity when testosterone is administered at nanomolar concentrations (Gkika et al., 2020), we found that picomolar testosterone-induced currents occurred independently of the expression of canonical forms of the androgen receptor (Alarcón-Alarcón et al., 2022). Hence, we found a testosterone-dependent protective function of TRPM8 (Fig. 1, mechanism in **e**) independent of the androgen receptor, which could explain the acute effects of testosterone treatments (Rosano et al., 1999). This non-transcriptional activity also substantiates fast-acting behavioral effects of testosterone observed just 30 min to one hour after administration, such as the effects on affective behavior found in rodent models (Alarcón-Alarcón et al., 2022; Frye, Edinger, & Sumida, 2008; Mohandass et al., 2020; Rosano et al., 1999). Additional male-specific effects of TRPM8 activity have been evidenced in constitutive knockout mice, with responses to testosterone attenuated in the amygdala and changes in ventral tegmental area that were in correlation with enhanced aggressiveness and reduced sexual satiety (Mohandass et al., 2020). In the same line, aged TRPM8 knockout males develop low bone mineral density as if they were females, whereas the individuals of this sex do not alter their wild-type phenotype after the genetic deletion of TRPM8 (Lelis Carvalho et al., 2021). In the context of persistent pain, androgenic TRPM8 activity may constitute a pain-relieving mechanism present in other models of migraine or chronic pain that also display sexual dimorphism (Lesnak, Inoue, Lima, Rasmussen, & Sluka, 2020; Viero et al., 2022; Watanabe et al., 2022). However, testosterone is a controlled substance that can have deleterious or undesirable effects that prevent its widespread use. The design of TRPM8 agonists that are void of activity over the androgen receptor could represent a potential therapeutic strategy for women or migraine patients with low testosterone levels and may uncover as well additional benefits in light of the results obtained in preclinical models (Lelis Carvalho et al., 2021; Mohandass et al., 2020).

### 2.4. Other thermoTRP channels

Although most of studies have been focused on the role of TRPA1, TRPV1 and TRPM8 in migraine, there are also relevant findings on less studied thermoTRP channels that could provide insight on migraine sexual dimorphism in the near future (Fig. 1, mechanism in **i**). For instance, TRPV4, a channel activated by hypoosmolarity and membrane stretching, is also expressed in the trigeminal ganglia and shows significantly higher expression in female vs. male mice (Mecklenburg et al., 2020). Interestingly, the lack of TRPV4 increases bone mass and decreases bone elasticity selectively in male mice, and there is a genetic polymorphism linked to fracture risk in men (van der Eerden et al., 2013). The potential relevance of this receptor for migraine was found in a rat model of headache where pain responses increased after dural application of a specific TRPV4 agonist (Wei, Edelmayer, Yan, & Dussor, 2011). Unfortunately, the study was conducted only in males and no sex differences have been reported so far in migraine models. Another genetic study found significant association of migraine with aura with a SNP variant of TRPV3 (Carreño et al., 2012). Remarkably, this thermoTRP modulates the production of NO in the skin independently of nitric oxide synthases and its deletion in mice produces thermosensory deficits selectively expressed in females (Miyamoto, Petrus, Dubin, & Patapoutian, 2011). Finally, the mechano- and thermosensory channel TRPM3 is prominently functional in trigeminal fibers of mouse meninges especially in females (Held, Voets, & Vriens, 2015; Krivoshein, Tolner, Maagdenberg, & Giniatullin, 2022) and is sensitive also to the endogenous neurosteroid pregnenolone sulfate. Its demonstrated participation in pain behaviors in rodent models (Held et al., 2015; Kelemen et al., 2021) suggests the needs of understanding the functionality of this receptor in migraine-related conditions for a complete understanding of migraine sexual dimorphism.

## 3. Sexual dimorphism in chemotherapy-induced peripheral neuropathy

CIPN is a severe adverse effect produced by cancer chemotherapy. It is a highly prevalent disease occurring in up to 90% of the patients receiving most of chemotherapeutic drugs (Burgess et al., 2021). CIPN

symptoms are characterized by paresthesia, dysesthesia, spontaneous and burning pain, mechanical and thermal hypersensitivity primarily arising in the hands and feet (glove-and-sock distribution) (Burgess et al., 2021). This sensory disorder resolves in 30% of patients after chemotherapy cessation but remains in 40–50% of patients for more than 1 year (Teng, Cohen, Egger, Blinman, & Vardy, 2022). Noteworthy, for some drug regimens a significant ≈30% of patients must stop their cancer treatment because the intense sensory dysfunction produced by CIPN unbearably affects their quality of life, and usually promotes comorbidities such as depression (Prutianu et al., 2022). Furthermore, poor adherence to chemotherapy because of CIPN frequently results in cancer progression, as oncologists are forced to use alternative drugs that are less efficient fighting the tumor. Taking together, CIPN represents an important health problem that affects up to 4% of the population, considering the prevalence of cancer.

Despite its high incidence, there is no effective treatment approved to alleviate CIPN symptoms. Different pharmacological and non-pharmacological interventions have been recommended in several clinical practice guidelines (Jordan et al., 2020; Loprinzi et al., 2020). However, these recommendations come from studies of patients suffering neuropathic pain caused by other diseases rather than CIPN. Among pharmacological interventions, only duloxetine showed a moderate effect in reducing CIPN symptoms of chemotherapy-treated patients and has been recommended in the guidelines of the American Society of Clinical Oncology (ASCO) (Loprinzi et al., 2020; Smith et al., 2013). Since the incidence of this pathology is increasing, there is an urgent need to unveil the underlying mechanisms leading to the peripheral neuropathy, and to develop treatments that increase the quality of life of cancer patients through chemotherapy and promote their adherence to the best anti-tumoral drug regime. Currently, up to 200 clinical trials/studies are registered for testing different strategies for CIPN, although most of them are combination of known drugs or acupuncture methods (https://www.clinicaltrials.gov/ct2/home).

Clinical and pre-clinical studies are providing evidence on the presence of sex dimorphism in CIPN pathophysiology (Davidson et al., 2019; Ferrari, Araldi, Green, & Levine, 2020; Villalba-Riquelme et al., 2022; Wagner et al., 2021). In addition, sex differences in CIPN pharmacology have also been described (Ram et al., 2021), suggesting that adaptation of the therapeutic strategy to the patient sex appears an important factor for a satisfactory disease management. In support of this tenet, promising results were obtained when the chemotherapeutic dose was specifically adapted to each sex and age (Pfreundschuh et al., 2017).

The tight therapeutic window of chemotherapeutic drugs has brought special concerns regarding the existence of sex differences (Wang & Huang, 2007), and different studies are considering sex as a risk factor in the development and magnitude of CIPN (Mizrahi et al., 2021; Sałat, 2020). A summary of reported sex differences in CIPN symptoms for each chemotherapeutic agent is exhibited in Table 1. Among the most common clinical findings, women experience higher incidence, sensitivity and/or severity of peripheral neuropathy for most of the chemotherapeutic regimes (Lévy et al., 1998; Mols et al., 2016; Trendowski et al., 2021; Unger et al., 2022). Nonetheless, a study that analyzed different chemotherapeutic strategies for esophagogastric cancer revealed a greater incidence of CIPN in men for some therapeutic combinations (Davidson et al., 2019). However, a limitation of this study is that the percentage of men and women was not equal in all groups analyzed, which could have influenced the results to certain degree. Other studies such as the work of Yamada et al. (2020) did not find significant differences between sexes in peripheral neuropathy (grade ≥3) following combination of chemotherapeutic treatments. However, differences in baseline characteristics and tumor characteristics of male and female patients might have conditioned the results.

Despite the clinical evidence, the underlying molecular and cellular mechanisms involved in the sex dimorphism of CIPN remain unknown, primarily because most of the pre-clinical research has been performed in male subjects. In addition, CIPN-related sex differences have been less recognized by the scientific community than in migraine (Artero-Morales et al., 2018). Most likely, sex dimorphism in CIPN has been largely overlooked at least in part because it has been considered an adverse effect of cancer therapy and thus unrelated to the disease. Furthermore, identification of sex-driven mechanisms in CIPN has also been challenging because of its complex etiology along with the co-existence of the tumor and the therapeutic strategy associated. In this regard, factors such as tumor metabolism, surgical trauma, immune response, radiotherapy, interference of co-administered drugs, anti-hormonal therapy, and pharmacokinetics and/or pharmacodynamics of the drugs may contribute to CIPN etiology (Wagner, 2020). In addition, the combination of chemotherapeutic drugs adds another dimension to the disorder that further complicate understanding the pathophysiology of the syndrome (Table 1). Noteworthy, previous studies in CIPN incidence have focused on differences in drug pharmacokinetics, tumor biology, survival to cancer and overall drug toxicity (Cristina et al., 2018; Rubin et al., 2020; Sloan et al., 2002; Wagner et al., 2019), but have overlooked the presence of sex differences in CIPN. This lack of information on CIPN sex dimorphism has prevented the development of more adequate therapeutic regimes for women and men. Thus, it is urgent that pre-clinical studies are performed in both sexes to uncover the role of sex in the pathophysiology of CIPN, as this may provide insightful information for more efficient pharmacological approaches.

Recent studies pointed out to a key role of thermoTRP channels on CIPN as well as in the sex dimorphism exhibited by the peripheral neuropathy. The potential molecular mechanisms involved are represented in Fig. 3. In females, the development of mechanical pain in a model of paclitaxel induced-CIPN was described to arise from the IL-23/IL-17A/TRPV1 axis (Luo et al., 2021). This study detected an increase in IL-23 release only in females that was mediated by TRPV1, as it was absent in TRPV1 null mice. Our studies on a preclinical model of paclitaxel-induced nociceptor excitability showed that female sensory neurons exhibited higher spontaneous and evoked excitability than their male counterparts (Villalba-Riquelme et al., 2022). This difference was not apparently mediated by a differential effect of the taxane on TRPV1 functionality as the thermoTRP was similarly affected by the drug in sensory neurons of both sexes, suggesting the involvement of other nociceptor channels. Interestingly, in the same study paclitaxel potentiated TRPM8 activity more intensively in male than in female sensory neurons.

Akin to migraine, modulation of thermoTRP channel function by sexual hormones appears as a potential determinant of the sex dimorphism observed in CIPN. A study by Srinivasan et al. (2008) found that sex hormones play a role in sex differences observed in CIPN by modulating thermoTRP channel function and their signaling pathways. Another study found different levels of gonadal hormones in the peripheral nervous system in male and female rats (Caruso et al., 2013). In particular, testosterone concentration in the sciatic nerve was higher in males whereas 17-β-estradiol and progesterone derivatives (dihydroprogesterone, tetrahydroprogesterone) were increased in females, suggesting that a specific hormonally-activated pathway may be predominating in each sex. An estrogen-dependent sexual dimorphism was also found in rats treated with vincristine, where removal of the hormone abolished the greater mechanical hypersensitivity found in female rats when compared to males (Joseph & Levine, 2003). In this study, inhibition of PKC-ε, a modulator of TRPV1 activity, reduced vincristine-induced hyperalgesia in males and ovariectomized females (Joseph & Levine, 2003), suggesting that estrogens could generate hyperalgesia in females by promoting TRPV1 signaling (Goswami et al., 2011). In support of this tenet, Luo et al. (2021) showed that estrogens activated the IL-23/IL-17A/TRPV1 axis to induce mechanical pain in paclitaxel CIPN. In line with these results, in another paclitaxel model, ovariectomized rats showed an increased threshold to mechanical and thermal stimuli, thus exhibiting a reduced pain response (Wang, Li, Zhao, & Zhang, 2018). Intriguingly, other studies attributed a protective

**Table 1**
Sex differences found in CIPN pain symptoms after treatment with different chemotherapeutic agents in diverse clinical and/or pre-clinical studies.

| Chemotherapeutic Drug | Potential thermoTRPs Involved | Sex differences observed | Reference |
|---|---|---|---|
| Taxanes | | | |
| Paclitaxel | TRPV1<br>TRPM8 | Reduced rheobase, higher sensitivity in female rat DRG neurons exposed to paclitaxel | (Villalba-Riquelme et al., 2022) |
| | TRPV4 | Cold allodynia more robust in female mice | (Naji-Esfahani et al., 2016) |
| | TRPA1 | Greater magnitude of paclitaxel hyperalgesia in female rats | (Ferrari et al., 2020) |
| | | Higher TRPM8 expression in male rat DRG neurons | (Villalba-Riquelme et al., 2022) |
| | | Mechanical pain produced through estrogen dependent IL-23/IL-13/TRPV1 signaling axis only in female mice | (Luo et al., 2021) |
| | | No significant sex difference in the response to mechanical stimuli for male and female rats | (Hwang, Kim, Kim, Kwon, & Kim, 2012) |
| Docetaxel | TRPV1 | Not investigated alone | |
| Platinum-based compounds | | | |
| Oxaliplatin | TRPV1<br>TRPM8<br>TRPA1 | Reduction in nerve conduction amplitude in female mice | (Warncke et al., 2021) |
| Cisplatin | TRPV1<br>TRPV2 | Tendency in women with advanced non-small cell lung cancer to have more neurosensory deficits than men (clinical trials) | (Wakelee et al., 2006) |
| | TRPA1 | More persistent tactile allodynia in male than in female mice | (Woller, Corr, & Yaksh, 2015) |
| | TRPM8 | Bigger incidence of prolonged heat latency in male rats | (Wongtawatchai, Agthong, Kaewsema, & Chentanez, 2009) |
| Carboplatin | TRPA1 | Not investigated alone | |
| Vinca-alkaloids | | | |
| Vincristine | TRPV1 | Mechanical hyperalgesia was higher in female than in male rats | (Joseph & Levine, 2003) |
| | TRPV4 | Statistically significant reduced mechanical sensitivity threshold only in male rats | (Legakis, Diester, Townsend, Karim-Nejad, & Negus, 2020) |
| Proteasome inhibitor | | | |
| Bortezomib | TRPA1<br>TRPV1 | The prevalence of peripheral neuropathy was nearly double in women treated with bortezomib (65.3%) compared to men (36%) (retrospective study using clinical data) | (Martinez et al., 2019) |
| | | Significant lower threshold of mechanical sensitivity at day 30 in female but not in male Sprague-Dawley rats | (Legakis et al., 2020) |
| | | S1PR1 antagonists prevented bortezomib mechano-allodynia and mechano-hyperalgesia in male but not in female rats | (Stockstill et al., 2020) |
| | | Male sex was a predictor of bortezomib-induced CIPN development (retrospective analysis using clinical data) | (Kanbayashi et al., 2010) |
| Alkylating agents | | | |
| Ifosfamide | TRPA1? | Higher neurotoxicity in females | (Schmidt, Baumann, Hanschmann, Geissler, & Preiss, 2001) |
| Antibody-Drug Conjugates (ADC) | | | |
| Brentuximab-vedotin<br>Enfortumab-vedotin | Not investigated | Not disclosed, but likely similar to vincristine as auristatin E as both share a similar inhibitory mechanism | |
| Bevacizumab | Not investigated | More abdominal pain in females than males with advanced-stage non-small cell lung cancer (clinical trials) | (Brahmer et al., 2011) |
| Hormonal therapies: Aromatase inhibitors | | | |
| Anastrozole | TRPA1 | Not studied in male (breast cancer) | |
| Immunomodulatory drugs | | | |
| Thalidomide | TRPA1<br>TRPV4 | Not investigated | |
| Antimetabolites | | | |
| 5-Fluorouracil (Capecitabine) | Not investigated | Female patients with advanced colorectal cancer had significantly higher risk for hand-foot syndrome (clinical trials) | (Lévy et al., 1998) |
| Epothilones | | | |
| Ixabepilone | Not investigated | Not studied in male, only in female | |
| Combination therapies | | | |
| leucovorin + fluorouracil + oxaliplatin (FOLFOX) | Not investigated | Higher incidence of peripheral neuropathy and hand-foot syndrome in female patients with colorectal cancer (clinical trials) (Wagner et al., 2021) | (Wagner et al., 2021) |
| Combined (not mentioned) | Not investigated | Increased I-III grade neurological toxicities in female patients (clinical trials database, $N = 23256$ patients) | (Unger et al., 2022) |
| Combined | Not investigated | Female sex associated with higher neuropathy sum score after treatment of Hogkin's lymphoma (clinical trials) | (Eikeland et al., 2021) |
| Combined (ECF, ECX, EOF or EOX) | Not investigated | Males showed higher incidence of all-grade peripheral neuropathy in oesophagogastric cancer | (Davidson et al., 2019) |
| FOLFOX/ bevacizumab | Not investigated | No differences for grade ≥ 3 sensory neuropathy in patients with unresectable advanced or recurrent metastatic colorectal cancer | (Yamada et al., 2020) |
| Paclitaxel and/or Oxaliplatin | Not disclosed, but likely TRPV1, TRPA1 and TRPM8 | Female sex associated with higher neuropathy score (cohort study of 333 patients) | (Mizrahi et al., 2021) |

E: Epirubicin; C: Cisplatin; F: Fluorouracil; X: Capecitabine; O: Oxaliplatin. L: Leucovorin.

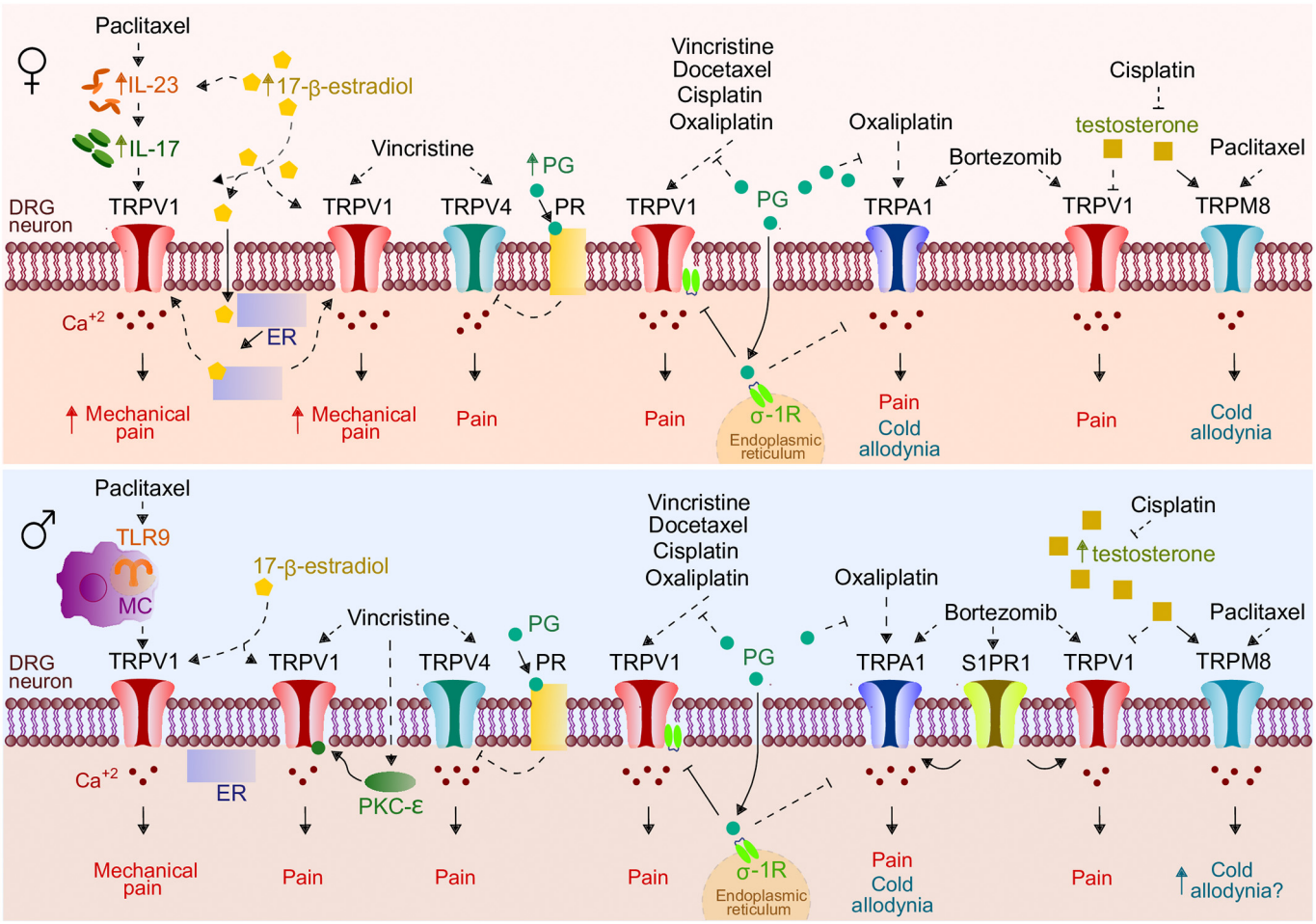


**Fig. 3. Schematic representation of potential mechanisms underlying sex dimorphism on CIPN.** Paclitaxel-induced mechanical pain was produced through IL-23/IL-17/TRPV1 signaling only in female mice (Luo et al., 2021). The IL-23 induced pain was promoted by the sex hormone 17-β-estradiol. The concentration of this hormone was higher in the peripheral nervous system of females, suggesting a major effect on this sex (Caruso et al., 2013). 17-β-Estradiol also showed a pivotal role on vincristine-induced neuropathy symptoms, since removal of this hormone reduced the greater mechanical hypersensitivity found in female rats compared to male (Joseph & Levine, 2003). As a major mechanism, 17-β-estradiol was found to increase TRPV1 expression through its binding to estrogen receptor (ER) (Payrits et al., 2017). In contrast, progesterone (PG) showed a protective role in the neuropathy induced by cisplatin, docetaxel, vincristine and oxaliplatin (Meyer et al., 2010; Roglio et al., 2009; Zaki et al., 2018). The reduction of pain behavior produced by progesterone could be the result of decreased TRPV1 levels and/or reduced TRPA1 activity through inhibition of σ-1R receptor or, in the case of vincristine, it could also be due to diminished expression of TRPV4 through binding to its progesterone receptor (Jung et al., 2009; Marcotti et al., 2022; Ortíz-Rentería et al., 2018). Plasma levels of progesterone were found to be higher in pre-menopausal women than in men (Tóthová, Ostatníková, Šebeková, Celec, & Hodosy, 2013). As male specific mechanisms, paclitaxel mechanical pain was modulated by TLR9 only in male, possibly through alteration of TRPV1 channel activity (Luo et al., 2019). In addition, inhibition of PKC-ε, a modulator of TRPV1 activity through phosphorylation, only reduced vincristine-induced hyperalgesia in males and ovariectomized females (Joseph & Levine, 2003). Furthermore, higher TRPM8 responses after paclitaxel exposure were observed on male DRG neuronal cultures (Villalba-Riquelme et al., 2022). TRPM8 has also been described as a testosterone receptor (Asuthkar et al., 2015). Testosterone was also postulated to decrease pain by reducing TRPV1 expression (Bai et al., 2018). Levels of this hormone were higher in the peripheral nervous system of males (Caruso et al., 2013). For bortezomib treatment, S1PR1 antagonists only prevented neuropathic pain on male rats (Stockstill et al., 2020). There, S1PR1 could evoke pain through TRPA1 and TRPV1 channels (Kittaka, DeBrecht, & Mishra, 2020). Dashed lines indicating indirect interaction. ER: estrogen receptor. MC: macrophage. PG: progesterone. PR: progesterone receptor. S1PR1: sphingosine-1-phosphate receptor.

role for 17-β-estradiol in CIPN symptoms. Miyamoto et al. (2021) described that estrogen depletion enhanced paclitaxel CIPN in female mice. Selective agonists of the estrogen receptor β (ERβ) reduced the allodynia induced by paclitaxel, oxaliplatin and vincristine (Ma, McFarland, Olsson, & Burstein, 2016). Nonetheless, their efficacy and potency were higher in male rats than in females (Ma et al., 2016). Despite these observations, estrogen antagonists are generally considered for providing pain relief (Paller, Campbell, Edwards, & Dobs, 2009). Indeed, 17-β-estradiol was previously described as a modulator of TRPV1 channel (Lu, Chen, Wang, & Wu, 2009). Due to the higher concentration of this hormone found in the female sciatic nerve, an estrogen-mediated pronociceptive pathway could predominate in this sex (Caruso et al., 2013).

Hormones such as progesterone have been postulated to play a protective role on CIPN development (Falvo, Diviccaro, Melcangi, & Giatti, 2020). In a recent study, a higher incidence of CIPN was found in post-menopausal compared to pre-menopausal women treated with paclitaxel Singh et al. (2022), which could be due to the drop in progesterone levels occurring in menopause. The analgesic effects of progesterone have been evidenced under different chemotherapeutic treatments. Zaki, Mohamed, Motawie, and Abdel Fattah (2018), reported that progesterone ameliorated cisplatin-induced peripheral neurotoxicity. A protective role of this sex hormone was also observed in docetaxel-induced neuropathy (Roglio et al., 2009). In addition, progesterone prevented the neuropathy and exerted an antinociceptive action in docetaxel- and vincristine-treated rats (Meyer, Patte-Mensah, Taleb, & Mensah-Nyagan, 2010; Roglio et al., 2009). Anti-nociceptive effects were also produced by progesterone derivatives such as allopregnanolone, which suppressed oxaliplatin-induced neuropathy (Meyer, Patte-Mensah, Taleb, & Mensah-Nyagan, 2011). A suitable explanation for this protective effect has been previously attributed to progesterone-driven downregulation of TRPV1, TRPA1 and TRPV4 channels (Jung et al., 2009; Ortíz-Rentería et al., 2018). In support of

this tenet, previous studies demonstrated that progesterone decreased TRPV1 plasma membrane levels through inhibition of σ1R receptor, a chaperone that binds to this channel (Ortíz-Rentería et al., 2018). In addition, Marcotti et al. (2022) showed that σ1R modulation of TRPA1 prevented oxalipatin-induced neuropathy. For vincristine-induced CIPN, the protective effect of progesterone could also arise from transcriptional TRPV4 repression through the progesterone receptor (Jung et al., 2009). Hence, progesterone could exert its antinociceptive effect through indirect disruption of TRPV1/TRPV4 channels.

Similarly, testosterone-related modulation of thermoTRP channels has also been shown in events related with cancer treatment. Testosterone has been described as a direct TRPM8 agonist and this channel is highly expressed in prostate cancer (Asuthkar et al., 2015). Furthermore, testosterone was reported to reduce TRPV1 expression in an inflammatory pain model (Bai, Zhang, & Zhou, 2018). Due to these findings and the higher levels of testosterone found in males when compared to female individuals, testosterone has been proposed as a relevant determinant in the sex dimorphism of chronic pain (Roglio et al., 2007; Tanzer & Jones, 2004). However, we have not identified studies investigating the role of testosterone in CIPN. Nonetheless, it was reported that CIPN-inducing agents such as cisplatin and docetaxel inhibited testosterone synthesis and reduced testosterone levels (García et al., 2012; Ryan et al., 2020). Notably, testosterone effect could predominate in males since DRG levels are higher in males than in females (Caruso et al., 2013).

Toll-like receptors (TLR) are immune-related receptors that signal through thermoTRP channels in nociceptors. Notably, sex differences in TLR9 and TLR4 signaling have been described (Luo et al., 2019). Thus, paclitaxel-induced mechanical pain was produced by promoting TRPV1 activity and attenuated by a TLR9 antagonist in male mice. Noteworthy, TLR4 showed a sex-dimorphic effect driving neuropathic pain that was also testosterone dependent (Sorge et al., 2011). TLR4 has also been linked to development of paclitaxel-induced CIPN through modulation of TRPV1 ion channel (Li et al., 2015), and cisplatin and carboplatin were described to act as ligands of TLR4 (Park, Stokes, Corr, & Yaksh, 2014).

Collectively, there are sufficient grounds for a sex dimorphism in CIPN that must be further studied at both clinical and preclinical levels. Clinically, it would be desirable to know the incidence and/or prevalence of the disorder in the different types of cancer and chemotherapeutic treatments. Pre-clinically, it would be important to use both live animal and *in vitro* models to investigate CIPN and its resolution in male and females, along with the effect of sex hormones on its intensity and/or resolution.

### 3.1. TRP channels in the pathophysiology of CIPN

CIPN can be produced by a wide variety of chemotherapeutic agents such as taxanes (e.g. paclitaxel, docetaxel), vinca-alkaloids (e.g. vincristine), platinum-based compounds (e.g. oxaliplatin, carboplatin, cisplatin), alkylating agents (e.g. ifosfamide), antimetabolites (e.g. 5-fluorouracil), epothilones (e.g. ixabepilone), immunomodulatory drugs (e.g. thalidomide), proteasome inhibitors (e.g. bortezomib) and immunotoxins (e.g. enfortumab) (Saif et al., 2001; Zajączkowska et al., 2019). Capecitabine (5-fluorouracil) provokes a palmar-plantar erithrodysesthesia (referred to as hand-foot syndrome), and even immunotherapy induces skin sensory abnormalities such as itch (e.g. pembrolizumab). These chemotherapeutic agents affect peripheral nociceptor endings to induce painful and disturbing sensory symptoms. Most of these agents alter the activity of the sensory neurons through a direct or indirect potentiation of their excitability. Although each class of compounds acts on different cellular targets inducing oxidative stress, mitochondrial and DNA damage, immunological processes and neuroinflammation, all commonly lead to sensitization of peripheral sensory terminals (Areti, Yerra, Naidu, & Kumar, 2014; Aromolaran & Goldstein, 2017; Lees et al., 2017). A core molecular and cellular mechanism in CIPN appears to be potentiation of nociceptor ion channels involved in the generation and propagation of action potentials (Aromolaran & Goldstein, 2017). Among these nociceptor ion channels, thermoTRP channels that mediate the generation of action potentials in peripheral terminals have emerged as pivotal contributors to the peripheral neuropathy caused by most chemotherapeutic agents (Table 1), particularly of TRPV1, TRPA1, TRPM8 and TRPV4. We turn next to describe the role of these channels in CIPN.

TRPV1 protein has been shown to be upregulated in nociceptors by chemotherapeutic drugs such as paclitaxel, docetaxel, oxaliplatin, cisplatin, bortezomib and vincristine (Table 1) (Chiba et al., 2017; Ertilav, Nazıroğlu, Ataizi, & Yıldızhan, 2021; Quartu et al., 2014; Ta et al., 2010; Villalba-Riquelme et al., 2022). TRPV1-enhanced expression was accompanied by an increase in channel function that led to an increase in neuronal excitability, which underlies the thermal hyperalgesia and mechanical allodynia produced by these agents. Noteworthy, Villalba-Riquelme et al. (2022), using a long-term primary nociceptor culture, reported that paclitaxel increases the expression and channel activity of TRPV1 in peptidergic (IB4(-)) and non-peptidergic (IB4(+)) sensory neurons. This enhanced activity contributed to the higher electrical activity displayed by these nociceptors upon drug exposure. Notably, this sensitizing effect was reversible peaking 48h after paclitaxel exposure and virtually resolving at 96h. Thus, cumulative evidence hints to a key role of this thermoTRP channel in the manifestation of CIPN painful symptoms.

Akin to TRPV1, TRPA1 expression and function was also increased after oxaliplatin, cisplatin, carboplatin, thalidomide and bortezomib treatment (De Logu et al., 2020; Miyano et al., 2019; Nativi et al., 2013; Ta et al., 2010; Trevisan et al., 2013). Aromatase inhibitors such as anastrozole, used as adjuvant therapy for hormone-dependent breast cancer, have been reported to ionotropically activate the TRPA1 channel (Fusi et al., 2014). A possible contribution of TRPA1 to paclitaxel CIPN has also been observed in animal models of peripheral neuropathy (Materazzi et al., 2012; Pittman, Gracias, Vasko, & Fehrenbacher, 2014). However, a recent study that evaluated the direct effect of the taxane in a long-term primary nociceptor culture did not find a significant change in TRPA1 expression or function (Villalba-Riquelme et al., 2022). A role of TRPA1 in ifosfamide-evoked visceral pain has also been suggested, as symptoms were attenuated by the channel antagonist HC-030031 (Pereira et al., 2013). However, no studies were found regarding the role of TRPA1 on ifosfamide-induced peripheral somatic pain in males and females.

Oxaliplatin, bortezomib and thalidomide-induced TRPA1 upregulation may contribute to the mechanical hyperalgesia characteristic of CIPN (De Logu et al., 2020; Li, Deng, Shang, Wang, & Xiao, 2018; Liu et al., 2019). Because TRPA1 has been proposed to be a sensor for noxious cold (<18°C), it has been suggested that this channel may also mediate the cold allodynia that suffer patients treated with oxaliplatin (Zhao et al., 2012). However, the involvement of TRPA1 in cold sensation is under intensive debate with studies supporting and questioning this role (Buijs & McNaughton, 2020). Alternatively, the cold hypersensitivity described after paclitaxel and oxaliplatin treatments was assigned to a potentiation of the TRPM8 channel, a thermoTRP channel gated by cold temperatures (<30°C) and refreshing substances such as menthol (Kawashiri et al., 2012; Villalba-Riquelme et al., 2022). In support of this tenet, TRPM8 mRNA levels increased in an animal model of cisplatin-induced CIPN (Ta et al. (2010)), as well as in long-term primary nociceptor cultures treated with paclitaxel (Villalba-Riquelme et al., 2022). Nonetheless, these studies need to be replicated for a solid support of TRPM8 as the mediator of cold allodynia as several ion channels contribute to this thermal sensation in nociceptors (Buijs & McNaughton, 2020).

Another thermoTRP channel that may be involved in the etiology of CIPN, particularly in mechanical hyperalgesia, is TRPV4, since it is an osmosensitive channel. Indeed, paclitaxel, thalidomide, and vincristine have been reported to increase its functionality (Alessandri-Haber,

Dina, Joseph, Reichling, & Levine, 2008; De Logu et al., 2020; Sánchez, Muñoz, & Ehrlich, 2020). Accordingly, TRPV4 contributed to the mechanical allodynia evoked by these compounds (Alessandri-Haber et al., 2008; De Logu et al., 2020). Less evidence has been found on the role of other thermoTRP channels in CIPN. In this regard, TRPV2 was upregulated in rat DRG treated with cisplatin (Hori, Ozaki, Suzuki, & Sugiura, 2010), although the possible role of TRPV2 on CIPN pain symptoms remains to be elucidated.

Several studies are evaluating thermoTRP channel modulators as a promising strategy for attenuating CIPN symptoms (Singh, Adhya, & Sharma, 2021). Among TRP receptors, TRPV1 is emerging as a key therapeutic target for this type of peripheral neuropathy. Duloxetine, the only medicine for painful CIPN treatment recommended by ASCO society, has shown some efficacy reducing paclitaxel-induced TRPV1 upregulation in rats (Wang et al., 2022), suggesting a mechanism of action for the drug. Furthermore, promising results have been obtained in clinical trials using capsaicin patches that desensitize TRPV1 (Qutenza®) (Privitera & Anand, 2021). As a result, capsaicin reduced pain intensity and improved the quality of life of the patients (Maihofner & Heskamp, 2013). Other clinical trials have also shown relief of CIPN symptoms with this treatment (Anand et al., 2019; Filipczak-Bryniarska et al., 2017), suggesting a high therapeutic potential (Maihöfner, Diel, Tesch, Quandel, & Baron, 2021).

An interesting therapeutic approach for topically targeting TRPV1 in peripheral terminals is the use of soft receptor antagonists (Serafini et al., 2018). TRPV1 soft antagonists are based in the capsaicin scaffold and have shown inhibitory efficacy on TRPV1 receptors at micromolar concentrations, both under basal and inflammatory conditions (Nikolaeva-Koleva et al., 2021). These soft drugs have the unique property of being hydrolyzed by dermal esterases, preventing by this way a systemic distribution that might interfere with the chemotherapeutic treatment. Their systemic administration is short-lived and does not produce hyperthermia (Serafini et al., 2018). Consequently, TRPV1 soft antagonists exhibit a high pharmacological safety. Notably, their local application significantly reduced histamine-induced itch (Nikolaeva-Koleva et al., 2021), paving the way for the development of topical ointments that help to mitigate the sensory symptoms of CIPN. In this regard, a preliminary report of a clinical proof-of-concept study that we performed revealed that an anhydrous topical formulation of the TRPV1 soft antagonist, AG1549 (IUPAC: *2-((4-hydroxy-2-iodo-5-methoxybenzyl)amino)-2-oxoethyl nonanoate)*, significantly alleviated grade I/II paclitaxel-induced CIPN sensory symptoms (IASP World Congress on Pain 2022, poster n° PFR325: *A topical formulation of a soft TRPV1 antagonist (AG1549) alleviates chemotherapy-induced peripheral neuropathy symptoms)*.

In addition, complementary studies are evaluating modulators of other thermoTRP channels as a promising strategy for CIPN symptoms. Application of a topical cream formulated with the TRPM8 activator menthol reduced pain scores in neuropathic pain patients with common CIPN symptoms (Fallon et al., 2015). Furthermore, riluzole, an inhibitor of TRPM8 overexpression, is currently being tested in clinical trials against oxaliplatin CIPN symptoms (Kerckhove et al., 2019), but no data are still available. Collectively, all this information suggests that modulation of thermoTRP channels could be a promising pharmacological strategy for reducing CIPN pain symptoms in male and female patients and this modulation could be adjusted depending on the sex dimorphism promoted by the chemotherapeutic agent or the oncological condition.

## 4. Outlook

Sex dimorphism in human pathology, and particularly in chronic pain, is an emerging topic that must be considered for designing and developing better treatments that help to reduce the negative impact of this disease in our society. It is becoming evident the existence of a sex hormone – thermoTRP axis that contributes to define differences in chronic pain incidence between women and men. Furthermore, as sex hormones vary throughout our life this proposed axis may also contribute to define the evolution of pain symptoms at different ages, particularly the higher incidence of most of the chronic pain conditions in aged individuals. Although still in its infancy, this axis warrants intense investigation as both sex hormones and thermoTRPs are found in the peripheral and the central nervous system. Notably, some thermoTRP channels are hormone receptors that may contribute to the sexual dimorphism observed in chronic pain. Underpinning the molecular and cellular details of this relationship may provide novel therapeutic targets for sex-specific pharmacological interventions. Apart from validating thermoTRPs as interesting therapeutic targets for analgesic intervention, novel exploitable drug target sites can also be suggested. For instance, the testosterone-binding site in TRPM8 appears as an interesting site for testosterone derivates that specifically target the thermoTRP without acting on the androgen receptor, which could be interesting for treating women suffering of chronic migraine pain (Alarcón-Alarcón et al., 2022). Similarly, it could be a valid approach for improving paclitaxel-induced CIPN treatments in men (Villalba-Riquelme et al., 2022). Because chronic pain can exhibit a strong peripheral component contributed by thermoTRPs, photopharmacology could also become an excellent therapeutic strategy in the near future, along with topical ointment formulations of thermoTRP modulators.

Collectively, the lesson learnt is that preclinical studies must use both male and female-based models to identify similarities and differences in the pathophysiological mechanisms that help to define more personalized therapeutic strategies for patients. In addition, clinical studies should also be sensitive to sex, as a differential driver of pharmacological efficacy, potency and/or side effects of disease treatments. Understanding the underlying mechanisms involved in the sex dimorphism of chronic pain will help to reduce the notable societal burden and cost of this disabling syndrome.

## Data availability

Data will be made available on request.

## Declaration of Competing Interest

Asia Fernández-Carvajal and Antonio Ferrer-Montiel are inventors of the patent TRPV1 modulator compounds (EP3621950B1) protecting a family of TRPV1 soft antagonists based on the capsaicin scaffold. David Cabañero, Eva Villalba-Riquelme and Gregorio Fernández-Ballester declare no conflict of interest.

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