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REVIEW

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Sex difference in TRPM3 channel functioning in nociceptive and vascular systems: an emerging target for migraine therapy in females?

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Abstract

Transient Receptor Potential Melastatin 3 (TRPM3) channels are Ca^{2+} permeable ion channels that act as polymodal sensors of mechanical, thermal, and various chemical stimuli. TRPM3 channels are highly expressed in the trigeminovascular system, including trigeminal neurons and the vasculature. Their presence in dural afferents suggests that they are potential triggers of migraine pain, which is originating from the meningeal area. This area is densely innervated by autonomous and trigeminal nerves that contain the major migraine mediator calcitonin gene-related peptide (CGRP) in peptidergic nerve fibers. Co-expression of TRPM3 channels and CGRP receptors in meningeal nerves suggests a potential interplay between both signalling systems. Compared to other members of the TRP family, TRPM3 channels have a high sensitivity to sex hormones and to the endogenous neurosteroid pregnenolone sulfate (PregS). The predominantly female sex hormones estrogen and progesterone, of which the levels drop during menses, act as natural inhibitors of TRPM3 channels, while PregS is a known endogenous agonist of these channels. A decrease in sex hormone levels has also been suggested as trigger for attacks of menstrually-related migraine. Notably, there is a remarkable sex difference in TRPM3-mediated effects in trigeminal nociceptive signalling and the vasculature. In line with this, the relaxation of human isolated meningeal arteries induced by the activation of TRPM3 channels is greater in females. Additionally, the sex-dependent vasodilatory responses to CGRP in meningeal arteries seem to be influenced by age-related hormonal changes, which could contribute to sex differences in migraine pathology. Consistent with these observations, activation of TRPM3 channels triggers nociceptive sensory firing much more prominently in female than male mouse meninges, suggesting that pain processing in female patients with migraine may differ. Overall, the combined TRPM3-related neuronal and vascular mechanisms could provide a possible explanation for the higher prevalence and even the more severe quality of migraine attacks in females. This narrative review summarizes recent data on the sex-dependent roles of TRPM3 channels in migraine pathophysiology, the potential interplay between TRPM3 and

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CGRP signalling, and highlights the prospects for translational therapies targeting TRPM3 channels, which may be of particular relevance for women with migraine.

Keywords TRPM3, Migraine, Sex dimorphism, Nociception, Progesterone, Estrogen, Pregnenolone sulfate

Introduction

Migraine is a complex neurovascular brain disorder characterised by recurrent attacks of often unilateral, throbbing headache with associated neurological symptoms, such as an increased sensitivity to light and sound, nausea and vomiting. Migraine affects ~ 15% of the general population world-wide [1, 2]. Up to one-third of patients also experience auras that are believed to be caused by waves of cortical spreading depolarization (CSD); hence there is a distinction between migraine with and migraine without aura [3]. Migraine is three times more prevalent in women than in men and it is now well recognized that sex hormones play a role in this sex difference [4, 5]. Notably, attacks in women are more often associated with a higher intensity and longer duration than in men, and, in women, are more frequently accompanied by associated symptoms [6, 7]. Moreover, in women with migraine, attacks are more likely to occur during the perimenstrual period, hence labelled as menstrual migraine [8]. As a consequence, migraine is a very disabling disease [9] with a higher disability in women [10]; especially in women between age 15 and 49 years [11].

Different mechanisms have been proposed to explain the sex difference observed in migraine [12–14]. Among these, the modulatory role of the sex hormonal milieu on peripheral sensory afferents and the surrounding vasculature is particularly prevailing [15, 16]. Sensitization and activation of sensory nerve endings in the dura mater have long been recognized as major factors contributing to the generation of migraine headaches [17–19]. This key mechanism is believed to be mediated by increased activity of pro-nociceptive ion channels in trigeminal afferents that are triggered by the release of main migraine mediator neuropeptide calcitonin gene-related peptide (CGRP) [2, 20, 21] or, in patients with migraine with aura, also by CSD [22]. Notably, CGRP expression was increased for 24 h in rats that underwent multiple CSD events [23]. Notwithstanding, the relevance of CSD in activating headache mechanisms has been debated [24], regardless of accumulating evidence for such a role, either through direct neuronal activation of the trigeminovascular system [25] or, as was shown recently, through the flow of cerebrospinal fluid (CSF)-borne solutes released after CSD, which carry signals from the cortex to cell bodies in the trigeminal ganglia (TG) [26] thereby activating peripheral nociceptors. Importantly, activation and sensitization of peripheral ion nociceptors occurs in a sexually dimorphic manner that is conserved across species and likely relevant to a variety of pain conditions in humans [27]. For instance, transcriptome analyses revealed sex differences in RNA expression, likely relevant to the function of sensory nociceptors, in dorsal root ganglia (DRG) of mice [28, 29] and humans [30]. Among the most intriguing findings is the observed sexual dimorphism at the transcript level of CGRP with a higher expression in females in a DRG subpopulation [31]. Sexual dimorphism in gene expression in human DRG was also shown for non-neuronal astrocytes [32] that also have a role in migraine pathophysiology [33]. Current evidence suggests that pro-nociceptive ion channels and mechanisms of their activation and sensitization in peripheral tissue are key events in generating migraine pain, and that these differ between males and females.

In this review, we focus on transient receptor potential melastatin 3 (TRPM3) ion channels as potential triggers of nociception in migraine. TRPM3 channels are expressed in a variety of cell types and tissues in various species, including humans, in both the central nervous system (CNS) and the peripheral nervous system (PNS). In the PNS they are predominantly expressed in TG and DRG sensory neurons [34–36] where they detect temperature, mechanical and chemical stimuli and transmit this information to the CNS [37]. TRPM3 channels belong to the melastatin subfamily within the mammalian transient receptor potential (TRP) superfamily of channels [38]. Among the TRP channels, TRPM3 channels have gained particular attention in the migraine field, as they: (1) are considered a promising drug target for treating chronic pain [39], as well as migraine [40]; (2) were shown to act in peripheral sensitization [41]; and (3) cation-selective channels known to be directly activated by sex hormones [42] and because of this have been implicated in sex-related differences in migraine pain [40, 43].

The importance of TRPM3 channels in the CNS has been recognized since the first functional analyses of the channels [44, 45]. Their implication for brain physiology, not only in the healthy brain [46] but also in the context of disease-causing mutations in the *TRPM3* gene [47, 48], have been the topic of recent reviews. Hence, we will here focus mainly on the role of TRPM3 channels in the nociceptive system in the context of migraine. To this end, we will summarize findings on the functional roles of TRPM3 channels in physiology, the mechanisms by which they are activated (for a summary, see Fig. 1), their direct interaction and modulation by sex hormones and CGRP, and highlight possibilities for pharmacological intervention in the context of migraine. Of note, given the specific effects of TRPM3 channels in females, their

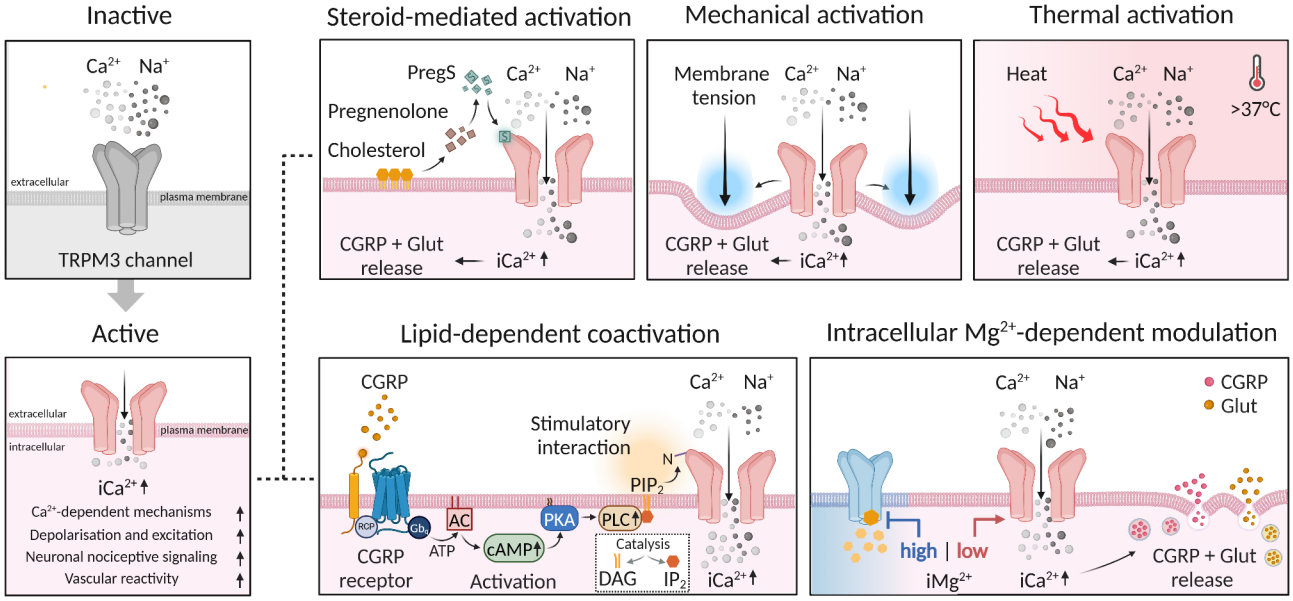

Fig. 1 Modulation of TRPM3 channels. TRPM3 channels can be modulated by various mechanisms, either they activate or inhibit TRPM3 channel activity (only the mechanisms relevant to migraine pathophysiology are mentioned). One modulation is steroid-mediated activation, primarily via pregnenolone sulfate (PregS), which is synthesized from pregnenolone, itself derived from cholesterol. Other activation mechanisms include mechanical activation due to membrane tension and temperature-dependent activation when temperatures exceed 37 °C, and intracellular lipid-signalling, particularly via phosphatidylinositol 4,5-bisphosphate (PIP_2). Upon activation, TRPM3 channels increase the level of intracellular Ca^{2+} (iCa^{2+}), triggering the release of calcitonin gene-related peptide (CGRP) and glutamate (Glut), both of which are key signalling molecules involved in migraine nociception. Enhanced Ca^{2+} influx initiates Ca^{2+}-dependent mechanisms that increase neuronal depolarization and excitation ultimately promoting nociceptive signalling and vascular reactivity. TRPM3 channel activity can be inhibited by high intracellular Mg^{2+} (iMg^{2+})-dependent mechanisms, while low intracellular Mg^{2+} levels facilitate channel activation. This activation of TRPM3 channels influences the release of CGRP, contributing to nociceptive signalling. Abbreviations: TRPM3, Transient Receptor Potential Melastatin 3; CGRP, Calcitonin gene-related peptide; Glut, glutamate; PregS, Pregnenolone sulfate; iCa^{2+}, intracellular calcium; iMg^{2+}, intracellular magnesium; PIP_2, Phosphatidylinositol 4,5-bisphosphate; DAG, Diacylglycerol; IP_3, Inositol 1,4,5-trisphosphate; ATP, Adenosine triphosphate; AC, Adenylyl cyclase; cAMP, Cyclic adenosine monophosphate; PKA, Protein kinase A; PLC, Phospholipase. *Created with BioRender.com*

activity may, at least in part, explain the higher prevalence and more severe phenotype of migraine in women, potentially paving the way for more tailored women-specific migraine therapies.

Principle structure and isoforms of TRPM3 channels

TRPM3 channels are encoded by the *TRPM3* gene that consists of 24 exons and produces a protein of 1555 amino acids in humans [44]. TRPM3 channels have a transmembrane topology composed of four subunits arranged around a central pore. Being part of the melastatin subfamily, the N-terminus lacks ankyrin repeats but instead contains an extended TRPM homology domain. Each subunit consists of six transmembrane segments (S1-S6) connected by extracellular and intracellular loops. In contrast to other TRP channels, the transmembrane domain of TRPM3 channels is divided into two functional cation-conducting pores: one non-canonical pore is formed by segments S1-S4, analogous to the structure of the voltage-sensor domain of voltage-gated ion channels, and one central canonical pore formed by segments S5 and S6 (interconnected by a hydrophobic pore-forming loop). The length of this pore-forming loop determines the TRPM3 isoform type and thereby most of the physiological and pharmacological properties of the channel [49]. Notably, the *TRPM3* gene is subject to profound alternative splicing resulting in a considerable number of isoforms [50–52]. The isoforms produced by the mouse *Trpm3* gene are classified in three groups (TRPM3α, TRPM3β and TRPM3γ) [53] of which TRPM3α1 and TRPM3α2 functionally are the best characterized [54]. TRPM3α1 has 13 amino acids inserted in the pore-forming loop ("long pore variant") compared to TRPM3α2–α6 ("short pore variants") [54]. This variation gives isoforms not only distinct pharmacological and physiological properties, but is also associated with different expression profiles. For example, whereas TRPM3α2 is predominantly expressed in the PNS, especially in DRG neurons, and is activated by PregS, TRPM3α1 is more abundantly expressed in the CNS and insensitive to PregS but instead sensitive to clotrimazole [54]. In fact, most of the TRPM3 isoforms are differentially expressed in the CNS and PNS, but since they have not yet been functionally characterized their relative role in migraine pathophysiology remains a mystery.

TRPM3 channels and migraine

Expression of TRPM3 channels within the migraine nociceptive system

The trigeminovascular system is considered the primary anatomical and physiological substrate of migraine nociception [1, 2]. A main component of the system is the pseudo-unipolar sensory neurons that primarily originate from the TG and upper cervical DRG. The peripheral nerve fiber projections innervate the cranial meninges and surrounding blood vessels, while the central fiber projections form synapses in the trigeminal caudal nucleus of the brainstem, as well as in the upper two cervical divisions, collectively known as the trigeminocervical complex (TCC). Activation and sensitization of TG and DRG fibers, triggered by mechanical, chemical or temperature changes, release vasoactive peptides, inducing local inflammatory reactions are considered relevant to migraine pain initiation [1]. Subsequently, through activation and sensitization of second-order neurons in the TCC, information reaches third-order neurons in the thalamus and ultimately the somatosensory cortex [55]. However, the exact molecular mechanisms underlying this sensitization and activation of peripheral primary afferents in the context of migraine pain remain an enigma.

A growing body of research suggests that TRP channels are particularly well-suited for encoding and transducing information of noxious stimuli from primary TG and DRG sensory afferents to other parts of the brain. Recent studies in mice revealed that the sensing of noxious stimuli depends on three types of TRP channels: transient receptor potential vanilloid 1 (TRPV1), transient receptor potential ankyrin 1 (TRPA1), and TRPM3 [37, 56]. Functional expression of TRPM3 channels in small-diameter of DRG sensory neurons (in ~78% of neurons) and in TG sensory neurons (in ~82%) of adult mice was, for the first time, demonstrated by Vriens et al. [57]. Direct evidence of functional expression of TRPM3 channels in *human* DRG (in ~52%) and stem cell-derived sensory neurons (in ~58%) comes from whole-cell patch-clamp recordings and intracellular calcium measurements, reported by Vangeel et al. [58]. More recently, electrophysiological recordings of nociceptive signals from peripheral parts of TG meningeal afferents, which contain thinly myelinated Aδ and unmyelinated capsaicin-responsive C fibers, in isolated hemiskulls, revealed proof of functional expression of TRPM3 channels in ~98% of fibers in female mice and ~80% of fibers in male mice as well [41]. Of note, activation and sensitization of these fibers seems of particular relevance to the generation of migraine pain [2, 59]. Most of the TRPM3-expressing human sensory neurons also respond to capsaicin, indicating their co-expression with TRPV1 channels, the main pain transducers. Using cluster analysis of the nociceptive signals recorded from mouse TG meningeal fibers, Krivoshein et al. [41] showed co-activation of the same fibers in response to TRPM3 and TRPV1 channel agonists, suggesting that 'superreactive' fibers detect and integrate multiple TRPM3- and TRPV1-specific stimuli, transducing them into nociceptive activation. Previously, trichrome immunofluorescence of various rat ganglia preparations showed co-expression of TRPM3, TRPV1 and CGRP, albeit with some variability that depends on sensory ganglion location [60]. Notably, some 70% of TRPM3-immunoreactive neurons in TG also had TRPV1 immunoreactivity, whereas almost half of the TRPM3-immunoreactive neurons exhibited CGRP immunoreactivity. With respect to their respective subcellular localization, as revealed by high-magnification confocal microscopy, in rat sensory ganglia, TRPM3 channels are localised at the periphery (submembrane) of a subset of cell bodies, which is markedly different from the localization of other TRP channels (TRPV1 and TRPA1), present throughout the cytoplasm of the cell body [61].

In addition to neurons of the trigeminovascular system, also cerebral and meningeal blood vessels play an important role in migraine pathophysiology, likely through vasodilatation by triggering neighboring nociceptors, thereby leading to a further release of inflammatory neuropeptides thereby fuelling "the migraine pain cycle" [62]. According to one study [63], TRPM3 channels are present in contractile and proliferating vascular smooth muscle cells, as well as in the adventitia layer of blood vessels, resulting in contraction of vessels upon activation of these channels. In contrast, another study [64] suggested that the expression of TRPM3 channels is restricted to the endings of neurons making contact with blood vessels, with their activation leading to vasodilation rather than contraction. Recently, the controversy was further addressed, demonstrating that *functional* TRPM3 channels are present both in human isolated dermal arteries (mainly in smooth muscle cells and to lesser extent in endothelial cells) and perivascular sensory nerves innervating the adventitial layer of arteries. Most notably in the context of this review, TRPM3 channel activation by pregnenolone sulfate (PregS) induces a release of CGRP. Paradoxically, the functional vasodilatory response to PregS was not affected by CGRP receptor antagonist olcegepant, suggesting that this functional response is independent from CGRP [65].

Functional properties of TRPM3 channels and the relation to migraine pathophysiology

Ca^{2+} permeability and sensitivity to Mg^{2+} of TRPM3 channels

Originally, TRPM3 channels were identified as constitutively permeable to Ca^{2+} ions, as demonstrated by in vitro investigation [45]. Further electrophysiological analysis revealed that TRPM3α2 (the most extensively studied

isoform) has ten-times greater permeability to Ca^{2+} (and other divalent) cations than the TRPM3α1 isoform, which is more permeable to monovalent ions [66]. Thus, activation of isoform-specific TRPM3 channels could mediate not only depolarization, leading to spike generation in neuronal cells, but also to variable levels of Ca^{2+} influx in various types of cells. Notably, both neuronal depolarization and increased Ca^{2+} levels in trigeminal neurons and vascular cells are deemed critical mechanisms for the activation and sensitization of neurons that may directly or indirectly modulate vascular tone relevant to migraine pathophysiology [64]. Most relevant in the context of this review, however, is that transient rises in Ca^{2+} serve as triggering factor for the release of CGRP and glutamate from peripheral and central nerve endings of trigeminal neurons [21, 67]. Also of relevance is that a *sustained* elevated level of Ca^{2+}, as often found in cancer, typically results in hyperalgesia and headache [68]. Finally, in particular, elevated levels of extracellular K^+ observed during CSDs, along with Na^+ and Ca^{2+} influx and glutamate release from central neurons, are believed to cause dendritic depolarization in a non-synaptic manner. TRPM3 channels are known to be inhibited by high levels and activated by low levels of intracellular Mg^{2+} [50] (see also Fig. 1). Clinical and preclinical studies have found low Mg^{2+} levels in blood and CSF of migraine patients, suggesting that they may benefit from correcting this deficiency [69]. Low Mg^{2+} levels in migraine patients may increase TRPM3 channel activity as a result of reduced inhibition, leading to enhanced release of CGRP, potentially exacerbating migraine symptoms. However, the involvement of TRPM3 channels in Mg^{2+} signalling in the context of migraine has not been investigated in detail. Therefore, while the precise mechanisms remain unclear, Mg^{2+} supplementation appears beneficial as a strategy for migraine management, possibly due to TPRM3's sensitivity to this ion and its potential involvement in migraine pain generation.

Lipid signalling modulates activity of TRPM3 channels

TRPM3 channel activity, similar to the activity of various other members of the TRPM subfamily, strongly depends on the availability of membrane-signalling lipids, such as phosphatidylinositol 4,5-bisphosphate (PIP2) [70] and phosphatidylinositol (3,4,5)-trisphosphate (PIP3) [71, 72] with more potential enhancement by the latter (see also Fig. 1). PIP2 was shown to interact with TRPM3 channels through amino acid residues in the S1-S4 and pre-S1 segments [73], that overlap with the N-terminal calmodulin binding domains [74]. Of note, phospholipase C (PLC) enzyme activity, which is responsible for catalysing the hydrolysis of PIP2, was found increased in the CSF of patients with migraine without aura in the ictal phase [75], and more so in patients with more comorbidities [76]. Certainly, the interaction of CGRP with its receptor not only activates protein kinase A (PKA) through Gβγ subunit activation and increased levels of cAMP [77] but also stimulates PLC activity [78]. Therefore, there is the rationale for considering modulation of phosphoinositide metabolism, specifically the rapid depletion of PIP2 by PLC activation, which quickly suppresses TRPM3 activity [79], as potential therapeutic strategy for migraine.

Plasma membrane microdomains, known as lipid rafts, which are enriched with cholesterol and sphingolipids, have been identified crucial for TRP channel functioning [80]. In vitro investigation revealed that disrupting lipid rafts with, for instance, methyl-β-cyclodextrin (MCD) reduced the agonist-induced activation of TRP channels, such as TRPV1, TRPA1, and TRPM8, in trigeminal neurons, but this, surprisingly, had no effect on TRPM3 channel activation [81]. Carboxamido-steroid compound (C1), which is used for lipid raft disintegration by cholesterol depletion [82], resulted in a decreased activation of TRPM3 channels in trigeminal neurons [81, 83]. A recent in vivo animal study demonstrated that disrupting lipid rafts through cholesterol depletion via MCD or C1 had an anti-nociceptive effect on icilin-induced nocifensive behavior via TRPM3 channels [84], suggesting a peripheral analgesic effect of MCD. Similar to a possibly beneficial effect of dietary intake of Mg^{2+}, albeit mostly through inhibition of NMDA receptors [85] and not so much TRPM3 channel modulation, also dietary intake of n-3 long-chain polyunsaturated fatty acids, which has been shown to positively affect lipid raft aging and changing neuronal plasticity as shown for hippocampus [86], may be considered as possible migraine therapeutic and was shown to have at least some efficacy in patients [87].

There are also endogenous agonists of TRPM3. Foremost, a cholesterol derivative, pregnenolone, increases TRPM3 activity [88]. Addition of a sulfate group, resulting in PregS, significantly enhances TRPM3 activator potency [89]. Since PregS is a direct precursor of various sex hormones it likely plays a relevant role in the TRPM3-related sex difference seen in a migraine context. Also sphingolipids, including D-erythro-sphingosine, can act as TRPM3 channel agonist [90]. Sphingolipids have been implicated in central sensitization in chronic migraine models [91–93]. For example, blockage of sphingosine receptors alleviated central sensitization and inhibited microglia activity in a mouse model for chronic migraine, in which nitroglycerin was repeatedly administered via intraperitoneal injection [93].

Mechanical sensitivity of TRPM3 channels and mechanical pain in migraine

Mechanical pain — more specifically allodynia, mechanical hyperalgesia, and pulsating pain — is a major attributor of migraine pathophysiology [94]. TRPM3 channels

were shown to play a role in mechanical sensitivity (see also Fig. 1), as was first evidenced by Ca^{2+} entry through TRPM3-expressing HEK293 cells following exposure of the cells to a hypotonic solution [45], even though Piezo channels are now considered the most specialized sensors of mechanical stimuli [95]. Although a role of TRPM3 channels as mechanotransducers based on the experiments with hypotonic stimuli has been debated [46], recent studies with distension of afferent nerves revealed clear TRPM3 mechanosensitive features [96, 97]. Moreover, a contribution of TRPM3 channels to mechanical hypersensitivity (and allodynia) was reported in various pathological pain conditions [98–101]. Finally, TRPM3 channels are also involved in mechanosensing in vascular smooth muscle cells and aortic contraction [63] and in sinoatrial and atrioventricular nodes that are sensitive to physiochemical stimuli [102]. The observation that TRPM3, TRPV1 and mechanosensitive Piezo channels are co-localized in the same nerve fiber [41] again suggests that such fibers could serve as 'supermechanosensitive nociceptors' in the context of mechanical pain in migraine.

Thermal sensitivity of TRPM3 channels

Thermal stimuli, likely given their important biological role in survival, are recognized by several specialized membrane receptors, primarily from the TRP family, such as TRPV1, TRPA1, TRPM3 and TRPM8 [37]. Among them, TRPM3 channels are specialized for the detection of painful temperatures [57] (see also Fig. 1). For instance, it was shown that *Trpm3* knockout (*Trpm3*$^{-/-}$) mice exhibit partial, but significant, deficits in response to noxious heat while they showed no deficits to noxious cold. In the same study it was demonstrated that *Trpm3*$^{-/-}$ mice failed to develop inflammatory heat hyperalgesia following local injection of complete Freund's adjuvant. Paricio-Montesinos et al. [103] showed in TRPV1, TRPM3 and TRPA1 triple knockout mice, a complete loss of responses to noxious heat stimuli in heat sensitivity of Aδ and C fibers. Therefore, it was suggested that TRPM3 channels are predominantly located on primary sensory neurons of DRG and TG that play a key role in noxious heat sensation transmitting nociceptive signals to the cortex but that they are dispensable for warm sensing. Of interest to migraine, extracranial arteries and myofascial structures, innervated by unmyelinated TG nerve fibers, contain various neuropeptides, such as CGRP, which are released during migraine attacks [104]. One can, therefore, at least speculate that middle meningeal artery dilation, which is involved in triggering migraine attacks, increases the temperature in the head region supplied of blood by that vessel. In this context it is noteworthy that a small asymmetry in temperature, particularly in the frontal and temporal regions of the pain side, was observed in patients with unilateral headaches [105]. One can also hypothesize that the action of heat- and mechanosensitive TRPM3 channels might reflect some neurochemical imbalance and that the resulting vasodilation of facial microcirculation leads to nociceptive heat sensations and the transmission of pain signals. Since proinflammatory compounds can change the threshold temperature of TRPV1 channels [106], the threshold may also be reduced for TRPM3 receptors expressed in sensitized trigeminal neurons.

TRPM3 channels modulation by sex steroid hormones

Since long, have TRPM3 channels been shown to be ionotropic steroid receptors that are activated by natural PregS [88] (see also Fig. 1). Because of the negatively charged sulfate group, PregS is highly lipophobic and functions as a membrane-impermeable ligand, only activating the channel when applied to the extracellular side, indicating that the steroid-binding site of TRPM3 is located extracellularly [88]. Notably, at a concentration in the range found in blood, PregS in mice evokes much stronger responses at normal body temperature (37 °C) than at room temperature, in line with PregS acting as endogenous agonist of TRPM3 channels [57]. Moreover, Wagner et al. [88] showed that other endogenous substances closely related to pregnenolone, such as dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS), also can activate TRPM3 at room temperature. Taken together, this suggests that, in vivo, TRPM3 channels may be activated when levels of these endogenous substances are elevated. Later, Majeed et al. [107] found the opposite effect on TRPM3 channel activation for the female sex hormone progesterone, which they showed to inhibit responses to PregS (Fig. 2). Inhibition of TRPM3 channels by progesterone was independent of any competition by an exogenous agonist, so acted as a mode-independent inhibitor, although not through classical progesterone receptors. The authors observed that pre-treatment with progesterone reduced PregS-evoked Ca^{2+} influx in human vascular smooth muscle cells, however, this did not inhibit PregS-evoked currents in granulosa cells isolated from bovine ovarian follicles. In fact, metabolites of progesterone (i.e., pregnanolone (5β), allopregnanolone (5α), 17-hydroxy progesterone (17-OH), 21-hydroxy progesterone (21-OH)) and 17β-estradiol) as well as metabolites of testosterone, dihydrotestosterone (DHT), were all shown to have inhibitory effects on PregS-evoked Ca^{2+} influx, but these effects were relatively small compared to the effect of progesterone [107]. However, in contrast to such inhibitory effect of progesterone and estradiol on PregS-evoked Ca^{2+} influx, Persoons et al. [42] claimed that four steroid hormones (progesterone, estradiol, DHEAS, and testosterone) can *also* act as weak partial

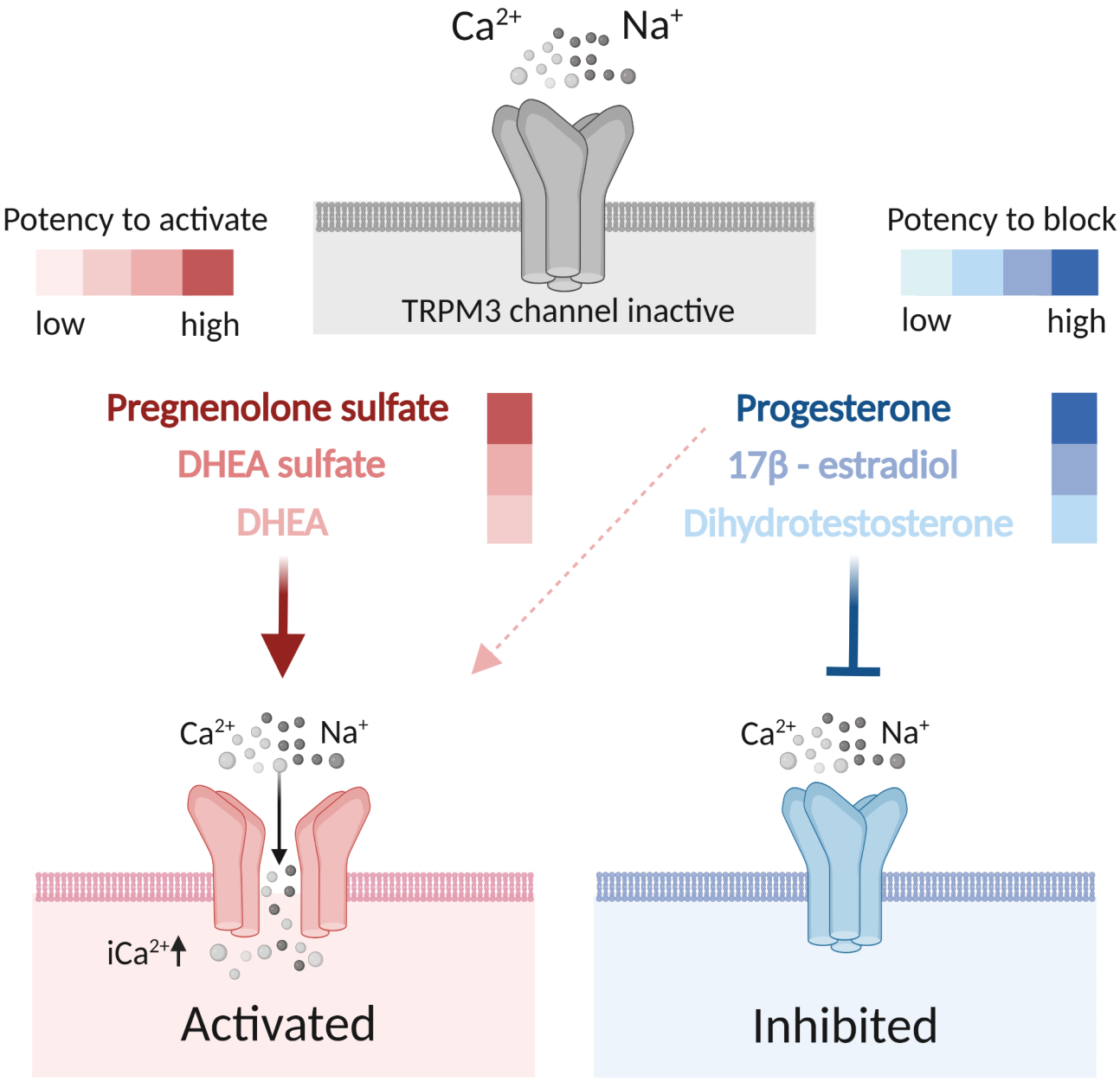

Fig. 2 Modulation of TRPM3 channels by sex steroid hormones and their metabolites. TRPM3 channels are modulated by sex steroid hormones and their metabolites, which have varying potencies to activate or inhibit the channels. Pregnenolone sulfate and dehydroepiandrosterone (DHEA), with and without sulfate conjugation, serve as activators of TRPM3 channels. In contrast, progesterone, 17β-estradiol, and potent testosterone metabolite dihydrotestosterone act as channel inhibitors. Furthermore, progesterone, 17β-estradiol, DHEA, and testosterone (not shown) may also function as weak partial agonists of TRPM3 channels (dot array), highlighting their dual roles in channel regulation. Abbreviations: TRPM3, Transient Receptor Potential Melastatin 3; iCa^{2+}, intracellular calcium; DHEA, Dehydroepiandrosterone. *Created with BioRender.com*

agonists and can activate TRPM3 channels at physiological body core temperature. The authors also showed that these neurosteroids compete for the interaction site of TRPM3 channels with PregS and activate the non-canonical pore leading to massive cationic influxes through TRPM3 channels. Of the four neurosteroids, DHEAS is the most potent agonist (likely because it also carries a sulfate group that is important for channel activation, similar to PregS), followed by estradiol, testosterone, and progesterone. The notion that these neurosteroids can both function as full or partial agonists (in the latter case, depending on the presence of agonists with higher intrinsic activity also as antagonists) of TRPM3 channels, fuels the believe that they may have a role in the sex difference of migraine nociception. Relevant to the latter, the interaction of TRPM3 and sex hormones is also suggested by

the fact that estrogen and progesterone can attenuate facilitation of vasoconstriction via TRPM3 channels in the vascular system [108].

Sex difference in migraine and relation to TRPM3 channels

Influence of sex hormones in migraine prevalence

After puberty, migraine is much more prevalent in women than in men, with an age-standardised prevalence of 18.9–20.7% for women and 8.0-9.7% for men [11, 13, 109–111]. Among the proposed mechanisms that can explain this sex-dependent difference are menstrual cycle-related hormonal fluctuations of ovarian steroid hormones, specifically estrogen and progesterone [112, 113]. In prepubertal children, however, where sex hormones have not yet reached the levels seen during puberty, migraine prevalence is similar for boys (3.0%) and girls (4.0%) [114]. With the onset of puberty, hormonal fluctuations directly impact migraine prevalence, which increases in both sexes, but with a higher prevalence in girls than in boys (6.4% and 4.0%, respectively) [114]. This sex-related difference in migraine attacks persists throughout life during the fertile period (i.e., menstruation, pregnancy, and perimenopause) and declines with advanced age when hormone levels drop (i.e., menopausal and post-menopausal stages) [112, 115, 116]. Evidently, the sex differences in migraine attacks highlight the role of sex hormones in migraine pathophysiology, with an increase in attacks following the onset of menarche and a decrease after menopause. Migraine attacks (without aura) (1) are triggered by a decline in estrogen levels during the late luteal phase of the menstrual cycle [4] (see also Fig. 3); (2) decrease or are absent during the first trimester of pregnancy and/or the first month of breastfeeding, when increased estrogen levels might raise the pain threshold [117], suggesting that stably elevated estrogen levels protect against migraine attacks; and (3) are precipitated (e.g., menstrual migraine) or not during estrogen or progesterone withdrawal, respectively [118–120]. Hence, the prevalence of migraine attacks is linked to a function of the hypothalamic-pituitary-ovarian axis [112].

Fluctuations in estrogen and progesterone throughout different menstrual cycle phases can also alter pain perception via peripheral nociceptive channels [121]. The impact of sex hormones on nociceptive channels in brain areas associated with migraine initiation, such as the meninges and trigeminal neurons, likely leads to their activation and the triggering of migraine pain, or, in some cases, provides a protective effect [122]. Moreover, progesterone, which is primarily active during the luteal phase exerts protective effects against migraine attacks.

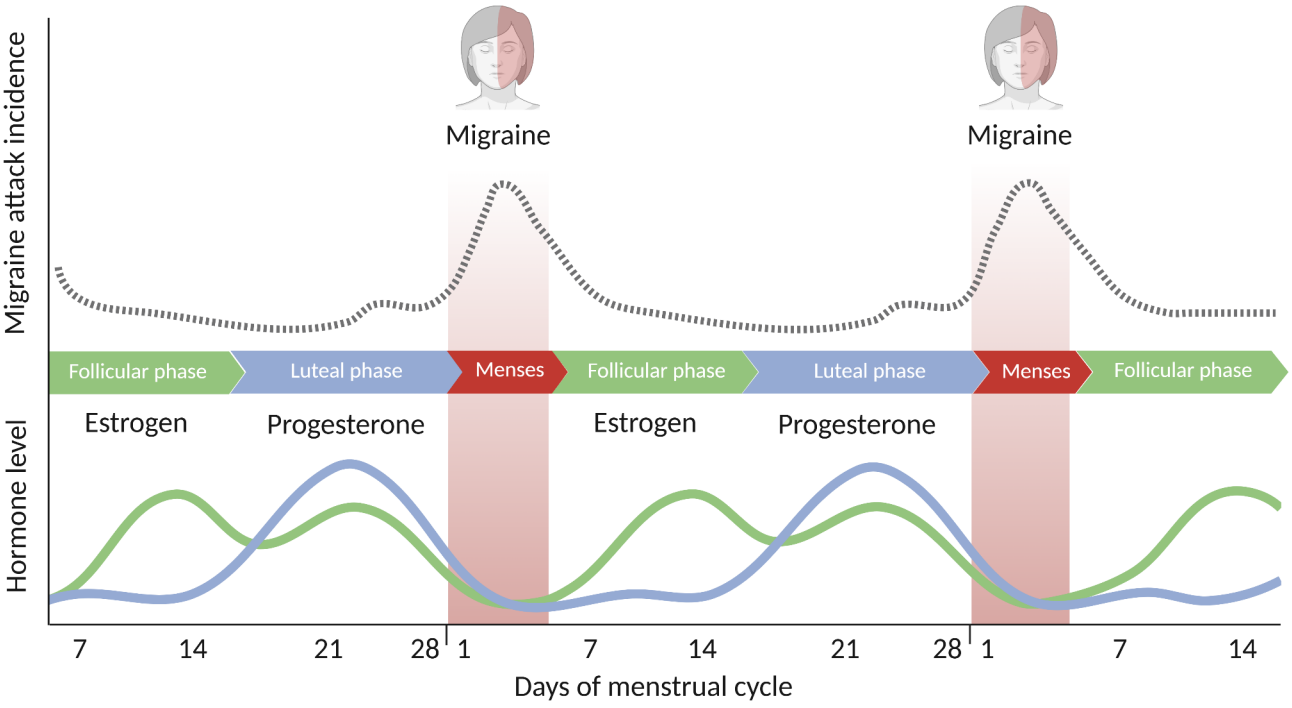

Fig. 3 Hormonal fluctuations and migraine incidence in females. Hormonal fluctuations of estrogen and progesterone across the menstrual cycle are mapped to the follicular and luteal phases, with day one marking the onset of menses. Among females of reproductive age, the incidence of their migraine attacks (top part) tends to peak in response to the drop of estrogen and progesterone levels (bottom part), which typically occurs just prior to menses onset. This hormonal shift is associated with heightened pain sensitivity, as evidenced by increased hyperalgesia and a lowered pain threshold during this time period. *Created with BioRender.com*

Unlike estrogen, its decline before menstruation does not coincide with worsening migraine symptoms [120].

The role of testosterone in determining the susceptibility to migraine attacks in men has also been noted but its modulatory role in the prevalence and pathophysiology of migraine has not yet been clarified. Men with episodic migraine exhibit high levels of testosterone-free β-estradiol [123], while men with chronic migraine show low levels of total testosterone compared to men without migraine [124], suggesting that there could be a slightly different function of the hypothalamic-pituitary-gonadal axis in men with migraine compared to those without migraine. It remains, however, unknown whether fluctuations in testosterone levels are associated with the frequency of migraine attacks in men. Interestingly, in men with migraine, the frequency of clinical symptoms related to androgen deficiency is higher compared to patients without migraine [125].

Role of sex hormones in migraine pathophysiology: interaction with CGRP and TRPM3 channels

Hormonal fluctuations of estrogen and progesterone modulate central nervous activity, pain sensitivity, and vascular tone, thereby contributing to the development of migraine attacks. At the CNS level, estrogen and progesterone can modulate the release, function and/or expression of CGRP [117, 126] and TRP channels, including TRPM3 channels [43]. In this respect, estrogen influences the release of and sensitivity to CGRP in the trigeminovascular system [126, 127], while a withdrawal of estrogen increases CGRP expression in brain regions involved in autonomic control and pain processing [128, 129]. Whether TRPM3 channel agonists can also promote the release of the neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP), which like CGRP is known to induce migraine-like attacks in patients [130], remains unexplored. With respect to any sex differences, plasma levels of CGRP are higher in women of reproductive age than in men, increasing even more during pregnancy [131] or in women undergoing hormonal contraception treatment [132]. Furthermore, there is a fluctuation in CGRP levels during the menstrual cycle, suggesting hormone-dependent changes in CGRP release [133, 134]. Therefore, the relationship between estrogen fluctuation and CGRP levels might explain the higher susceptibility to migraine attacks in women. Unlike estrogen, progesterone exerts an opposite effect by inhibiting the release of CGRP and modulating sensory neurotransmission, vascular responses, and neurogenic inflammation [127, 135]. Expanding on the pivotal role of CGRP, also TRP channels (including TRPM3 channels) seem to play a key role in migraine pathophysiology and the observed sex difference, considering that they (1) are expressed in the trigeminal system innervating the meninges; (2) can induce CGRP release from sensory nerves; and (3) are modulated by sex hormones [41, 43, 57, 107, 136]. In this context, the inhibitory effects of progesterone and 17β-estradiol on TRPM3 channel activity underscore a complex sex-dependent mechanism that influences nociceptive pathways [43]. Considering that sex hormone levels drop during the menstrual cycle, one might speculate that the activity and/or expression of TRPM3 channels could increase, potentially contributing to central sensitization in migraine (Fig. 4). Therefore, the blocking action of TRPM3 channel function by estrogen and/or progesterone may represent an endogenous mechanism of pain inhibition in women with menstrual migraine, based on the assumption that when their concentrations decrease, TRPM3 channel activity will increase, as would happen prior to menstruation. It is worth mentioning that progesterone inhibits the permeability of TRPM3 channels at levels typical for the luteal phase of the menstrual cycle [107]. Evidence has shown that *TRPM3* mRNA expression fluctuates significantly throughout the menstrual cycle, with a lower expression during the menses compared to the follicular and late luteal phases, when estrogen and progesterone are elevated [137]. Moreover, preclinical studies in female mice have corroborated these findings, demonstrating an upregulation of *Trpm3* gene expression during the proestrus stage of the estrous cycle [138], which parallels the human follicular phase [139]. Furthermore, a significant sex difference was observed in nociceptive activity recorded from mouse meningeal afferents, with TRPM3-mediated firing being much more pronounced in female mice [41]. Additionally, women with migraine exhibit significantly reduced neurosteroid levels, with serum levels of the steroid pre-hormones DHEA, DHEAS, and pregnanolone being lower [140]. A parallel study found that serum levels of PregS, along with pregnanolone, were also lower in women with menstrually-related migraine [141]. It has also been shown that PregS is a potent activator of TRPM3-mediated gene transcription [142], whereas both pregnenolone and progesterone have been indicated to interfere with PregS-mediated gene upregulation. In this regard, it is intriguing that so-called gain-of-function mutant TRPM3 channels exhibit increased sensitivity to endogenous PregS [143, 144]. Given that PregS stimulates TRPM3 channels one can hypothesize that the reduction of levels of PregS, together with that of DHEA and DHEAS, in plasma may lead to decreased activation of TRPM3 channels, prompting the body to upregulate the expression of the TRPM3 channels in an attempt to restore normal function and maintain homeostasis. Clearly, current evidence suggests that TRPM3 channels, which are influenced by hormonal fluctuations and neurosteroids, may contribute to the sex-specific characteristics of migraine, warranting further exploration into

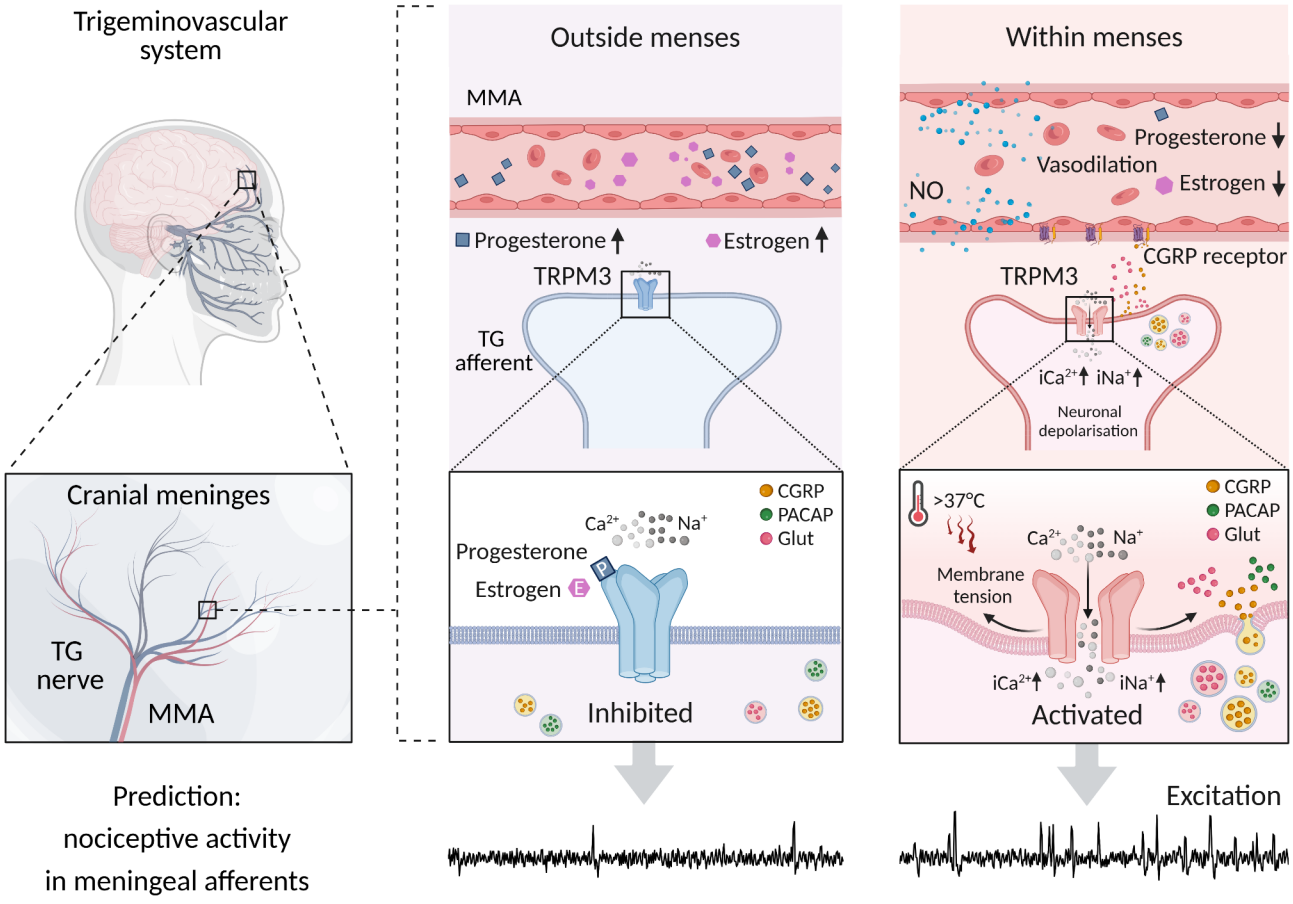

Fig. 4 Proposed hormonal modulation of TRPM3 channels and nociceptive signalling within the menstrual cycle. The trigeminovascular system is a critical anatomical structure in migraine pathophysiology, consisting of the cranial meninges innervated by peripheral meningeal nerves and vascularized by vessels originating from the middle meningeal artery (MMA) and branches of the trigeminal nerve (TG). The afferents of the TG and MMA closely intersect, exerting reciprocal influences on each other. Increased nociceptive activity within meningeal afferents during menses seems to suggest that, outside of menses, TRPM3 channel activity is inhibited by elevated levels of progesterone and/or estrogen. This hormonal inhibition prevents afferent activation and subsequent neuronal depolarization. However, during menses, declining levels of progesterone and estrogen remove the inhibition, activating TRPM3 channels and resulting in increased calcium (Ca^{2+}) influx into TG afferents. The Ca^{2+} influx stimulates the release of calcitonin gene-related peptide (CGRP) into the extracellular space, where it binds to receptors on nearby vessels, triggering the release of nitric oxide (NO), causing vasodilation and increased local temperature. Nerve fibers subsequently release additional factors, including glutamate (Glut), and pituitary adenylate cyclase-activating polypeptide (PACAP), further depolarizing TG meningeal afferents. The sustained activation may drive neurons into a hyperexcitable state, leading to ectopic discharges and ultimately resulting in the perception of pain. Abbreviations: MMA, Middle meningeal artery; TG, Trigeminal ganglion nerve; TRPM3, Transient receptor potential melastatin 3; iCa^{2+}, intracellular calcium; iNa^{+}, intracellular natrium; CGRP, Calcitonin gene-related peptide; NO, Nitric oxide; PACAP, Pituitary adenylate cyclase-activating polypeptide; Glut, glutamate. *Created with BioRender.com*

their role as potential therapeutic targets for managing migraine, including menstrual migraine.

At the vascular level, sex hormones exert a protective effect on the cardiovascular system through the modulation of vascular tone [117, 126]. In this respect, estrogen, progesterone and testosterone induce (1) vasodilation via the inhibition of Ca^{2+} influx [145, 146]; (2) the release of nitric oxide, prostacyclins, cyclic guanosine monophosphate, or cyclic adenosine monophosphate; changes in expression of their receptors; or (3) changes in Ca^{2+} and/or K^{+} channel activity [146, 147]. Regarding the potent vasodilator effect of CGRP, it has been demonstrated that vascular responses mediated by CGRP are similar in men with and without migraine, whereas in women there is an increase in the CGRP-dependent dermal blood flow that correlates with hormonal fluctuations, as vascular reactivity to capsaicin is increased during the menstrual cycle [148] and reduced in postmenopausal women [133]. Moreover, vascular reactivity to capsaicin is more pronounced in women with migraine [148] due to the increase in CGRP release. Likewise, in cranial vasculature (i.e., middle meningeal arteries, a proxy for the trigeminovascular system) CGRP shows a sex-specific vasodilator effect. CGRP is less effective in inducing relaxation responses in isolated middle meningeal arteries from women younger than 50 years of age compared with that induced in arteries from men of the same age range, without differences in the relaxation responses in arteries

from women and men older than 50 years [149]. These differences may be explained by differential expression of CGRP receptors and/or age-dependent fluctuations in sex hormone levels [149], which can induce desensitization of CGRP receptors in women.

Concerning sex hormone-mediated vascular function of TRPM3 channels, a few studies have demonstrated that TRPM3 channel function is mediated by PregS to induce relaxation responses in different vascular beds [64, 65, 150]. TRPM3 channel-mediated vasodilation has been shown to be sex-dependent, as responses to PregS in human meningeal arteries are more prominent in arteries isolated from women than from men [151]. This observation suggests that sex hormones might influence TRPM3 channel activity, or that there is a higher expression or sensitivity to these receptors in women. In fact, it has been suggested that TRPM3 channel-induced relaxation might be mediated by progesterone in pregnant women [65]. Additionally, evidence suggests that TRPM3 channels and glutamate receptors, particularly NMDA receptors, interact to modulate vascular tone. In this regard, it is noteworthy that PregS can also modulate NMDA receptors [65]. Notably, PregS-induced vasodilation in human meningeal arteries is mediated by the activation of NMDA receptors in females but not in males, as the antagonist MK-801 was able to inhibit the relaxation responses induced by PregS only in female arteries [151]. The differential responses induced by PregS, as well as the differential role of NMDA receptors might offer a new perspective for understanding sex dimorphism in migraine, as well as represent new therapeutic options for migraine treatment.

TRPM3 channel inhibitors as possible anti-migraine therapy

Despite preclinical evidence that TRPM3 channels are expressed in migraine-relevant tissue and that trigeminal neurons are activated by TRPM3 channel agonists, modulators of TRPM3 channels are not yet ready to be used as anti-migraine therapy. Regardless, both synthetic and plant-derived compounds have been identified and characterized as pharmacological TRPM3 antagonists [38]. Some have analgesic effectivity in preclinical mouse and rat models and are being considered for novel analgesic therapy [152]. Likely, specific TRPM3 channel antagonists still need to be developed for clinical trials in migraine. An overview of TRPM3 antagonists tested in various animal models is provided below.

Selective TRPM3 channel antagonists

Pharmaceutical industry has been very active in developing selective TRP antagonists, including for TRPM3 channels, for various pain indications [152], even though efforts for migraine are lagging behind. One highlight is that, recently, the highly selective TRPM3 antagonist BHV-2100 was presented, as a first-in-class compound, at the 2024 *Annual Meeting of the American Academy of Neurology*. BHV-2100 effectively alleviated pain, with a favorable side effect profile, in preclinical cell and rat models with a much higher selectivity over a panel of ion channels and receptors, including pro-nociceptive TRPV1 and TRPA1 receptors.

Repurposing existing drugs as TRPM3 channel antagonists

Non-steroid anti-inflammatory drugs Mefenamic acid, a non-steroid anti-inflammatory drug (NSAID) that reversibly inhibits cyclooxygenase [153] stands out as one of the most potent and selective TRPM3 antagonists, with an in vitro half-maximal inhibitory concentration (IC_{50}) of 6.6 µM [154], which is within the range of plasma concentrations obtained after administration of a clinical dosage [155]. It effectively inhibited both cytoplasmic Ca^{2+} influx and *TRPM3* gene transcription in cells expressing activated TRPM3 channels [142], the latter being confirmed in another study [156]. In the context of migraine, mefenamic acid is an effective preventative medication, and seems particularly useful for menstrually-related migraine [157, 158] with the additional benefit of relieving dysmenorrhea. Moreover, clinical guidelines recommend mefenamic acid use as a symptomatic acute therapy for patients with menstrually-related migraine [159, 160], albeit under careful monitoring due to an increased risk of gastrointestinal complications [161, 162] and the risk for medication overuse headache development [163, 164]. Despite the clear connection between mefenamic acid and blockade of TRPM3 channels, their effective inhibition by mefenamic acid in the context of menstrually-related migraine remains understudied.

Diclofenac, another NSAID, was also characterized as TRPM3 antagonist [165], as it inhibited PregS-evoked TRPM3 channel responses in a concentration-dependent manner in Ca^{2+} and electrophysiological assays in cell lines expressing isoforms of TRPM3. Other TRP channels exhibited either resistance to diclofenac or had minimal inhibitory effects, emphasizing its strong selective inhibitory action on TRPM3 channels [165]. Diclofenac is indicated for the treatment of acute and chronic migraine; a recent open-label study evaluating the pharmacokinetics and safety of diclofenac revealed that diclofenac potassium for oral solution exhibited a favorable pharmacokinetic and safety profile in young migraine patients with and without aura [166]. Another randomized, placebo-controlled study demonstrated that a peripherally injected single dose of diclofenac is effective for the acute treatment of migraine attacks, offering a relatively safe, effective, and well tolerated alternative to specific acutely acting medications for migraine management [167].

Anti-diabetic drugs Anti-diabetic drugs rosiglitazone and troglitazone, which belong to the class of thiazolidinediones, were developed to reduce insulin resistance in type two diabetes mellitus [168]. Notably, the authors claim that inhibitory effects on TRPM3 channels occurred rapidly in a biphasic concentration-dependent manner. Rosiglitazone has also been shown to inhibit Kir6.1-containing K_{ATP} channels, though at relatively high concentrations [169]. Emerging evidence suggests the involvement of K_{ATP} channels in the pathophysiology of migraine and recent research has demonstrated that activation of K_{ATP} channels can trigger migraine attacks in migraineurs [170]. Regardless, there should, of course, be reasonable concern when administrating anti-diabetes medication to migraine patients, already because of its ability to alter the metabolic balance, particularly in glucose and fat metabolism. Consequently, it remains unclear whether this type of medication is a fruitful new avenue for treating migraine patients. Still, very recently agonism of glucagon-like peptide-1 receptors—which are expressed in various brain regions including hypothalamus, cortex and hippocampus, and are involved in regulating glucose homeostasis and satiety [171]—has been proposed as promising for the treatment of headache and pain disorders [172].

Anti-depressant and anti-convulsant drugs Subtherapeutic concentrations of tetracyclic anti-depressant maprotiline and anti-convulsant primidone inhibited pure-PregS and clotrimazole-PregS responses in vitro and attenuated heat- and PregS-induced nocifensive behavior and inflammatory hyperalgesia in vivo [173]. Primidone was shown to improve symptoms in TRPM3-linked epilepsy [174], but there are no publications showing a potential synergistic or additive benefit of combining it for migraine treatment.

Flavonoids as powerful inhibitors of TRPM3 channels

Flavonoids, particularly fruit flavanones and their derivatives, are since long considered one of the more powerful groups of biologically active substances [175]. Recently, Bakirhan et al. [176] demonstrated that flavanone intake seemed correlated with a reduced migraine severity, while a lower intake was associated with more severe migraine attacks. It was also shown that genistein-based soy isoflavones, which mimic the action of estrogen by binding to estrogen receptors [177], significantly reduced the frequency and duration of migraine attacks, as well as CGRP levels [178]. Preclinical in vivo studies exploring mechanisms by which genistein could alleviate migraines, also evidenced by decreased migraine-like symptoms of thermal and mechanical allodynia in nitroglycerin-induced migraine rats, indicate a potential therapeutic efficacy in migraine [179, 180]. Although the exact pathophysiological mechanisms underlying the correlations remain unclear, one may speculate that flavanones and their derivatives (isoflavones) might exert analgesic efficacy by modulating the activity of TRPM3 channels. In this context it is relevant to note that citrus fruit flavanones, such as hesperetin, naringenin, eriodictyol, and ononetin, seem potent and selective blockers of TRPM3 channel activity [181]. As citrus itself is sometimes reported to be a migraine trigger [182], potentially due to its putrescine content, which may inhibit histamine catabolism in the intestines [183], purified flavanones are better considered to have therapeutic benefit. Isosakuranetin, whose glycoside is found in blood oranges and grapefruits, and liquiritigenin, displayed the most potent inhibition of TRPM3 channels. Almost two decades ago, hesperetin was proposed to control pathophysiological disturbances of brain excitability, which also has relevance to what happens in a migraine brain [184]. Straub et al. [185]. showed that isosakuranetin and liquiritigenin exhibited marked specificity for TRPM3 compared with other sensory TRP channels, and blocked PregS-induced signals in isolated DRG neurons. Furthermore, isosakuranetin and hesperetin significantly reduced the sensitivity of mice to noxious heat and PregS-induced chemical pain in vivo [185]. Anti-nociceptive effects of isosakuranetin were revealed in animals, where it dose-dependently alleviated mechanical, thermal, and cold hyperalgesia with no effect on motor performance [186]. In a recent study intraperitoneal injection of isosakuranetin, effectively reduced the oxaliplatin-induced pain behavior in response to cold and mechanical stimulation in mice [101]. In addition, the TRPM3 channel blocker ononetin reversed a complete Freund's adjuvant-induced hypersensitivity in mice [187]. Finally, a study showed that ononetin, isosakuranetin, and naringenin related antagonism of TRPM3 channel signalling can prevent pain mechanohypersensitivity [100]. Notwithstanding the research on the various TRPM3 channel antagonists, the potential benefit of these molecules in a migraine context is still in its infancy but deserves more thorough investigation.

Concluding remarks and future perspectives

An increasing number of experimental studies indicate high functional activity of TRPM3 channels in the brain and peripheral tissues, and most relevant to the topic of this review, in neurons and the vasculature, which are relevant to migraine pathophysiology. Among the most interesting findings for migraine, thus far, is the surprisingly strong activity of TRPM3 channels observed in trigeminal afferents of female mice, aligning with clinical observations that migraine is more prevalent and severe in women compared to men. The high sensitivity of TRPM3 channels to female sex hormones and related steroids further reinforces the proposed role of TRPM3 channels in the sex difference observed in migraine.

Moreover, the vascular activity of TRPM3 warrants attention, as TRPM3 channels have been implicated in modulating vascular tone and permeability, which could influence migraine-associated neurovascular changes. Therefore, the interplay between neuronal and vascular TRPM3 activity might provide a more comprehensive understanding of the mechanisms underlying sex-related differences in migraine. Some attractive, yet still missing, elements in TRPM3 research in migraine include investigations into (1) how TRPM3 channels activate not only CGRP release but also the release of other migraine mediators, such as PACAP; (2) potential synergies between different modes of TRPM3 activation; (3) crosstalk with other pronociceptive ion channels; and (4) testing of classical and new selective TRPM3 antagonists in migraine-relevant animal models. Based on such knowledge, this research could guide future clinical trials for migraine. With regard to the various modulators of TRPM3 function that were discussed, whereas it is worthwhile further evaluated their potential as migraine treatment, one has to realize that the bioavailability of for instance the flavonoids is very low. To conclude, we propose that TRPM3 channel activity may help explain the sex difference observed in migraine prevalence, while TRPM3 channel antagonism could represent a promising therapeutic avenue for the treatment of (menstrual) migraine pain in females, highlighting its potential as a target for the development of a new class of anti-migraine treatments.

Abbreviations

CSD	Cortical spreading depolarization
CGRP	Calcitonin gene–related peptide
CSF	Cerebrospinal fluid
TG	Trigeminal ganglion
DRG	Dorsal root ganglion
TRPM3	Transient receptor potential melastatin 3
CNS	Central nervous system
PNS	Peripheral nervous system
TRP	Transient receptor potential
TCC	Trigeminocervical complex
TRPV1	Transient receptor potential vanilloid 1
TRPA1	Transient receptor potential ankyrin 1
PregS	Pregnenolone sulfate
NMDA	N–methyl–D–aspartate
PIP2	Phosphatidylinositol 4,5–bisphosphate
PIP3	Phosphatidylinositol (3,4,5)–trisphosphate
PLC	Phospholipase C
PKA	Protein Kinase A
MCD	Methyl–β–cyclodextrin
C1	Carboxamido–steroid compound
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulfate
DHT	Dihydrotestosterone
PACAP	Pituitary adenylate cyclase–activating polypeptide
NSAID	Non–steroidal anti–inflammatory drugs

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