Hormonal influences in migraine — interactions of oestrogen, oxytocin and CGRP

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Abstract | Migraine is ranked as the second highest cause of disability worldwide and the first among women aged 15–49 years. Overall, the incidence of migraine is threefold higher among women than men, though the frequency and severity of attacks varies during puberty, the menstrual cycle, pregnancy, the postpartum period and menopause. Reproductive hormones are clearly a key influence in the susceptibility of women to migraine. A fall in plasma oestrogen levels can trigger attacks of migraine without aura, whereas higher oestrogen levels seem to be protective. The basis of these effects is unknown. In this Review, we discuss what is known about sex hormones and their receptors in migraine-related areas in the CNS and the peripheral trigeminovascular pathway. We consider the actions of oestrogen via its multiple receptor subtypes and the involvement of oxytocin, which has been shown to prevent migraine attacks. We also discuss possible interactions of these hormones with the calcitonin gene-related peptide (CGRP) system in light of the success of anti-CGRP treatments. We propose a simple model to explain the hormone withdrawal trigger in menstrual migraine, which could provide a foundation for improved management and therapy for hormone-related migraine in women.

Migraine is a major neurological disorder that is characterized by recurring headaches and that disproportionately affects women. Approximately 17% of all women have migraine, and women account for up to 75% of all patients with migraine[1–3]. In addition, women with migraine have attacks that are more frequent, more severe, longer-lasting and more difficult to treat than those in men[4,5]. Headache pain in women is typically unilateral, pounding, pulsating, or throbbing and is more often accompanied by nausea, photophobia and phonophobia than in men[2,6]. These debilitating attacks last 4–72 hours and have negative impacts on quality of life and family, employment, and community responsibilities. In the Global Burden of Disease Study, migraine is ranked as the leading cause of disability among women of reproductive age (15–49 years) worldwide[1,2,7–9].

Despite the high prevalence and enormous burden of migraine among women, the mechanisms that underlie the sex disparities in this disorder are understudied[2,5]. The successful introduction of drugs that inhibit calcitonin gene-related peptide (CGRP) has heightened interest in migraine pathophysiology and the development of novel treatments[10,11], but a better understanding of hormonal and genetic influences on the mechanisms of migraine is needed to specifically improve the treatment of migraine in women[5,12,13].

In this Review, we summarize the known targets of reproductive hormones in the trigeminovascular and central pain pathways that are related to migraine. The receptors for oestrogen are of primary interest as this hormone substantially influences migraine attacks in women. However, we also consider possible roles of progesterone, oxytocin and their receptors. Oxytocin is of interest in hormone-related migraine as this neuropeptide is regulated by oestrogen and has anti-migraine effects. In light of the recent success of migraine drugs that target CGRP[10], we also discuss the interactions of reproductive hormones with CGRP. We propose a model to explain how oestrogen could regulate the balance of pro-migraine and anti-migraine factors, such that oestrogen withdrawal shifts the balance in a way that lowers the threshold for a migraine attack. Finally, we suggest possible therapeutic approaches based on the current view of how hormones affect migraine mechanisms, which could improve treatment of migraine in women.

Reproductive hormones and migraine

Migraine is a heterogeneous disorder and the presentation in women varies with age, hormonal status and migraine type. The incidence of migraine attacks across the female lifespan is characteristic[1,2,13–15]: incidence rises steeply at puberty, peaks during the reproductive years

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Key points

- All three oestrogen receptor subtypes are widely expressed throughout migraine-related pain and nociceptive pathways in the CNS and in the peripheral trigeminal ganglia.
- Central and peripheral regions related to migraine co-express oestrogen receptors with calcitonin gene-related peptide (CGRP), CGRP receptors, oxytocin and/or oxytocin receptors, suggesting functional interactions.
- Hormonal fluctuations in women are thought to influence oscillating migraine neural networks and alter the threshold for a migraine attack and influence its intensity and/or duration.
- Oestrogen-regulated oxytocin could be a factor in menstrual and other hormone-related migraine attacks.
- We suggest a model to explain the oestrogen withdrawal theory of menstrual migraine, in which oestrogen regulates the balance of pro-migraine factors, such as CGRP, and anti-migraine factors, such as oxytocin, within the trigeminal ganglion.
- Development of selective oestrogen agonists or oxytocin agonists could be a strategy to improve the treatment of hormone-related migraine in women.

and subsides after menopause. Attack frequency also varies over the menstrual cycle (FIG. 1) and during pregnancy, the postpartum period and perimenopause[2,16–19]. The incidence of migraine does not differ between the sexes in children but this changes at puberty when prevalence sharply increases in females[2,3]. Together, these observations indicate a strong correlation between reproductive hormones and migraine attacks in women. However, this association is not straightforward and the ways in which hormones influence migraine pathophysiology are not yet clear.

The influence of oestrogen. The prevailing view is that oestrogen is the sex hormone that primarily influences the occurrence of attacks in women who have a biological predisposition to migraine[20]. In migraine without aura — the most common type of migraine — the greatest risk of an attack in women is at the time around menstruation[17] (FIG. 1). This association of migraine with hormonal status was recognized as early as the ninth century when the Persian physician al Razi described women who experienced migraines during menstruation[21]. This condition is often referred to as menstrual migraine, a term used by Critchley and Ferguson in 1933 to define a distinct clinical entity[22]. Yet, even now, the precise classification and diagnostic criteria for menstrual migraine are still under discussion[23] and the basis for the influence of oestrogen in migraine is not yet understood.

Attacks of migraine without aura are most likely to occur when plasma oestrogen levels decline to low levels in the late luteal (premenstrual) phase[19,24] (FIG. 1). This observation led to the hypothesis that withdrawal of oestrogen precipitates an attack[25,26] and that higher levels of oestrogen during other menstrual phases protect against migraine without aura. In agreement with this hypothesis, attacks of migraine without aura tend to abate during pregnancy, especially when plasma oestrogen levels are elevated, and return post-partum when oestrogen levels fall[18,27]. Furthermore, treatment with oral contraceptives or hormone replacement therapy that stabilize levels of oestrogen is preventive[27,28]. Cessation of contraceptive use is associated with an increase in attacks[29], consistent with the oestrogen withdrawal theory. However, acute oestrogen treatment does not stop an ongoing attack[25,26]. These lines of evidence indicate that migraine without aura is associated with changes in circulating oestrogen, particularly when oestrogen levels decline rapidly. Nevertheless, the key questions of what oestrogen does that could be protective and why a decrease in oestrogen triggers attacks remain unanswered.

To add to the complexity, other types of migraine attacks are affected differently by sex hormones. In migraine with aura, the highest risk of attacks in women is during states of high oestrogen such as during pregnancy or use of oral contraceptives and hormone replacement therapy[18,26]. Women with menstrual migraine can also experience attacks of migraine with aura that are apparently unrelated to the menstrual cycle[24,30].

The influence of progesterone. Differences in migraine between the sexes and across the reproductive stages in women could involve reproductive hormones other than oestrogen[20,31]. Levels of the ovarian hormone progesterone fluctuate over the reproductive lifespan of women and, in particular, its plasma levels decrease just before menstruation, in parallel with oestrogen levels (FIG. 1). In classic studies from the 1970s[25,32], the effects of withdrawal of the two hormones were assessed separately by injecting either oestrogen or progesterone to maintain high levels during the premenstrual phase. These studies demonstrated that migraine was triggered by withdrawal of oestrogen but was not associated with decreases in progesterone[25,32]. Moreover, the administration of progesterone did not protect against menstrual attacks[32]. On the basis of these findings, the current view is that progesterone does not play a major role in triggering migraine attacks[20,28].

Nevertheless, given that the data are limited, possible influences of progesterone on some aspects of migraine, such as fluctuations in pain sensitivity and/or pain chronification, cannot be ruled out. Migraine attacks are not only more likely to occur at the time of menstruation but are often more severe than attacks at other times. Some evidence suggests that progesterone can suppress nociception in the trigeminal pathway[31,33] and therefore a drop in circulating progesterone at the time of menstruation could explain the higher intensity of attacks. In agreement with this hypothesis, some evidence suggests that treatment with a progestogen can modestly reduce the intensity and duration of migraine attacks[34]. However, cyclical exposure to progestogens from oral contraceptives adversely affects migraine; thus, continuous forms of progestogen treatment are preferable[28]. In a study published in 2019, the sensitivity of cutaneous Aδ pain fibres increased during the luteal phase of the menstrual cycle and this effect correlated with circulating progesterone levels[35]. Together, these findings make clear that further study is needed to understand the effects of progesterone in migraine and the expression and function of progesterone receptors[36] in migraine-related brain regions and the trigeminovascular system[37].

In addition, progesterone could have downstream effects via its enzymatic conversion to the neurosteroid allopregnanolone (3α,5α-tetrahydroprogesterone)[36,38–40]. Allopregnanolone is a positive allosteric modulator of $GABA_A$ receptors and can suppress nociceptive transmission in peripheral sensory neurons, the dorsal horn and the trigeminal nucleus caudalis (TNC; also known as Sp5)[39,41,42]. Studies in animal models of peripheral nerve pain suggest that progesterone and allopregnanolone are both antinociceptive and anti-inflammatory and can attenuate allodynia[38,41]. The $GABA_A$ receptor is widely expressed on trigeminal neurons[43] and allopregnanolone seems to be involved in neural–glial communication in sensory nerves and ganglia[39]. Furthermore, synthesis of neurosteroids, such as allopregnanolone, can occur locally in Schwann cells that surround sensory nerves and in satellite glia in sensory ganglia[44]. Together, these observations suggest that allopregnanolone could influence migraine pathophysiology and a better understanding of its mechanisms and its influence during different reproductive states could lead to novel treatment strategies using neurosteroids[41].

The influence of oxytocin. To better understand how oestrogen influences migraine, we also need to look at reproductive hormones that are regulated by oestrogen. One such hormone that is of particular interest is oxytocin, as some evidence indicates that this neuropeptide hormone can prevent migraine attacks[45,46] and oestrogen is known to increase oxytocin levels and expression of the oxytocin receptor[47–51].

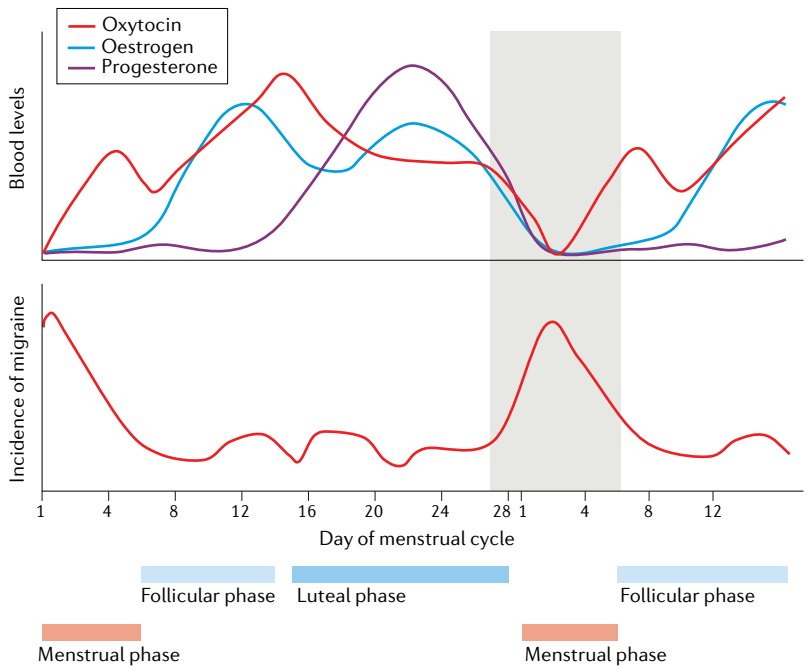


Fig. 1 | **Fluctuations in the incidence of migraine and hormone blood levels over the menstrual cycle.** In women with menstrual migraine, attacks of migraine without aura primarily occur around the time of menses, which correlates with a steep decline in levels of oestrogen, progesterone and oxytocin. Oestrogen withdrawal is thought to precipitate an attack[25] and attacks can be avoided by the administration of oestrogen but not of progesterone at this time[32]. A drop in oxytocin could also contribute to the mechanism of menstrual attacks. Based on data from REFS[24,26,63].

Oxytocin is one of the oldest known neuropeptide hormones, first discovered in 1906 as a neurohypophysial substance that triggers uterine contractions[52]. Oxytocin, a peptide composed of nine amino acids[53], is best known for its role in childbirth — administration of exogenous oxytocin or its analogues has long been used clinically to regulate uterine contractions and lactation[54]. It is released as a circulating hormone from the posterior pituitary gland and also has widespread CNS effects[55,56]. Oxytocin is now known to play many important roles in physiology, behaviour and various disorders[55,57,58] — its effects include the promotion of social interactions, enhancement of mood, reduction of anxiety and stress and, of greatest relevance to migraine, suppression of pain[59].

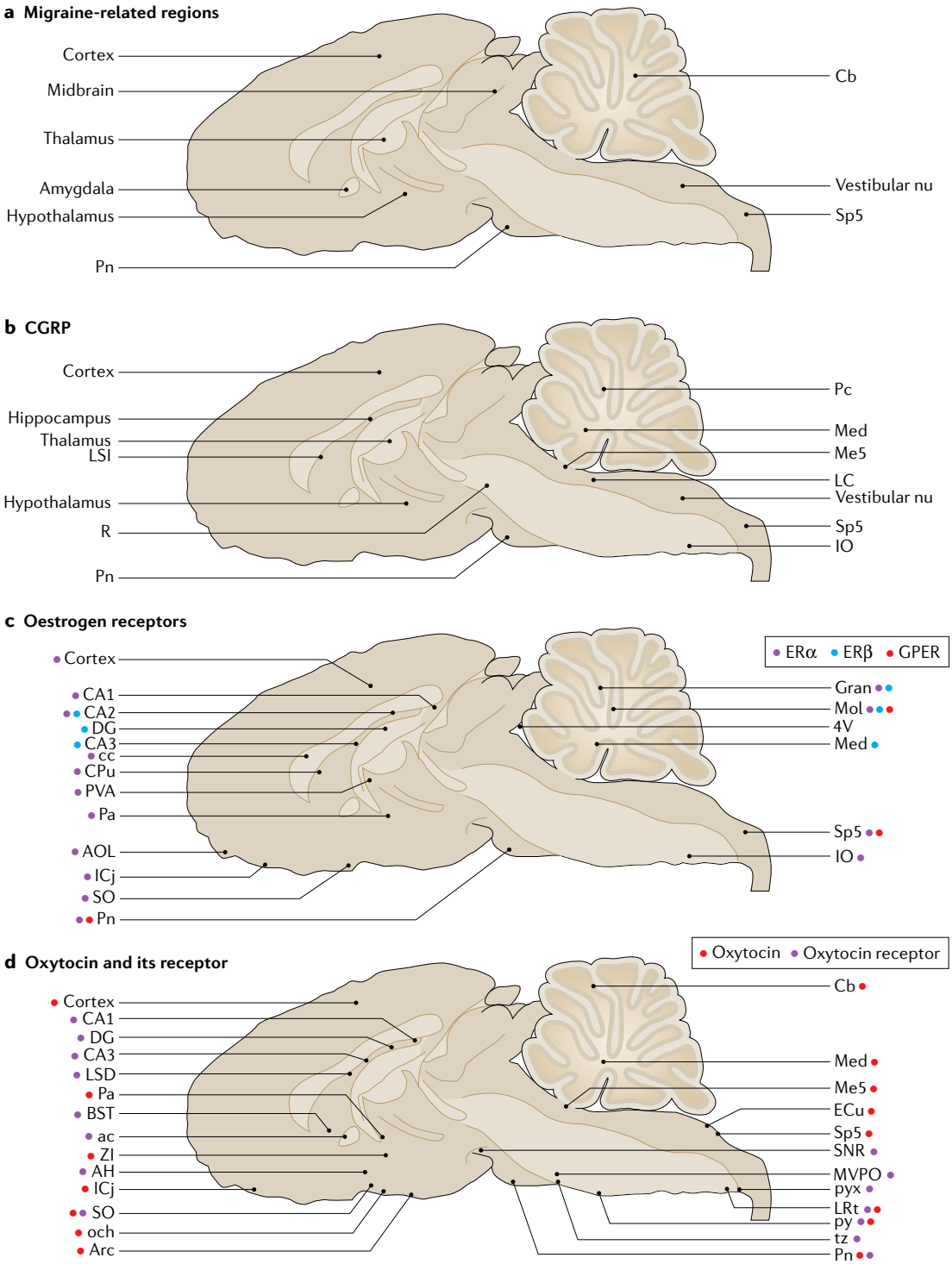
Oxytocin and its receptor are altered during various reproductive states[48,51,60,61]. Fluctuations in plasma levels of oxytocin during the menstrual cycle mirror those of oestrogen[62,63]. This relationship means that a drop in oestrogen levels is accompanied by a drop in oxytocin levels (FIG. 1), raising the possibility that withdrawal of oxytocin could be a factor in triggering menstrual migraine. In line with this idea, the oxytocin receptor is expressed in the trigeminal ganglia[64,65] and in migraine-related brain areas[66,67], suggesting that oxytocin has an important influence on migraine pathophysiology.

Though oxytocin is of particular interest for the reasons described, other hypothalamic neuropeptides and hormones also have anti-nociceptive effects and are regulated by oestrogen. These hormones, including vasopressin[68–70], prolactin[71–74] and orexin[75–77], could therefore also contribute to the influence of oestrogen on migraine. Little is known about the involvement of these neuropeptides in migraine but further research in this area could reveal new therapeutic targets.

Migraine circuitry

An important step in understanding the influence of reproductive hormones in migraine is to identify hormonal targets within the neural pathways that are thought to underlie migraine pathophysiology. The headache phase of a migraine attack has long been associated with the trigeminovascular nociceptive pathway[78–80]. Trigeminal ganglia contain pseudo-unipolar sensory neurons that innervate the cranial vasculature and dura mater[78] and stimulation of these peripheral nerves evokes the sensation of head pain. This knowledge led to the long-held theory that migraine is triggered by changes in the intracranial (cerebral and meningeal–dural) vasculature and/or by inflammation in the dura[10,81]. Nociceptive information is processed in the ganglion and transmitted to the CNS via projections of the trigeminal neurons that terminate in the trigeminocervical complex, which consists of the TNC and the upper cervical levels of the spinal cord (C1 and C2), notably in laminae I and II of the dorsal horn[82,83]. At these central sites, trigeminal input is relayed to second-order neurons of the pain pathway that project, via the brainstem and midbrain, to subcortical and cortical pain regions[84,85].

Migraine is a complex neurological disorder and activity in various brain regions is altered before, during and after an attack[80,86,87] (FIG. 2). Functional neuroimaging data indicate that activity in specific brain



areas precedes clinical symptoms of an attack, such as headache, and suggest a neural rather than vascular basis for migraine[86,87]. In particular, the hypothalamus seems to play a key role in migraine initiation[87,88]. Imaging studies also indicate that specific nuclei in the brainstem (the dorsal rostral pons) and midbrain (the periaqueductal grey) and areas of the cortex, thalamus, amygdala, cerebellar deep nuclei and vestibular nucleus are also involved[86,89]. Furthermore, through functional MRI studies, a dynamic picture is emerging of cyclical alterations in specific interactions among components of the pain network in patients with migraine[87,88,90–92]. Evidence suggests that endogenous pain modulation by descending pathways is dampened and sensory thresholds are lowered before an attack[88,90,91,93].

Despite these recent insights into migraine pathophysiology, little attention has been given to sex differences in functional MRI studies of migraine[94]. Whether and how oestrogen affects functional activity or connectivity in the brains of patients with migraine is unknown. One diagnostic trial is in progress in which multimodal MRI is being used to assess perimenopausal women

◀ Fig. 2 | **Localization of signalling molecules and receptors in migraine-related regions. a** | Regions involved in migraine pathophysiology[166], marked on a schematic of the rat brain to correspond with findings in parts b, c and d. **b** | Localization of calcitonin gene-related peptide (CGRP) in the rat brain. **c** | Localization of oestrogen receptor-α (ERα), oestrogen receptor-β (ERβ) and G protein-coupled oestrogen receptor (GPER) in the rat brain. **d** | Localization of oxytocin and its receptor in the rat brain. Data from REFS[67,102,107]. 4V, fourth ventricle; ac, anterior commissure; Arc, arcuate hypothalamic nucleus; AH, anterior hypothalamic area; AOL, anterior olfactory nucleus; BST, bed nucleus stria terminalis; CA1, field CA1 of the hippocampus; CA2, field CA2 of the hippocampus; CA3, field CA3 of the hippocampus; Cb, cerebellum; cc, corpus callosum; CPu, striatum; DG, dentate gyrus; ECu, external cuneate nucleus; Gran, cerebellar granular layer; ICj, islands of Calleja; IO, inferior olive; LC, locus coeruleus; LSD, lateral septal nucleus, dorsal part; LSI, lateral septal nucleus, intermediate part; LRt, lateral reticular nucleus; Me5, mesencephalic trigeminal nucleus; Med, medial cerebellar nucleus; Mol, cerebellar molecular layer; MVPO, medioventral periolivary nucleus; nu, nuclear; och, optic chiasm; Pa, paraventricular hypothalamic nucleus; Pc, Purkinje cells; Pn, pontine nuclei; PVA, paraventricular thalamic nucleus; Py, pyramidal tract; pyx, pyramidal decussation; R, red nucleus; SNR, substantia nigra reticular part; SO, supraoptic nucleus; Sp5, trigeminal nucleus caudalis; tz, trapezoid body; ZI, zona incerta.

whose migraine attacks are associated with declines in oestrogen levels[95]. Neuroimaging studies are also needed in younger women with hormone-related migraine in order to determine CNS activity over the menstrual cycle.

CGRP in migraine

The neuropeptide CGRP has an important role in migraine pathophysiology and its signalling could be a target of hormones that influence migraine[37]. Increased CGRP release from the trigeminal ganglia is a key component of a migraine attack[10,96]. Antibodies against CGRP or the CGRP receptor are highly effective in treating migraine[10] and the fact that they do not cross the blood–brain barrier demonstrates that therapeutic intervention within the peripheral trigeminal pathway[97] is sufficient to abort or prevent migraine attacks[10].

Four monoclonal antibodies to either CGRP (fremanezumab, galcanezumab and eptinezumab) or the CGRP receptor (erenumab) have been approved for prophylactic treatment of migraine[98]. No sex differences in responses to CGRP antibodies were reported in the clinical trials, although such differences were not specifically studied. These drugs are clearly effective in women but whether their actions are affected by hormonal status is not known. Data from a phase III trial of erenumab was used for a post hoc subgroup analysis of women with a history of menstrual migraine[99]. The analysis showed that the drug was safe and effectively reduced monthly migraine days; however, no distinction was made between attacks that occurred during the perimenstrual and intermenstrual periods. An observational case study of women with menstrual migraine looked specifically at the effects of erenumab in the premenstrual, menstrual and non-menstrual periods and showed that erenumab reduced the number of headache days in all phases of the cycle[100]. However, even in patients who responded to erenumab, the drug was somewhat less effective during the menstrual period. Further study is needed to specifically assess the effects of CGRP antibodies on migraine attacks that are associated with hormonal changes.

CGRP signalling can also be suppressed with gepants, which are small-molecule CGRP receptor antagonists[10,98]. The second-generation gepants ubrogepant and rimegepant have been approved for the acute treatment of migraine attacks. As for the CGRP antibodies, sex differences in efficacy and specific use in menstrual migraine have not yet been studied for these new drugs. However, telcagepant, a previous-generation gepant, was studied in women with perimenstrual migraine[101]. In this randomized trial, women took telcagepant or a placebo for 7 consecutive days around the time of menstruation for 6 months. Perimenstrual headaches but not total monthly headaches were reduced in the patients who received telcagepant, indicating a preventive effect of the drug. This study suggests that blockade of CGRP signalling is an effective strategy for hormone-related migraine.

CGRP also seems to play a role in central migraine mechanisms as CGRP and its receptor are expressed in numerous migraine-related brain regions, including the TNC, brainstem, hypothalamus, thalamus, vestibular nucleus, cerebellum and cerebral cortex[102] (FIG. 2). Evidence suggests that reproductive hormones affect CGRP mechanisms in both central and peripheral migraine pathways[37].

Hormone targets in migraine circuitry

Receptors for oestrogen and oxytocin are expressed in CNS regions that human imaging studies have shown to be involved in migraine pathophysiology (FIG. 2) and in the peripheral trigeminal pathway. In this section, we review what is known about these receptors and their effects.

Oestrogen in the CNS. The primary endogenous oestrogen is 17β-oestradiol, a lipophilic ovarian hormone that can access the CNS from the circulation. Much attention has been paid to plasma levels of oestrogen in migraine but, to fully understand the effects of oestrogen, we also need to understand the receptors involved. Oestrogen acts via several receptors[103] and knowledge of the subtypes that have an influence on migraine mechanisms could enable the development of selective therapies.

Oestrogen receptor-α (ERα) and ERβ are the two classic nuclear receptor subtypes that mediate the effects of oestrogen on gene expression[103]. In addition, membrane-associated forms of ERα and ERβ activate second messenger signalling such as the mitogen-activated protein kinase (MAPK) and protein kinase B pathways[104]. A third oestrogen receptor has also been described, the G protein-coupled oestrogen receptor (GPER), which is a G protein-coupled membrane receptor[105].

Oestrogen receptors are expressed at a number of sites that are involved in migraine pathophysiology[13,106–108] (FIG. 2). All three receptor subtypes are present in the dorsal horn of the spinal cord (primarily laminae I and II), which is the first relay point in trigeminal transmission of painful stimuli from the periphery to the brain[106,109,110]. In mice, knockout of ERβ increased levels of CGRP in the dorsal horn, suggesting that oestrogen normally suppresses CGRP signalling at this location[110]. In addition, ERα, ERβ and GPER are expressed in the TNC in the medullary dorsal horn. The TNC also receives

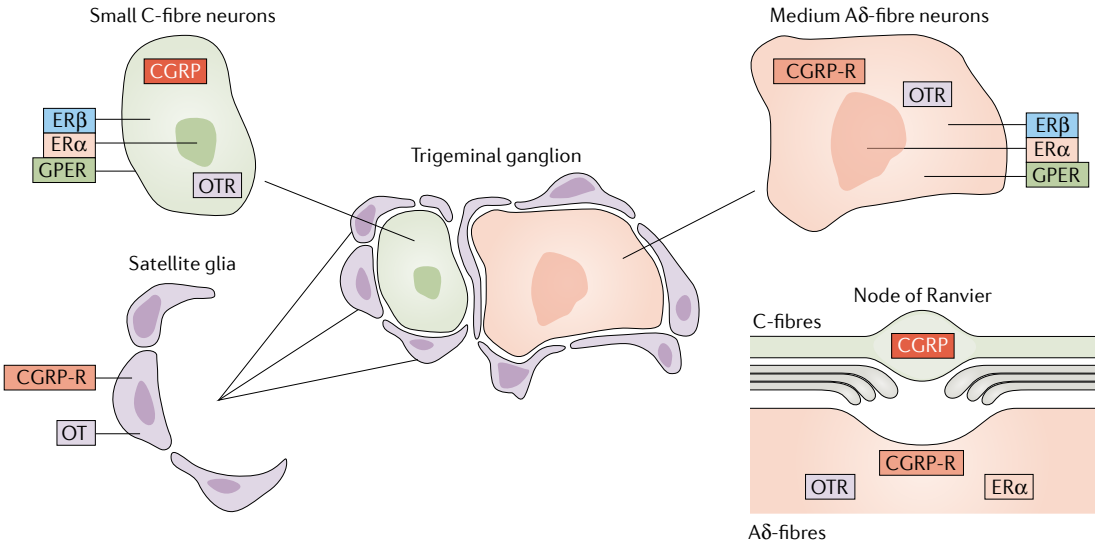


Fig. 3 | **Localization of oestrogen receptors, oxytocin receptors, CGRP and CGRP receptors in cells of the trigeminal ganglia.** Calcitonin gene-related peptide (CGRP) is expressed in the cytoplasm of small C-fibre neurons (top left) and the CGRP receptor (CGRP-R) is expressed in the medium Aδ-fibre neurons (top right). Oestrogen receptor-β (ERβ), G protein-coupled oestrogen receptor (GPER) and oxytocin receptor (OTR) are expressed in the cytoplasm of both the smaller C-fibre and the medium Aδ-fibre neurons. Oestrogen receptor-α (ERα) is expressed in the nuclei of both neurons. Oxytocin (OT), in addition to the CGRP-R, are expressed in the thin cytoplasm of the glial cells that surround the neurons (bottom left). A schematic of the relationship between C fibres and Aδ fibres (bottom right) illustrates how CGRP-containing C-fibre boutons align with nodes of Ranvier on Aδ fibres. These Aδ fibres express CGRP receptors, OTR and ERα. The arrangement suggests this site is a point of axon–axon interaction through CGRP release and is therefore a site of action for gepants and the novel monoclonal antibodies to alleviate migraine. Data from REFS[64,97,107,148].

trigeminal afferents[37,106,107,111] and neurons in the TNC are activated by peripheral noxious stimuli[111].

Abundant evidence has demonstrated that oestrogen modulates the processing of nociceptive input in central pain networks[112]. Unsurprisingly, therefore, oestrogen receptors are present in brain areas that are related to various aspects of pain perception and modulation[107,108,112,113]. The expression of ERα (in the cell nuclei) and GPER (in the cell nuclei, cytoplasm and fibres) is strong in neurons of the pontine nuclei[107], an area of the brainstem that is important for trigeminal nociceptive processing and pain pathology[89]. ERα is also highly expressed in the periaqueductal grey region[114]. The cerebellum, which has been implicated in migraine in imaging studies, expresses ERα, ERβ and GPER[107]. In a study of rats, GPER-immunoreactive cells were observed in the amygdala and dorsal hippocampus and, of particular interest, the number of these cells varied during the oestrus cycle and differed between males and females[115]. All three oestrogen receptors are also expressed in the hypothalamus, a critical region for migraine initiation[13]. ERβ seems to predominate in the supraoptic area and paraventricular nucleus[116].

Expression of ERα and ERβ has been observed in the cerebral cortex[13,107], suggesting that oestrogen can also modulate pain perception at the highest cognitive levels and influence pain sensitivity via effects on descending pathways. Cortical expression of oestrogen receptors could also explain the ability of oestrogen to stimulate migraine with aura. In rodents, including a mouse model of familial hemiplegic migraine type 1, oestrogen initiates cortical spreading depression, the presumed cause of migraine aura[117,118]. Furthermore, this effect was blocked by an oestrogen receptor antagonist, though the specific receptor subtype involved was not identified[117].

Receptor localization studies have therefore demonstrated that oestrogen acts throughout migraine-related regions and pathways in the CNS. However, the specific effects of oestrogen and its receptors in each brain region and the mechanisms of these effects are still unclear and under investigation; numerous studies (reviewed in detail elsewhere[15,119–121]) suggest several mechanisms, including regulation of serotonin[122] and other neurotransmitters and neuropeptides[37], modulation of transient receptor potential channels[123] and other ion channels[124,125], and effects on inflammatory mechanisms[126].

Oestrogen in the trigeminal ganglion. All three oestrogen receptor subtypes are abundantly expressed in the trigeminal ganglion, so oestrogen acts directly on cells in this tissue[31,37,106,107,124,127–129] (FIG. 3). Numerous small and medium-sized trigeminal neurons express ERα, which is localized in the nuclei[106,107] and cytoplasm[129]. ERα is also present in thicker neuronal fibres that are characteristic of myelinated Aδ axons that express the paranodal marker contactin-associated protein 1 (CASPR) at the nodes of Ranvier[107]. The ERβ receptor is also present in trigeminal ganglia[106,107]; ERβ immunoreactivity can be seen in most trigeminal neurons, localized in the cytoplasm with a staining pattern that resembles that of the Golgi apparatus[107]. In addition, GPER[105–109] is expressed in the cell membranes and cytoplasm of most trigeminal neurons[102,107]. Therefore, oestrogen can act on receptors

in trigeminal ganglia to mediate acute and longer-term genetic effects but little is known about the specific roles of the different oestrogen receptor subtypes in trigeminal function.

The trigeminal ganglion exhibits sexual dimorphism as underscored by a recent comprehensive analysis of neuronal gene expression in the trigeminal ganglia of male and female (in oestrus) mice[130]. More genes were expressed selectively in ganglia from females (594 genes) than in those from males (369 genes). In addition, the genes selectively expressed in females were related to regulation of nociception, inflammation, neuronal excitability, plasticity and pain chronicity. By contrast, in dorsal root ganglion neurons, fewer and different genes were selectively expressed in females, illustrating key differences between the two sensory tissues[130]. Whether the increased gene expression in female trigeminal neurons is due to oestrogen remains to be determined.

Hormonal cycles are known to affect the peripheral trigeminovascular system. For example, in a study that involved dural activation of the trigeminal nerve over the rat oestrous cycle, the sensitivity of this system was highest in the latter stages of the cycle (proestrus and oestrus)[131]. In addition, trigeminal neurons from female rats in proestrus or oestrus were more excitable and had lower action potential thresholds than neurons from rats in dioestrus or metoestrus[125]. These changes observed in the latter half of the rodent oestrous cycle seem relevant to the patterns seen in patients with menstrual migraine but caution is needed when equating the different species[37]. The rodent cycle is only 4–5 days long and oestrogen levels fluctuate more quickly than in humans (FIG. 1); oestrogen peaks during proestrus (day 3) and falls to its lowest level the next day (oestrus). The effects of oestrogen on gene expression take time to manifest and therefore the effects of high or low blood levels of oestrogen on functions assessed on the same day are difficult to interpret.

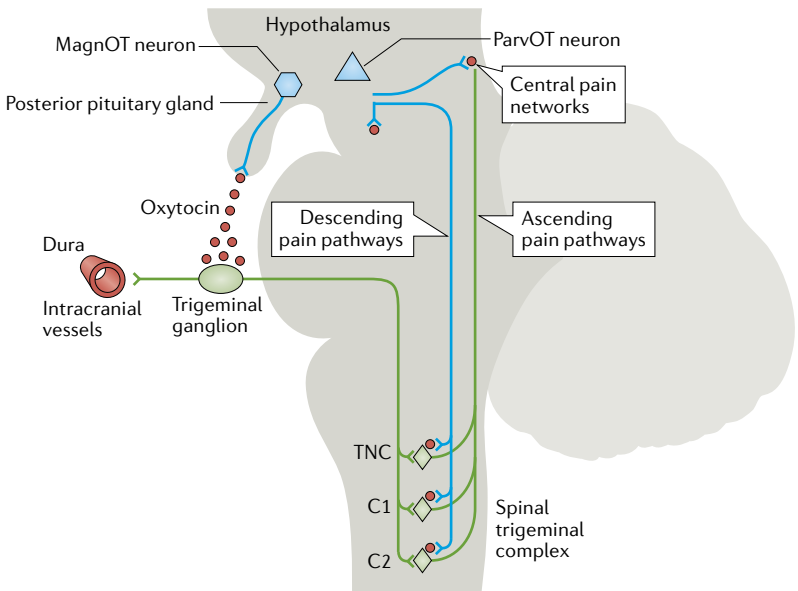


Fig. 4 | **Oxytocin pathways.** Oxytocin is synthesized in the paraventricular nucleus and supraoptic nucleus of the hypothalamus. The magnocellular oxytocin (MagnOT) neurons project to the posterior pituitary and secrete oxytocin into the peripheral circulation. Parvocellular oxytocin (ParvOT) neurons project to brain areas involved in central pain networks and to the spinal trigeminal complex, which receives primary sensory afferents from the trigeminal ganglion. TNC, trigeminal nucleus caudalis.

Oxytocin in the CNS. The discovery that oxytocin can suppress migraine attacks[45] has prompted re-examination of oxytocin and its receptor in migraine circuitry. Interestingly, hypothalamic regions that are involved in migraine initiation[87] are also the source of all oxytocin in the brain and the periphery. Neurons in the paraventricular nucleus (PVN) and supraoptic nucleus of the hypothalamus have widespread oxytocin projections throughout the brain and spinal cord[55,67,132] (FIGS 2,4). In addition, magnocellular neurosecretory neurons in these hypothalamic regions project to the posterior pituitary to release oxytocin into the circulation[56,57] (FIG. 4).

Oestrogen is a known stimulus of oxytocin mRNA expression and oxytocin production in the hypothalamus, suggesting that oxytocin could also be important in menstrual migraine[116,133]. Oestrogen-stimulated oxytocin production in the hypothalamus seems to be mediated by ERβ, the expression of which is colocalized with oxytocin in PVN neurons of rodents and humans[116,134]. The expression of oxytocin receptors in the ventromedial hypothalamus is also upregulated by oestrogen — in rats, this upregulation occurs at the time of parturition, during proestrus and upon administration of oestrogen after ovariectomy[48,135]. Evidence from pharmacological and knockout studies suggests involvement of both ERα and ERβ in this process[116,133]. The mechanisms that mediate the increase in oxytocin receptor expression involve interactions of oestrogen receptors with the oestrogen response element on the gene that encodes oxytocin receptors as well as effects of second messenger signalling (extracellular receptor kinase pathway signalling) activated by oestrogen receptors[133].

Oxytocin fibres are part of the descending hypothalamic projection to sensory regions of the spinal cord and medulla that play an important role in suppressing nociceptive inputs from trigeminal nerves[66,136,137] (FIG. 4). Oxytocin receptors are present in the TNC and the dorsal horn of the spinal cord[138,139]. Local application of oxytocin or stimulation of the oxytocin descending pathway inhibits firing of spinal cord and TNC neurons that receive nociceptive input from C and Aδ sensory afferents but not from Aβ sensory afferents[66,136,137]. These effects can be blocked by selective oxytocin receptor antagonists[66,136,137]. In one elegant study published in 2016, viral vector and optogenic techniques were used to identify oxytocin neurons and enable the selective activation of oxytocin release in the hypothalamus or the dorsal horn[56]. This approached revealed a subset of parvocellular oxytocin neurons in the PVN that project to both the dorsal horn and to magnocellular neurons in the supraoptic nucleus; activation of these neurons inhibited dorsal horn neuronal firing in response to nociceptive inputs and stimulated the release of oxytocin into the circulation. Thus, these hypothalamic neurons effectively couple central and peripheral oxytocin signalling.

Oxytocin fibres and oxytocin receptor expression have been identified in several other brain regions

associated with migraine and nociceptive processing[67,132] (FIG. 2). Oxytocin is localized mainly in long, slender nerve fibres (for example, in the amygdala, cerebral cortex and cerebellar cortex)[67], whereas oxytocin receptors are present primarily in cell somas located in the pons, substantia nigra, amygdala and hippocampus[67]. Oxytocin in these areas can influence pain processing[132]. For example, local injection of oxytocin into the central nucleus of the amygdala suppresses nociceptive behavioural responses in rats and this effect is blocked by a selective oxytocin receptor antagonist[140].

Oxytocin in the trigeminal pathway. The primary source of peripheral oxytocin is the magnocellular neurons in the hypothalamus that project to the posterior pituitary gland and secrete oxytocin into the blood[57] (FIG. 4). Plasma levels of oxytocin are increased by oestrogen acting on hypothalamic receptors[47,62]. Circulating oxytocin has anti-nociceptive effects[70,132] and intranasal administration of oxytocin suppresses migraine attacks[45]. Given that the peptide does not cross the blood–brain barrier, these actions must involve peripheral sites such as the trigeminal ganglion[69,141].

Trigeminal ganglia express oxytocin receptor mRNA and protein[64,65,142], indicating that oxytocin has direct regulatory effects at these sites. In a study of the rat trigeminal ganglion, oxytocin receptors were expressed in ~80% of medium-sized neurons and in thick axons that are characteristic of Aδ sensory fibres[64] (FIG. 3). Approximately one-third of smaller trigeminal neurons, which were probably C fibre neurons, also expressed oxytocin receptors[64]. Little is known about the processes mediated by oxytocin receptors in trigeminal neurons but the current understanding of this receptor indicates that it is a G protein-coupled receptor capable of activating multiple G proteins, with diverse effects on cellular function[57,143]. Oxytocin binding to the oxytocin receptor has been shown to stimulate or inhibit adenylyl cyclase (via G_s and $G_{i/0}$, respectively), stimulate potassium channel currents (via G_i) and activate phospholipase C (via G_q)[57,143]. Oxytocin can cause membrane hyperpolarization, primarily via G_q signalling that leads to calcium-dependent activation of potassium channels[143]. This hyperpolarization has been observed in sensory neurons of the dorsal root ganglion, where activation of oxytocin receptors decreased the excitability of these neurons[144,145].

The oxytocin peptide has also been detected in the trigeminal ganglion[146,147], primarily in satellite glial cells[64]. However, oxytocin mRNA could not be detected in the ganglion[64], indicating either that the level of synthesis is very low or that cellular uptake of circulating oxytocin leads to its accumulation in the glia.

Oestrogen, oxytocin and CGRP. A number of studies indicate that CGRP signalling is influenced by reproductive hormones and also exhibits sex differences[37]. Receptor mapping studies provide strong evidence that oestrogen and oxytocin have regulatory roles in migraine-related regions of the brain that are also rich in CGRP (FIG. 2). In particular, an integrative picture is beginning to emerge regarding hormonal targets and cellular relationships within the trigeminal ganglion (FIG. 3). Given the prominent role of trigeminal CGRP in migraine attacks[10], a key aspect for study is the expression of hormonal receptors on cells that either produce or respond to CGRP.

CGRP is produced in the small trigeminal neurons associated with C fibres[10,148] and these cells seem to be regulated by oestrogen via multiple receptor subtypes (FIG. 3). Double immunohistochemistry studies have shown that ERα is localized in the nuclei of neurons that contain CGRP[107]. In addition, CGRP neurons express ERβ, which colocalizes with CGRP in the Golgi apparatus[107]. Similarly, double immunohistochemistry studies have shown that most CGRP-positive neurons also express GPER[107]. These observations suggest that oestrogen can modulate CGRP synthesis or release via genomic mechanisms and second messenger signalling[37]. This hypothesis is supported by findings in ovariectomized female rats, in which loss of oestrogen greatly increased CGRP expression in the trigeminal ganglion, whereas subsequent treatment with oestrogen reduced CGRP levels[149]. In a rodent model of chronic migraine, females expressed lower levels of trigeminal CGRP receptors than males, also suggesting modulation by sex hormones[150]. Studies of the effects of selective oestrogen receptor agonists and antagonists are needed to clarify the roles of the different oestrogen receptors in these effects on CGRP.

Some CGRP-expressing neurons also seem to be regulated by oxytocin; CGRP and oxytocin receptors are co-expressed in approximately one-third of small neurons in the rat trigeminal ganglion[64]. However, oxytocin did not affect K^+-evoked CGRP release from either the rat trigeminal ganglion or dural afferents[64]. Under inflammatory conditions in the rat, levels of oxytocin receptors in the trigeminal ganglion increased and a much higher percentage of CGRP neurons expressed oxytocin receptors[65]. The same study also showed that oxytocin could inhibit CGRP release though high concentrations of oxytocin were used, raising questions about the physiological relevance of this finding.

The trigeminal ganglion also contains medium-sized neurons that are associated with thinly myelinated Aδ sensory fibres. These cells express components of the CGRP receptor but not the peptide itself[10], suggesting that they are a target of CGRP. These neurons express ERα, ERβ and GPER in rat ganglia[107], indicating that they can also be regulated by oestrogen. Furthermore, Aδ neurons in rat ganglia strongly express oxytocin receptors[64], suggesting dual, possibly opposing, regulation of these neurons by CGRP (a pro-migraine peptide[10]) and oxytocin (an anti-migraine peptide[45]) (FIG. 3). CGRP and oxytocin receptors are also present in the Aδ fibres themselves[10,64,151].

Oestrogen and oxytocin could also influence axon–axon communication that occurs at the nodes of Ranvier as a result of CGRP release from C fibres and its interaction with CGRP receptors on adjacent Aδ fibres[151]. ERα and oxytocin receptors are also located at the nodes of myelinated Aδ fibres[64,107] (FIG. 3) and therefore regulation of axonal crosstalk could be a mechanism by which oestrogen and oxytocin influence the

transmission of nociception signals and/or affect the sensitization of these nerve fibres.

A theory of menstrual migraine

Advances in our understanding of where reproductive hormones act in migraine-related pathways provide a new perspective on the possible mechanisms that underlie the hormone withdrawal phenomenon of menstrual migraine. Understanding of these mechanisms is crucial because a loss of oestrogen does not, in itself, explain why an attack is triggered. Oestrogen is not thought to be a component of migraine pathogenesis — oestrogen alone does not have direct anti-migraine effects nor does acute administration of oestrogen suppress an attack.

Hormonal balance. In trying to understand how a decline in oestrogen might precipitate an attack of migraine without aura, the apparent widespread influence of this hormone on peripheral and central migraine pathways must be considered. Neuroimaging of patients with migraine indicates that connectivity in key pain circuits oscillates over time, resulting in cyclical changes in pain modulation and sensory thresholds, both of which decline just before an attack[88,90,93]. Studies of functional connectivity in patients with migraine indicate that the hypothalamus–thalamus–brainstem network mediates changes in threshold and initiates migraine attacks[87,93]. Given that oestrogen receptors are located throughout this network, oestrogen is likely to influence its functional connectivity. A similar type of hormone-mediated modulation of functional networks has been observed before: sex steroids, hormonal contraceptives and different phases of the menstrual cycle all alter functional connectivity in various brain networks in women such as those that mediate emotional processing, cognitive functions, vision and coordination[152,153].

Thus, we propose that oestrogen acts throughout the migraine-related circuits to increase thresholds and suppress initiation of an attack, either directly or indirectly via oxytocin or other oestrogen-regulated signalling molecules (FIG. 5). In this context, a sharp decline in oestrogen levels would shift the balance towards a pro-migraine state, thereby increasing the susceptibility to initiation of an attack. Therefore, in women with menstrual migraine, the fluctuating cycle of hormone regulation is superimposed on oscillating migraine networks.

Implications for treatment. Most women with menstrual migraine currently use standard anti-migraine medications to treat their symptoms as discussed in several recent reviews[5,12,23,154,155]. However, more rigorous study of the various options in well-defined menstrual attacks is needed[23]. For acute management, triptans and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used but the longer-acting triptan, frovatriptan[156,157], might be preferable in attacks that occur around menstruation as they often last longer and are more difficult to treat than attacks that occur at other times in the menstrual cycle. The gepants, which are a new option, still need to be evaluated specifically for acute treatment of menstrual migraine. For long-term prophylaxis, standard migraine treatments, such as topiramate[158] and the new CGRP-related antibodies[100], are recommended. However, few studies have specifically addressed the effects of these drugs in menstrual migraine. Owing to the relatively predictable, episodic nature of the attacks, some attention has been paid to the use of short-term perimenstrual prophylaxis with NSAIDs, triptans or oestrogen[23].

The use of hormone preparations (for example, oestradiol patches, implants and oral contraceptives) is the only treatment approach that is specific for menstrual migraine. These treatments are given to prevent fluctuations in oestrogen levels and therefore prevent migraine attacks[29,159,160]. This strategy is effective but oestrogen-related preparations carry the risk of serious adverse effects, including an increased risk of cardiovascular events (thromboembolism and stroke)[161,162] and breast cancer[163,164]. Furthermore, oestrogen acts at numerous sites throughout the body with myriad effects that are unrelated to migraine.

Alternative approaches could be developed to improve hormone treatment. The use of selective oestrogen receptor agonists or selective oestrogen receptor modulators, such as raloxifene or tamoxifen[165], could reduce off-target and adverse effects. Another possibility is to develop drugs or treatment regimens with effects that are limited to certain sites of action and/or constrained time periods. The trigeminal ganglion is increasingly considered a therapeutic target in migraine[10,79] and oestrogen modulates CGRP and oxytocin signalling — both of which directly influence migraine attacks — at these ganglia[10,149]. Therefore, hormonal regulation at the trigeminal ganglion could be a target for intervention.

We propose a novel hypothesis that oestrogen influences the balance of factors related to migraine susceptibility within the trigeminal ganglia (FIG. 5). In the presence of oestrogen, migraine symptoms that involve the trigeminal pathway are suppressed (FIG. 5) and a drop in oestrogen levels as a result of different physiological or pharmacological states would shift the balance to migraine vulnerability and decrease the threshold for an attack without aura to occur (FIG. 5). Although this view is somewhat simplistic, it predicts that effective treatment for menstrual migraine attacks could involve the suppression of CGRP (with antibodies or gepants) or administration of oxytocin agonists in the perimenstrual period (FIG. 5).

Conclusions, challenges and perspectives

In order to gain insight into why migraine is more prevalent among women during specific reproductive phases, we have focused on what is known about hormonal targets within the neural circuitry associated with migraine. Migraine is a complex neurological disease in which altered interactions among the ascending, integrative and descending pain pathways are thought to result in episodic decreases in the initiation threshold for a migraine attack. We highlight the widespread influence of oestrogen on these brain networks on the basis that all three oestrogen receptor subtypes — ERα, ERβ and GPER — are extensively expressed throughout

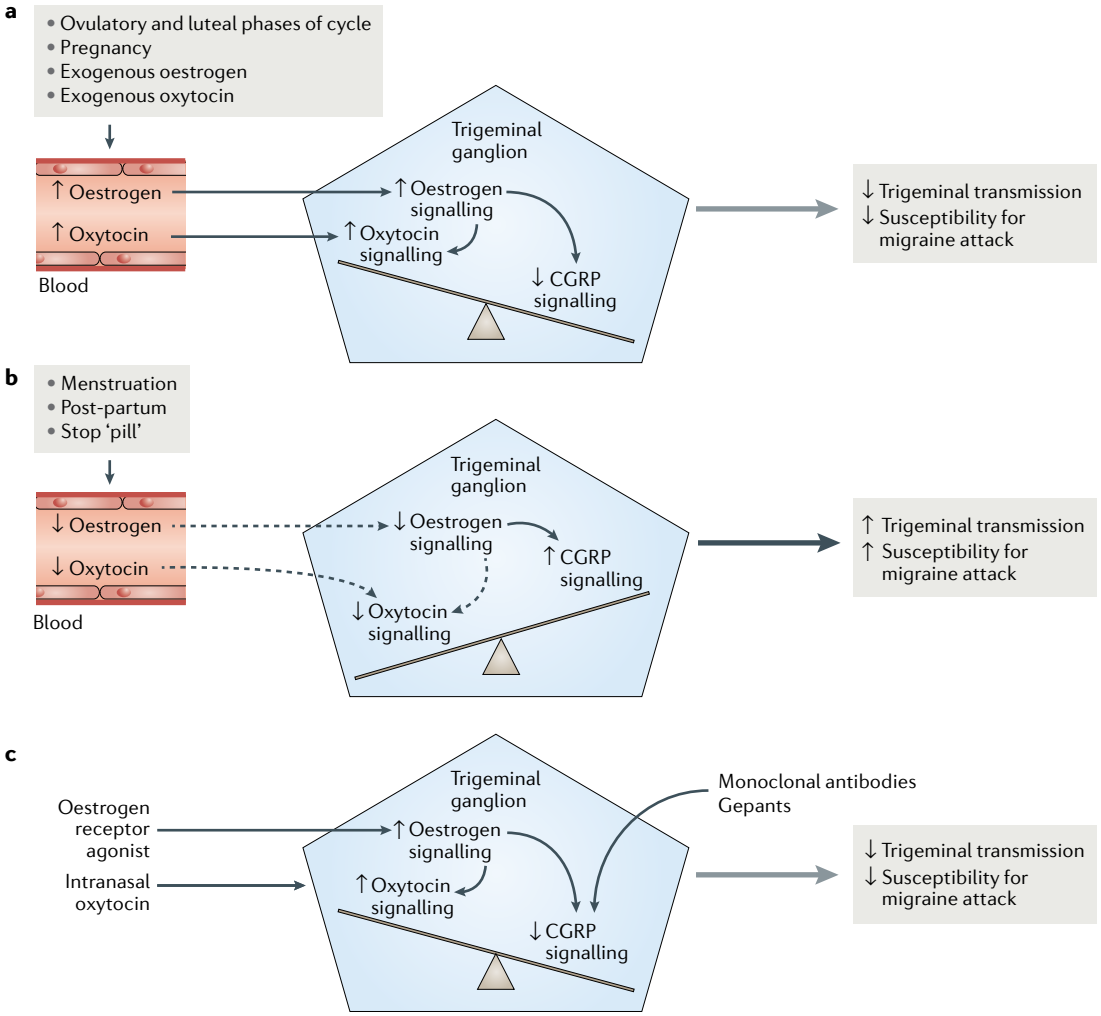


Fig. 5 | **Theory of hormonal balance in the trigeminal ganglion and the impact of hormone withdrawal in menstrual migraine. a** | In the ovulatory and luteal phases of the menstrual cycle, during pregnancy, or when exogenous oestrogen and oxytocin are administered, blood levels of oestrogen and oxytocin are high. High oestrogen signalling in the trigeminal ganglion suppresses calcitonin gene-related peptide (CGRP) signalling, whereas oxytocin signalling in the trigeminal ganglion is increased by oestrogen. This balance of signalling suppresses trigeminal transmission, reducing the likelihood of a migraine attack. **b** | During menstruation, the post-partum period or discontinuation of oral contraception, blood levels of oestrogen and oxytocin decrease. The reduced oestrogen signalling at the trigeminal ganglion allows an increase in CGRP signalling, which outweighs the effects of reduced oxytocin signalling. Trigeminal transmission is consequently facilitated, increasing the likelihood of a migraine attack. **c** | Proposed therapeutic strategies for menstrual migraine. Oestrogen receptor agonists, administration of oxytocin and suppression of CGRP signalling with monoclonal antibodies or gepants could alter the signalling balance at the trigeminal ganglion to reduce the likelihood of hormonally related migraine attacks.

migraine-related regions, in particular the hypothalamus, which is a putative migraine initiator, and areas of the brainstem, thalamus, cortex and cerebellum. The trigeminal nociceptive pathway is also a key oestrogen target, with the three receptor subtypes expressed in the trigeminal ganglia as well as in the spinal trigeminal complex, the central entry point for trigeminal sensory afferents that convey the sensation of headache pain. The precise actions mediated by these receptors have yet to be determined but they are likely to involve interactions with CGRP and oxytocin signalling as many of these regions exhibit colocalization of oestrogen receptors, CGRP, CGRP receptors, oxytocin and/or oxytocin receptors. We propose a novel role for oxytocin in hormone-related migraine on the basis that this neuropeptide, which inhibits migraine attacks, and its receptor are directly regulated by oestrogen. A perimenstrual drop in oxytocin levels parallels that of oestrogen and could contribute to the withdrawal trigger for menstrual attacks. Appropriately timed treatment with oxytocin agonists could be a new approach to therapy.

In addition to expanding our understanding of the mechanisms by which reproductive hormones influence migraine pathophysiology, it will be important to determine whether sex differences in gene expression in nociceptive pathways contribute to the higher incidence of migraine in women[15,130]. Current challenges include the need for more research in females, both

clinical and preclinical, and the development of relevant animal models for this human disorder that can be used to study hormonal effects and sex differences. The enormous burden of migraine in women underscores the great need to continue to advance our understanding of hormone-related migraine and its treatment.

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1. GBD. 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **388**, 1545–1602 (2016).
2. Vetvik, K. G. & MacGregor, E. A. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. *Lancet Neurol.* **16**, 76–87 (2017).
3. Lipton, R. B. et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* **68**, 343–349 (2007).
4. Lipton, R. B. et al. Identifying natural subgroups of migraine based on comorbidity and concomitant condition profiles: results of the chronic migraine epidemiology and outcomes (CaMEO) Study. *Headache* **58**, 933–947 (2018).
5. Gazerani, P. & Cairns, B. E. Sex-specific pharmacotherapy for migraine: a narrative review. *Front. Neurosci.* **14**, 222 (2020).
6. Bolay, H. et al. Gender influences headache characteristics with increasing age in migraine patients. *Cephalalgia* **35**, 792–800 (2015).
7. Steiner, T. J., Stovner, L. J., Vos, T., Jensen, R. & Katsarava, Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? *J. Headache Pain* **19**, 17 (2018).
8. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **17**, 954–976 (2018).
9. Steiner, T. J. et al. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. *J. Headache Pain* **21**, 137 (2020).
10. Edvinsson, L., Haanes, K. A., Warfvinge, K. & Krause, D. N. CGRP as the target of new migraine therapies — successful translation from bench to clinic. *Nat. Rev. Neurol.* **14**, 338–350 (2018).
Review of the role of CGRP in migraine and the successful development of migraine-specific therapies that block CGRP (antibodies and receptor antagonists).
11. Haanes, K. A. & Edvinsson, L. Pathophysiological mechanisms in migraine and the identification of new therapeutic targets. *CNS Drugs* **33**, 525–537 (2019).
12. Maasumi, K., Tepper, S. J. & Kriegler, J. S. Menstrual migraine and treatment options: review. *Headache* **57**, 194–208 (2017).
13. Borsook, D. et al. Sex and the migraine brain. *Neurobiol. Dis.* **68**, 200–214 (2014).
14. Faubion, S. S., Batur, P. & Calhoun, A. H. Migraine throughout the female reproductive life cycle. *Mayo Clin. Proc.* **93**, 639–645 (2018).
15. Gupta, S. et al. Potential role of female sex hormones in the pathophysiology of migraine. *Pharmacol. Ther.* **113**, 321–340 (2007).
16. Petrovski, B. E., Vetvik, K. G., Lundqvist, C. & Eberhard-Gran, M. Characteristics of menstrual versus non-menstrual migraine during pregnancy: a longitudinal population-based study. *J. Headache Pain* **19**, 27 (2018).
17. MacGregor, E. A. & Hackshaw, A. Prevalence of migraine on each day of the natural menstrual cycle. *Neurology* **63**, 351–353 (2004).
18. Sacco, S. & Ripa, P. Migraine in pregnancy. *J. Headache Pain* **16**, A24 (2015).
19. MacGregor, E. A. Menstrual and perimenopausal migraine: a narrative review. *Maturitas* **142**, 24–30 (2020).
20. Delaruelle, Z. et al. Male and female sex hormones in primary headaches. *J. Headache Pain* **19**, 117 (2018).
21. Reading through the history of migraine. In: Migraine Matters. https://www.migraine-matters.com/reading-through-the-history-of-migraines/ (2016).
22. Critchley, M. F. & Fergusonritchley, F. R. Migrane. *Lancet* **221**, 123–126 (1933).
23. Vetvik, K. G. & MacGregor, E. A. Menstrual migraine: a distinct disorder needing greater recognition. *Lancet Neurol.* **20**, 304–315 (2021).
24. Martin, V. T. & Lipton, R. B. Epidemiology and biology of menstrual migraine. *Headache* **48** (Suppl. 3), S124–130 (2008).
25. Somerville, B. W. The role of estradiol withdrawal in the etiology of menstrual migraine. *Neurology* **22**, 355–365 (1972).
The classic study of the relationship between oestrogen levels and menstrual migraine that formed the basis of the oestrogen withdrawal theory.
26. MacGregor, E. A. Oestrogen and attacks of migraine with and without aura. *Lancet Neurol.* **3**, 354–361 (2004).
27. Warnock, J. K., Cohen, L. J., Blumenthal, H. & Hammond, J. E. Hormone-related migraine headaches and mood disorders: treatment with estrogen stabilization. *Pharmacotherapy* **37**, 120–128 (2017).
28. MacGregor, E. A. Migraine, menopause and hormone replacement therapy. *Post. Reprod. Health* **24**, 11–18 (2018).
29. Merki-Feld, G. S., Caveng, N., Speiermann, G. & MacGregor, E. A. Migraine start, course and features over the cycle of combined hormonal contraceptive users with menstrual migraine - temporal relation to bleeding and hormone withdrawal: a prospective diary-based study. *J. Headache Pain* **21**, 81 (2020).
30. Pavlovic, J. M. Evaluation and management of migraine in midlife women. *Menopause* **25**, 927–929 (2018).
31. Gupta, S., McCarson, K. E., Welch, K. M. & Berman, N. E. Mechanisms of pain modulation by sex hormones in migraine. *Headache* **51**, 905–922 (2011).
32. Somerville, B. W. The influence of progesterone and estradiol upon migraine. *Headache* **12**, 93–102 (1972).
33. Kim, M. J. et al. Progesterone produces antinociceptive and neuroprotective effects in rats with microinjected lysophosphatidic acid in the trigeminal nerve root. *Mol. Pain* **8**, 16 (2012).
34. Warhurst, S. et al. Effectiveness of the progestin-only pill for migraine treatment in women: a systematic review and meta-analysis. *Cephalalgia* **38**, 754–764 (2018).
35. Pogatzki-Zahn, E. M. et al. Progesterone relates to enhanced incisional acute pain and pinprick hyperalgesia in the luteal phase of female volunteers. *Pain* **160**, 1781–1793 (2019).
36. Guennoun, R. et al. Progesterone and allopregnanolone in the central nervous system: response to injury and implication for neuroprotection. *J. Steroid Biochem. Mol. Biol.* **146**, 48–61 (2015).
37. Labastida-Ramirez, A., Rubio-Beltran, E., Villalon, C. M. & MaassenVanDenBrink, A. Gender aspects of CGRP in migraine. *Cephalalgia* **39**, 435–444 (2019).
38. Hornung, R. S. et al. Progesterone and allopregnanolone rapidly attenuate estrogen-associated mechanical allodynia in rats with persistent temporomandibular joint inflammation. *Front. Integr. Neurosci.* **14**, 26 (2020).
39. Colciago, A., Bonalume, V., Melfi, V. & Magnaghi, V. Genomic and non-genomic action of neurosteroids in the peripheral nervous system. *Front. Neurosci.* **14**, 796 (2020).
40. Rustichelli, C. et al. Serum levels of allopregnanolone, progesterone and testosterone in menstrually-related and postmenopausal migraine: a cross-sectional study. *Cephalalgia* **40**, 1355–1362 (2020).
41. Coronel, M. F., Labombarda, F. & Gonzalez, S. L. Neuroactive steroids, nociception and neuropathic pain: a flashback to go forward. *Steroids* **110**, 77–87 (2016).
42. Cutrer, F. M. & Moskowitz, M. A. Wolff Award 1996. The actions of valproate and neurosteroids in a model of trigeminal pain. *Headache* **36**, 579–585 (1996).
43. Hayasaki, H. et al. A local GABAergic system within rat trigeminal ganglion cells. *Eur. J. Neurosci.* **23**, 745–757 (2006).
44. Schaeffer, V., Meyer, L., Patte-Mensah, C. & Mensah-Nyagan, A. G. Progress in dorsal root ganglion neurosteroidogenic activity: basic evidence and pathophysiological correlation. *Prog. Neurobiol.* **92**, 33–41 (2010).
45. Tzabazis, A. et al. Oxytocin and migraine headache. *Headache* **57** (Suppl. 2), 64–75 (2017).
This paper describes seminal clinical studies demonstrating that oxytocin, given intranasally, provides acute relief of migraine symptoms and also reports preclinical data indicating a role of oxytocin in the trigeminal pathway.
46. Phillips, W. J., Ostrovsky, O., Galli, R. L. & Dickey, S. Relief of acute migraine headache with intravenous oxytocin: report of two cases. *J. Pain Palliat. Care Pharmacother.* **20**, 25–28 (2006).
47. Amico, J. A., Seif, S. M. & Robinson, A. G. Oxytocin in human plasma: correlation with neurophysin and stimulation with estrogen. *J. Clin. Endocrinol. Metab.* **52**, 988–993 (1981).
48. Young, L. J., Muns, S., Wang, Z. & Insel, T. R. Changes in oxytocin receptor mRNA in rat brain during pregnancy and the effects of estrogen and interleukin-6. *J. Neuroendocrinol.* **9**, 859–865 (1997).
49. Welsh, T. et al. Estrogen receptor (ER) expression and function in the pregnant human myometrium: estradiol via ERα activates ERK1/2 signaling in term myometrium. *J. Endocrinol.* **212**, 227–238 (2012).
50. Murata, T., Narita, K. & Ichimaru, T. Rat uterine oxytocin receptor and estrogen receptor alpha and beta mRNA levels are regulated by estrogen through multiple estrogen receptors. *J. Reprod. Dev.* **60**, 55–61 (2014).
51. Miller, F. D., Ozimek, G., Milner, R. J. & Bloom, F. E. Regulation of neuronal oxytocin mRNA by ovarian steroids in the mature and developing hypothalamus. *Proc. Natl Acad. Sci. USA* **86**, 2468–2472 (1989).
A classic study that first showed that oxytocin gene expression in the hypothalamus (rat) is regulated by ovarian hormones, with increases at puberty and during lactation.
52. Dale, H. H. On some physiological actions of ergot. *J. Physiol.* **34**, 163–206 (1906).
53. Du Vigneaud, V., Ressler, C. & Trippett, S. The sequence of amino acids in oxytocin, with a proposal for the structure of oxytocin. *J. Biol. Chem.* **205**, 949–957 (1953).
54. Uvnas-Moberg, K. et al. Maternal plasma levels of oxytocin during physiological childbirth - a systematic review with implications for uterine contractions and central actions of oxytocin. *BMC Pregnancy Childbirth* **19**, 285 (2019).
55. Jirikowski, G. F. Diversity of central oxytocinergic projections. *Cell Tissue Res.* **375**, 41–48 (2019).
56. Eliava, M. et al. A new population of parvocellular oxytocin neurons controlling magnocellular neuron activity and inflammatory pain processing. *Neuron* **89**, 1291–1304 (2016).
In this study, individual hypothalamic oxytocin neurons were shown to suppress nociception via two pathways: direct inhibitory projections to spinal sensory neurons and stimulation of oxytocin release into the blood.
57. Jurek, B. & Neumann, I. D. The oxytocin receptor: from intracellular signaling to behavior. *Physiol. Rev.* **98**, 1805–1908 (2018).
58. Carter, C. S. et al. Is oxytocin "Nature's medicine"? *Pharmacol. Rev.* **72**, 829–861 (2020).
59. Poisbeau, P., Grinevich, V. & Charlet, A. Oxytocin signaling in pain: cellular, circuit, system, and behavioral levels. *Curr. Top. Behav. Neurosci.* **35**, 193–211 (2018).
60. de Geest, K., Thiery, M., Piron-Possuyt, G. & Vanden Driessche, R. Plasma oxytocin in human pregnancy and parturition. *J. Perinat. Med.* **13**, 3–13 (1985).
61. Murata, T., Narita, K., Honda, K. & Higuchi, T. Changes of receptor mRNAs for oxytocin and estrogen during the estrous cycle in rat uterus. *J. Vet. Med. Sci.* **65**, 707–712 (2003).
62. Amico, J. A., Seif, S. M. & Robinson, A. G. Elevation of oxytocin and the oxytocin-associated neurophysin in the plasma of normal women during midcycle. *J. Clin. Endocrinol. Metab.* **53**, 1229–1232 (1981).
63. Engel, S., Klusmann, H., Ditzen, B., Knaevelsrud, C. & Schumacher, S. Menstrual cycle-related fluctuations in oxytocin concentrations: a systematic review and meta-analysis. *Front. Neuroendocrinol.* **52**, 144–155 (2019).
This study demonstrates the fluctuation of oxytocin blood levels over the human menstrual cycle, indicating a sharp drop at the time of menstruation.

64. Warfvinge, K. et al. Oxytocin as a regulatory neuropeptide in the trigeminovascular system: localization, expression and function of oxytocin and oxytocin receptors. *Cephalalgia* **40**, 1283–1295 (2020).
65. Tzabazis, A. et al. Oxytocin receptor: expression in the trigeminal nociceptive system and potential role in the treatment of headache disorders. *Cephalalgia* **36**, 943–950 (2016).
66. Garcia-Boll, E., Martinez-Lorenzana, G., Condes-Lara, M. & Gonzalez-Hernandez, A. Oxytocin inhibits the rat medullary dorsal horn Sp5c/C1 nociceptive transmission through OT but not V1A receptors. *Neuropharmacology* **129**, 109–117 (2018).
67. Warfvinge, K., Krause, D. & Edvinsson, L. The distribution of oxytocin and the oxytocin receptor in brain: relation to regions active in migraine. *J. Headache Pain* **21**, 10 (2020).
68. Lagunas, N. et al. Estrogen receptor beta and G protein-coupled estrogen receptor 1 are involved in the acute estrogenic regulation of arginine-vasopressin immunoreactive levels in the supraoptic and paraventricular hypothalamic nuclei of female rats. *Brain Res.* **1712**, 93–100 (2019).
69. Dayanithi, G. et al. Vasopressin and oxytocin in sensory neurones: expression, exocytotic release and regulation by lactation. *Sci. Rep.* **8**, 13084 (2018).
70. Juif, P. E. & Poisbeau, P. Neurohormonal effects of oxytocin and vasopressin receptor agonists on spinal pain processing in male rats. *Pain* **154**, 1449–1456 (2013).
71. DiCarlo, L. M., Vied, C. & Nowakowski, R. S. The stability of the transcriptome during the estrous cycle in four regions of the mouse brain. *J. Comp. Neurol.* **525**, 3360–3387 (2017).
72. Franchimont, P. et al. Prolactin levels during the menstrual cycle. *Clin. Endocrinol.* **5**, 643–650 (1976).
73. Chen, Y., Navratilova, E., Dodick, D. W. & Porreca, F. An emerging role for prolactin in female-selective pain. *Trends Neurosci.* **43**, 635–648 (2020).
74. Avona, A. et al. Meningeal CGRP-prolactin interaction evokes female-specific migraine behavior. *Ann. Neurol.* **89**, 1129–1144 (2021).
75. Porkka-Heiskanen, T., Kalinchuk, A., Alanko, L., Huhtaniemi, I. & Stenberg, D. Orexin A and B levels in the hypothalamus of female rats: the effects of the estrous cycle and age. *Eur. J. Endocrinol.* **150**, 737–742 (2004).
76. Strother, L. C., Srikiatkhachorn, A. & Supronsinchai, W. Targeted orexin and hypothalamic neuropeptides for migraine. *Neurotherapeutics* **15**, 377–390 (2018).
77. Holland, P. & Goadsby, P. J. The hypothalamic orexinergic system: pain and primary headaches. *Headache* **47**, 951–962 (2007).
78. Edvinsson, J. C. A. et al. The fifth cranial nerve in headaches. *J. Headache Pain* **21**, 65 (2020).
79. Messlinger, K. & Russo, A. F. Current understanding of trigeminal ganglion structure and function in headache. *Cephalalgia* **39**, 1661–1674 (2019).
80. Dodick, D. W. A phase-by-phase review of migraine pathophysiology. *Headache* **58** (Suppl. 1), 4–16 (2018).
81. Pietrobon, D. & Moskowitz, M. A. Pathophysiology of migraine. *Annu. Rev. Physiol.* **75**, 365–391 (2013).
82. Edvinsson, L. Tracing neural connections to pain pathways with relevance to primary headaches. *Cephalalgia* **31**, 737–747 (2011).
83. Liu, Y., Broman, J. & Edvinsson, L. Central projections of the sensory innervation of the rat middle meningeal artery. *Brain Res.* **1208**, 103–110 (2008).
84. Liu, Y., Broman, J., Zhang, M. & Edvinsson, L. Brainstem and thalamic projections from a craniovascular sensory nervous centre in the rostral cervical spinal dorsal horn of rats. *Cephalalgia* **29**, 935–948 (2009).
85. Noseda, R. & Burstein, R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization and modulation of pain. *Pain* https://doi.org/10.1016/j.pain.2013.07.021 (2013).
86. May, A. Understanding migraine as a cycling brain syndrome: reviewing the evidence from functional imaging. *Neurol. Sci.* **38**, 125–130 (2017).
87. May, A. & Burstein, R. Hypothalamic regulation of headache and migraine. *Cephalalgia* **39**, 1710–1719 (2019).
In this study, the investigators propose that the hypothalamus has a central role in generating a migraine attack and participates in complex oscillating neural networks that alter susceptibility thresholds.
88. Schulte, L. H. & May, A. Of generators, networks and migraine attacks. *Curr. Opin. Neurol.* **30**, 241–245 (2017).
89. Napadow, V., Sclocco, R. & Henderson, L. A. Brainstem neuroimaging of nociception and pain circuitries. *Pain Rep.* **4**, e745 (2019).
90. Marciszewski, K. K. et al. Changes in brainstem pain modulation circuitry function over the migraine cycle. *J. Neurosci.* **38**, 10479–10488 (2018).
91. Karsan, N. & Goadsby, P. J. Imaging the premonitory phase of migraine. *Front. Neurol.* **11**, 140 (2020).
92. Tu, Y. et al. Abnormal thalamocortical network dynamics in migraine. *Neurology* **92**, e2706–e2716 (2019).
93. Peng, K. P. & May, A. Migraine understood as a sensory threshold disease. *Pain* **160**, 1494–1501 (2019).
94. Maleki, N. & Androulakis, X. M. Is there any MRI pattern that discriminates female from male migraine patients? *Front. Neurol.* **10**, 961 (2019).
95. Hu, B. et al. Structural and functional brain changes in perimenopausal women who are susceptible to migraine: a study protocol of multi-modal MRI trial. *BMC Med. Imaging* **18**, 26 (2018).
96. Iyengar, S., Johnson, K. W., Ossipov, M. H. & Aurora, S. K. CGRP and the trigeminal system in migraine. *Headache* **59**, 659–681 (2019).
97. Eftekhari, S. et al. Localization of CGRP, CGRP receptor, PACAP and glutamate in trigeminal ganglion. Relation to the blood-brain barrier. *Brain Res.* **1600**, 93–109 (2015).
98. Charles, A. & Pozo-Rosich, P. Targeting calcitonin gene-related peptide: a new era in migraine therapy. *Lancet* **394**, 1765–1774 (2019).
99. Pavlovic, J. M. et al. Efficacy and safety of erenumab in women with a history of menstrual migraine. *J. Headache Pain* **21**, 95 (2020).
100. Ornello, R. et al. Menstrual headache in women with chronic migraine treated with erenumab: an observational case series. *Brain Sci.* **11**, 370 (2021).
101. Ho, T. W., Ho, A. P. & Ge, Y. J. Randomized controlled trial of the CGRP receptor antagonist telcagepant for prevention of headache in women with perimenstrual migraine. *Cephalalgia* **36**, 148–161 (2016).
102. Warfvinge, K. & Edvinsson, L. Distribution of CGRP and CGRP receptor components in the rat brain. *Cephalalgia* **39**, 342–353 (2019).
103. Hewitt, S. C. & Korach, K. S. Estrogen receptors: new directions in the new Millennium. *Endocr. Rev.* **39**, 664–675 (2018).
104. Levin, E. R. Extranuclear steroid receptors are essential for steroid hormone actions. *Annu. Rev. Med.* **66**, 271–280 (2015).
105. Prossnitz, E. R. & Hathaway, H. J. What have we learned about GPER function in physiology and disease from knockout mice? *J. Steroid Biochem. Mol. Biol.* **153**, 114–126 (2015).
106. Bereiter, D. A., Cioffi, J. L. & Bereiter, D. F. Oestrogen receptor-immunoreactive neurons in the trigeminal sensory system of male and cycling female rats. *Arch. Oral. Biol.* **50**, 971–979 (2005).
107. Warfvinge, K. et al. Estrogen receptors alpha, beta and GPER in the CNS and trigeminal system - molecular and functional aspects. *J. Headache Pain* **21**, 131 (2020).
108. Rossetti, M. F., Cambiasso, M. J., Holschbach, M. A. & Cabrera, R. Oestrogens and progestagens: synthesis and action in the brain. *J. Neuroendocrinol.* https://doi.org/10.1111/jne.12402 (2016).
109. Dun, S. L. et al. Expression of estrogen receptor GPR30 in the rat spinal cord and in autonomic and sensory ganglia. *J. Neurosci. Res.* **87**, 1610–1619 (2009).
110. Fan, X., Kim, H. J., Warner, M. & Gustafsson, J. A. Estrogen receptor beta is essential for sprouting of nociceptive primary afferents and for morphogenesis and maintenance of the dorsal horn interneurons. *Proc. Natl Acad. Sci. USA* **104**, 13696–13701 (2007).
111. Amandusson, A. & Blomqvist, A. Estrogen receptor-alpha expression in nociceptive-responsive neurons in the medullary dorsal horn of the female rat. *Eur. J. Pain* **14**, 245–248 (2010).
112. Amandusson, A. & Blomqvist, A. Estrogenic influences in pain processing. *Front. Neuroendocrinol.* **34**, 329–349 (2013).
113. Greco, R. et al. Effect of sex and estrogens on neuronal activation in an animal model of migraine. *Headache* **53**, 288–296 (2013).
114. Vanderhorst, V. G., Gustafsson, J. A. & Ulfhake, B. Estrogen receptor-alpha and -beta immunoreactive neurons in the brainstem and spinal cord of male and female mice: relationships to monoaminergic, cholinergic, and spinal projection systems. *J. Comp. Neurol.* **488**, 152–179 (2005).
115. Llorente, R. et al. G protein-coupled estrogen receptor immunoreactivity fluctuates during the estrous cycle and show sex differences in the amygdala and dorsal hippocampus. *Front. Endocrinol.* **11**, 537 (2020).
116. Nomura, M., McKenna, E., Korach, K. S., Pfaff, D. W. & Ogawa, S. Estrogen receptor-beta regulates transcript levels for oxytocin and arginine vasopressin in the hypothalamic paraventricular nucleus of male mice. *Brain Res. Mol. Brain Res.* **109**, 84–94 (2002).
117. Sandweiss, A. J. et al. 17-β-Estradiol induces spreading depression and pain behavior in alert female rats. *Oncotarget* **8**, 114109–114122 (2017).
118. Eikermann-Haerter, K. et al. Genetic and hormonal factors modulate spreading depression and transient hemiparesis in mouse models of familial hemiplegic migraine type 1. *J. Clin. Invest.* **119**, 99–109 (2009).
119. Al-Hassany, L. et al. Giving researchers a headache - sex and gender differences in migraine. *Front. Neurol.* **11**, 549038 (2020).
120. Martin, V. T. & Behbehani, M. Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis — part I. *Headache* **46**, 3–23 (2006).
121. Allais, G. et al. Gender-related differences in migraine. *Neurol. Sci.* **41**, 429–436 (2020).
122. Paredes, S., Cantillo, S., Candido, K. D. & Knezevic, N. N. An association of serotonin with pain disorders and its modulation by estrogens. *Int. J. Mol. Sci.* **20**, 5729 (2019).
123. Artero-Morales, M., Gonzalez-Rodriguez, S. & Ferrer-Montiel, A. TRP channels as potential targets for sex-related differences in migraine pain. *Front. Mol. Biosci.* **5**, 73 (2018).
124. Bi, R. Y. et al. Estradiol upregulates voltage-gated sodium channel 1.7 in trigeminal ganglion contributing to hyperalgesia of inflamed TMJ. *PLoS One* **12**, e0178589 (2017).
125. Saleeon, W., Jansri, U., Srikiatkhachorn, A. & Bongsebandhu-Phubhakdi, S. The estrous cycle modulates voltage-gated ion channels in trigeminal ganglion neurons. *J. Physiol. Sci.* **65** (Suppl. 2), S29–S35 (2015).
126. Vermeer, L. M., Gregory, E., Winter, M. K., McCarson, K. E. & Berman, N. E. Behavioral effects and mechanisms of migraine pathogenesis following estradiol exposure in a multibehavioral model of migraine in rat. *Exp. Neurol.* **263**, 8–16 (2015).
127. Puri, J., Bellinger, L. L. & Kramer, P. R. Estrogen in cycling rats alters gene expression in the temporomandibular joint, trigeminal ganglia and trigeminal subnucleus caudalis/upper cervical cord junction. *J. Cell Physiol.* **226**, 3169–3180 (2011).
128. Puri, V. et al. Effects of oestrogen on trigeminal ganglia in culture: implications for hormonal effects on migraine. *Cephalalgia* **26**, 33–42 (2006).
129. Puri, V. et al. Ovarian steroids regulate neuropeptides in the trigeminal ganglion. *Neuropeptides* **39**, 409–417 (2005).
130. Mecklenburg, J. et al. Transcriptomic sex differences in sensory neuronal populations of mice. *Sci. Rep.* **10**, 15278 (2020).
A mouse study that offers insight into sex dimorphism by demonstrating that a large number of female-specific genes related to nociception are expressed uniquely in trigeminal ganglia.
131. Martin, V. T., Lee, J. & Behbehani, M. M. Sensitization of the trigeminal sensory system during different stages of the rat estrous cycle: implications for menstrual migraine. *Headache* **47**, 552–563 (2007).
132. Xin, Q., Bai, B. & Liu, W. The analgesic effects of oxytocin in the peripheral and central nervous system. *Neurochem. Int.* **103**, 57–64 (2017).
133. Hiroi, R. et al. The androgen metabolite, 5alpha-androstane-3beta,17beta-diol (3beta-diol), activates the oxytocin promoter through an estrogen receptor-beta pathway. *Endocrinology* **154**, 1802–1812 (2013).
134. Hrabovszky, E. et al. Estrogen receptor-beta in oxytocin and vasopressin neurons of the rat and human hypothalamus: Immunocytochemical and in situ hybridization studies. *J. Comp. Neurol.* **473**, 315–333 (2004).
135. Narita, K., Murata, T. & Matsuoka, S. The ventromedial hypothalamus oxytocin induces locomotor behavior regulated by estrogen. *Physiol. Behav.* **164**, 107–112 (2016).
136. Condes-Lara, M. et al. Paraventricular hypothalamic influences on spinal nociceptive processing. *Brain Res.* **1081**, 126–137 (2006).

137. Garcia-Boll, E., Martinez-Lorenzana, G., Condes-Lara, M. & Gonzalez-Hernandez, A. Inhibition of nociceptive dural input to the trigeminocervical complex through oxytocinergic transmission. *Exp. Neurol.* **323**, 113079 (2020).
138. Loup, F., Tribollet, E., Dubois-Dauphin, M., Pizzolato, G. & Dreifuss, J. J. Localization of oxytocin binding sites in the human brainstem and upper spinal cord: an autoradiographic study. *Brain Res.* **500**, 223–230 (1989).
139. Freeman, S. M., Inoue, K., Smith, A. L., Goodman, M. M. & Young, L. J. The neuroanatomical distribution of oxytocin receptor binding and mRNA in the male rhesus macaque (Macaca mulatta). *Psychoneuroendocrinology* **45**, 128–141 (2014).
140. Han, Y. & Yu, L. C. Involvement of oxytocin and its receptor in nociceptive modulation in the central nucleus of amygdala of rats. *Neurosci. Lett.* **454**, 101–104 (2009).
141. Moreno-Lopez, Y., Martinez-Lorenzana, G., Condes-Lara, M. & Rojas-Piloni, G. Identification of oxytocin receptor in the dorsal horn and nociceptive dorsal root ganglion neurons. *Neuropeptides* **47**, 117–123 (2013).
142. Kubo, A. et al. Oxytocin alleviates orofacial mechanical hypersensitivity associated with infraorbital nerve injury through vasopressin-1A receptors of the rat trigeminal ganglia. *Pain* **158**, 649–659 (2017).
143. Pierce, M. L., Mehrotra, S., Mustoe, A. C., French, J. A. & Murray, T. F. A comparison of the ability of Leu(8)- and Pro(8)-oxytocin to regulate intracellular Ca^{2+} and Ca^{2+}-activated K^+ channels at human and marmoset oxytocin receptors. *Mol. Pharmacol.* **95**, 376–385 (2019).
144. Gong, L. et al. Oxytocin-induced membrane hyperpolarization in pain-sensitive dorsal root ganglia neurons mediated by Ca^{2+}/nNOS/NO/KATP pathway. *Neuroscience* **289**, 417–428 (2015).
145. Hobo, S., Hayashida, K. & Eisenach, J. C. Oxytocin inhibits the membrane depolarization-induced increase in intracellular calcium in capsaicin sensitive sensory neurons: a peripheral mechanism of analgesic action. *Anesth. Analg.* **114**, 442–449 (2012).
146. Vecsernyes, M., Jojart, I., Jojart, J., Laczi, F. & Laszlo, F. A. Presence of chromatographically identified oxytocin in human sensory ganglia. *Brain Res.* **414**, 153–154 (1987).
147. Kai-Kai, M. A., Swann, R. W. & Keen, P. Localization of chromatographically characterized oxytocin and arginine-vasopressin to sensory neurones in the rat. *Neurosci. Lett.* **55**, 83–88 (1985).
148. Eftekhari, S. et al. Differential distribution of calcitonin gene-related peptide and its receptor components in the human trigeminal ganglion. *Neuroscience* **169**, 683–696 (2010).
149. Aggarwal, M., Puri, V. & Puri, S. Effects of estrogen on the serotonergic system and calcitonin gene-related peptide in trigeminal ganglia of rats. *Ann. Neurosci.* **19**, 151–157 (2012).
150. Stucky, N. L. et al. Sex differences in behavior and expression of CGRP-related genes in a rodent model of chronic migraine. *Headache* **51**, 674–692 (2011).
151. Edvinsson, J. C. A. et al. C-fibers may modulate adjacent Adelta-fibers through axon-axon CGRP signaling at nodes of Ranvier in the trigeminal system. *J. Headache Pain* **20**, 105 (2019).
152. Hidalgo-Lopez, E. et al. Human menstrual cycle variation in subcortical functional brain connectivity: a multimodal analysis approach. *Brain Struct. Funct.* **225**, 591–605 (2020).
153. Petersen, N., Kilpatrick, L. A., Goharzad, A. & Cahill, L. Oral contraceptive pill use and menstrual cycle phase are associated with altered resting state functional connectivity. *Neuroimage* **90**, 24–32 (2014).
154. Allais, G., Chiarle, G., Sinigaglia, S. & Benedetto, C. Menstrual migraine: a review of current and developing pharmacotherapies for women. *Expert Opin. Pharmacother.* **19**, 123–136 (2018).
155. Ansari, T., Lagman-Bartolome, A. M., Monsour, D. & Lay, C. Management of menstrual migraine. *Curr. Neurol. Neurosci. Rep.* **20**, 45 (2020).
156. Bartolini, M. et al. Frovatriptan versus almotriptan for acute treatment of menstrual migraine: analysis of a double-blind, randomized, cross-over, multicenter, Italian, comparative study. *J. Headache Pain* **13**, 401–406 (2012).
157. Brandes, J. L. et al. Short-term frovatriptan for the prevention of difficult-to-treat menstrual migraine attacks. *Cephalalgia* **29**, 1133–1148 (2009).
158. Allais, G. et al. Perimenstrual migraines and their response to preventive therapy with topiramate. *Cephalalgia* **31**, 152–160 (2011).
159. Calhoun, A. H. Understanding menstrual migraine. *Headache* **58**, 626–630 (2018).
160. MacGregor, A. Effects of oral and transdermal estrogen replacement on migraine. *Cephalalgia* **19**, 124–125 (1999).
161. Gartlehner, G. et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: evidence report and systematic review for the US Preventive services task force. *JAMA* **318**, 2234–2249 (2017).
162. Middeldorp, S. Oral contraceptives and the risk of venous thromboembolism. *Gend. Med.* **2** (Suppl. A), S3–9 (2005).
163. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet* **394**, 1159–1168 (2019).
164. Beaber, E. F. et al. Recent oral contraceptive use by formulation and breast cancer risk among women 20 to 49 years of age. *Cancer Res.* **74**, 4078–4089 (2014).
165. Smitherman, T. A. & Kolivas, E. D. Resolution of menstrually related migraine following aggressive treatment for breast cancer. *Headache* **50**, 485–488 (2010).
166. May, A. & Schulte, L. H. Chronic migraine: risk factors, mechanisms and treatment. *Nat. Rev. Neurol.* **12**, 455–464 (2016).

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