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The role and interaction of hypothalamic-related neurotransmitters in migraine

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Abstract

Migraine is a complex neurological disorder frequently associated with hypothalamic dysfunction. This brain region is essential for maintaining homeostasis due to its regulation of autonomic, endocrine, and circadian systems. While the pathophysiology of migraine remains incompletely understood, clinical features such as the cyclic nature of attacks and symptoms, including nausea, vomiting, yawning, irritability, and sensitivity to light, indicate a significant role for the hypothalamus. Further, potential triggers of migraine, such as stress and disruption to feeding habits, also impact hypothalamic mechanisms. The higher prevalence of migraine in women compared to men suggests a link to hormonal fluctuations involving estrogen, progesterone, and prolactin. These hormones interact with the hypothalamus, potentially influencing the onset and severity of migraine episodes. Additionally, the hypothalamus synthesizes neuropeptides such as orexins, neuropeptide Y, PACAP, oxytocin, and vasopressin, which are all implicated in migraine mechanisms. Understanding the interplay between the hypothalamus, sex hormones, and neuropeptides offers valuable opportunities for endogenous targeted migraine therapies. In this review we discuss hypothalamic contributions to migraine pathophysiology, highlighting the mechanisms affected by hypothalamic connections, neuropeptides, and hormones, and their role as migraine triggers, particularly focusing on factors like stress, fasting, and changes in sleep patterns.

Keywords Migraine, Hypothalamus, Sex hormones, Stress, Sleep alterations

Introduction

Migraine is generally accepted as a neurovascular disorder of the brain. This inevitably raises the question of which structures in the brain are responsible for triggering and sustaining migraine headache attacks and may lead to migraine chronicity [1–4]. The hypothalamus is a diencephalic structure critical for homeostasis and over recent years data have been generated that support its important role in migraine pathogenesis and physiology [5]. Neuroimaging studies have revealed activation within the hypothalamus prior to [6, 7] and during migraine headache [8], signaling the hypothalamus as a possible generator, or mediator, of migraine as well as having a direct role in specific symptoms, including headache and other associated symptoms [5, 9]. Coupled to this, it is known that many people living with migraine experience sleep alterations and autonomic symptoms that are regulated at the hypothalamic level, strengthening the possible relation between the hypothalamus and migraine mechanisms [3, 10, 11].

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Hypothalamic nuclei make connections with many other migraine-related structures and various hypothalamus-related neurotransmitters are thought to be involved in migraine mechanisms. As such, the hypothalamus can be considered as a possible endogenous target for treatment through its likely contribution to migraine pathogenesis. It is also relevant to consider these neurophysiological and neuropharmacological interactions in the context of migraine triggers and/or events that are more likely to precipitate migraine, as well as hypothalamic influence on possible sex differences in migraine, and how together these might help explain migraine pathogenesis and potential differential treatment responses. In this paper, we will review these hypothalamus-related neurotransmitters, and how they play a role in migraine mechanisms through the neural connections and interactions of hypothalamic nuclei with different brain structures, in the context of migraine triggers and sex differences.

Hypothalamic connectivity with migraine-related structures

It has been shown that neurons in the medullary trigeminal nucleus caudalis (TNC) and upper cervical region (trigeminocervical complex; TCC) that participate in codifying sensorial stimuli send projections to lateral, dorsomedial, suprachiasmatic and supraoptic (SON) hypothalamic nuclei [12]. Hypothalamic paraventricular (PVN), A11, and lateral hypothalamic neurons densely innervate the TCC, predominantly in the ventrolateral dorsal horn portion, which mainly receives trigeminal afferent projections within the ophthalmic division, with meningeal and cutaneous inputs [13, 14]. It is also noted that both A11 and lateral hypothalamic projections are bilateral, whereas PVN are ipsilateral only. The PVN also sends direct projections to the superior salivatory nucleus (SuS), the origin of cells of the cranial parasympathetic projection and the pathway thought to be responsible for cranial autonomic symptoms in both migraine and trigeminal autonomic cephalalgias [14].

Functionally, it is known that these structures modulate migraine-related dural-trigeminovascular neuronal activity at the level of TCC. Stimulating the A11 nucleus inhibits dural-nociceptive processing in the TCC, via dopamine D_2 receptors [15]. Decreased dopamine release from the A11 to TCC neurons is also known to modulate migraine-related trigeminal neuronal activation [16]. However, lesioning the A11 nucleus facilitates trigeminocervical neuronal responses to innocuous and noxious intra and extracranial stimulation. This suggests that A11 hypothalamic neurons provide ongoing control of trigeminocervical neurons [15]. This facilitation likely involves both dopaminergic and serotoninergic mechanisms at the level of the TCC [17]. Electrical stimulation of PVN decreased TCC neuronal responses to periorbital cutaneous stimulation, while neuronal responses to dural electrical stimulation of dura mater were modulated by local trigeminal oxytocin receptor antagonism [18]. Hypothalamic regulation of trigeminal processing could also be produced indirectly through thalamic or brainstem structures, such as the periaqueductal grey (PAG) and dorsal raphe nucleus (DR) [19–22]. Optogenetic inhibition of the posterior hypothalamus inhibits behaviors related to trigeminal neuropathic pain, which are mediated by the PAG and ventral thalamic nucleus [23]. The hypothalamus is connected to many brain structures involved in the modulation of pain conditions, including PAG, DR, locus coeruleus (LC), anterior insular cortex, amygdala, and rostral ventromedial medulla (RVM) [24–28] **(**Fig. 1**)**. Further, the role of stress in pain is modulated by RVM-dorsomedial hypothalamus (DMH) connections. While the RVM is significant in pain enhancement, the DMH may also contribute to conditions like migraine headache attacks. Direct pharmacological activation of the DMH increased sensitivity to mechanical stimulation in awake animals, confirming that the DMH can modulate hyperalgesic responses [29]. These findings highlight a link between the DMH and RVM, reinforcing that stress may exacerbate pain.

The role of hypothalamic peptides in migraine

Hypothalamic peptides represent a diverse collection of bioactive molecules that are synthesized and secreted by specialized neurons within the hypothalamus. These peptides serve as crucial signaling molecules, facilitating communication among neurons and influencing remote organs. Their roles are instrumental in regulating the secretion of various hormones and modulating a broad spectrum of essential functions. Figure. 2 illustrates some of the primary hypothalamic neuropeptides and the respective nuclei where they are produced or secreted. While not exhaustive, this review focuses on these hypothalamus-related molecules and their role in the pathophysiology of migraine, including orexins, neuropeptide Y, PACAP, dopamine, prolactin, melatonin, oxytocin, and vasopressin. There is also a particular emphasis on specific molecules and their involvement in potentially triggering migraine **(**Fig. 3**)**. The review further elucidates how hormones such as gonadotropin-releasing hormone (GnRH) and corticotropin-releasing hormone (CRH) activate the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal (HPA) axes, respectively, and how disruptions within these systems may contribute to physiological dysfunction relevant to migraine pathogenesis. We also highlight sex-linked variations within these systems, which could present potential targets for endogenous modulation.

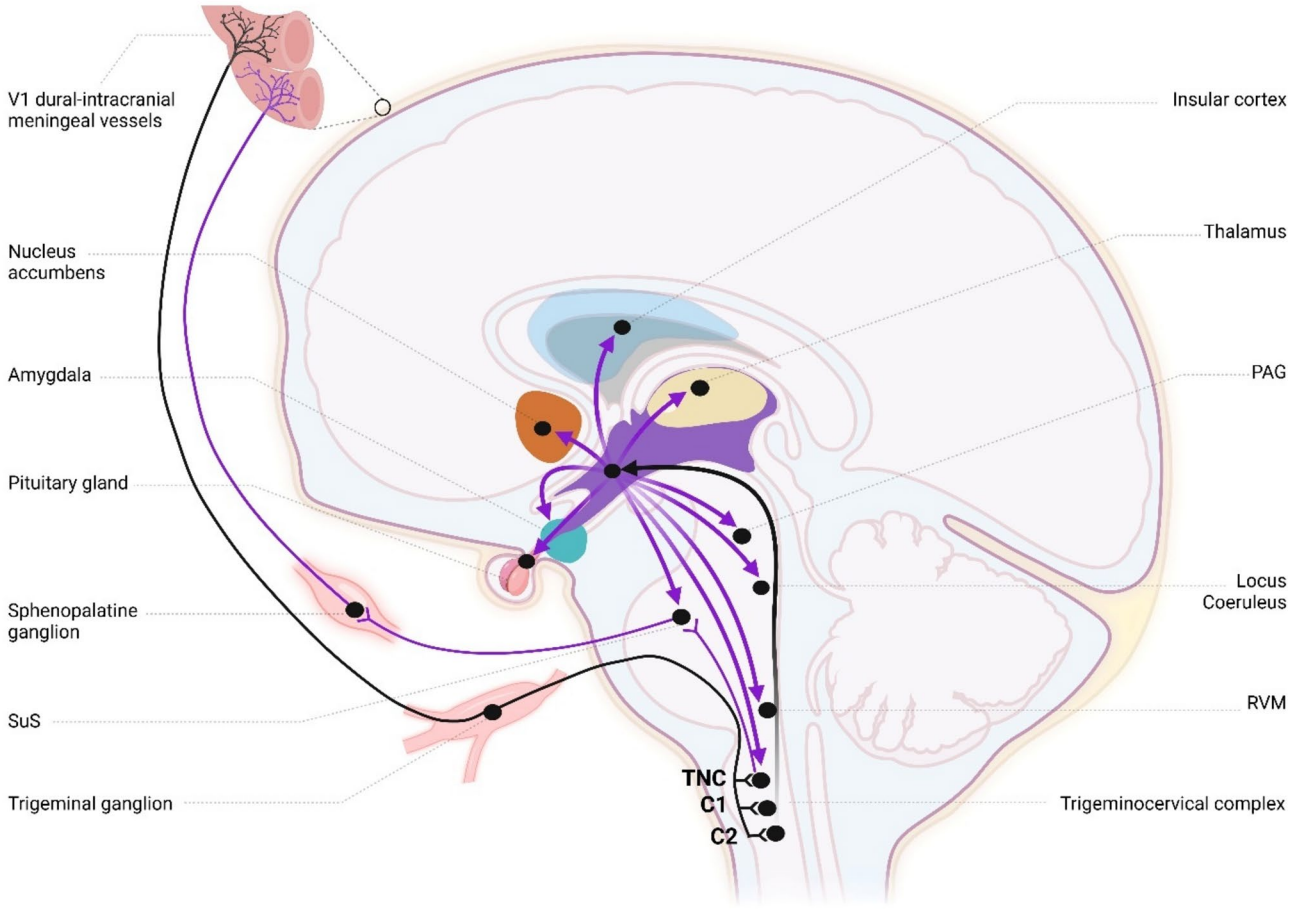

Fig. 1 Illustrative scheme for hypothalamic connections with migraine-related structures. In black, afferent fibers from the dural vasculature reach hypothalamic nuclei via the trigeminocervical complex (TCC). In violet, efferent projections from hypothalamic nuclei to the trigeminal system at the level of TCC and the superior salivatory nucleus (SuS). There are further projections to other structures involved in migraine pathophysiology, including the amygdala, insular cortex, locus coeruleus, nucleus accumbens, periaqueductal gray matter (PAG), pituitary gland, rostroventral medulla (RVM), and thalamus. Created with Biorender.com

Orexins

Orexins are neuropeptides derived from the 130-amino-acid precursor prepro-orexin through proteolytic cleavage. Orexin A (OxA) and orexin B (OxB) share 46% sequence homology and are almost exclusively secreted from neuronal cell bodies within the lateral hypothalamus [30, 31]. These peptides bind two G-protein-coupled receptors (GPCRs): OX_1 and OX_2. Their activation increases intracellular Ca^{2+} levels by stimulating Gq-mediated phospholipase C activity [30, 32]. The orexinergic system plays a crucial role in regulating neuroendocrine and autonomic functions, as well as modulating nociceptive processing [33]. Orexinergic neurons are exclusively located in the lateral hypothalamic area, projecting extensively throughout the central nervous system [34]. These projections target key regions, including the PAG, pituitary, cerebral cortex, ventrolateral reticular formation, PVN, parabrachial nucleus, amygdala, thalamus, nucleus tractus solitarius (NTS), spinal dorsal horn, spinal trigeminal nucleus, and other areas [35, 36].

Orexins play a crucial role in the regulation of homeostasis, and their dysregulation has been implicated in migraine pathogenesis. To this end, in clinical studies, cerebrospinal fluid (CSF) OxA levels were shown to be elevated in patients with chronic migraine (CM) and medication-overuse headache (MOH) compared to controls [37]. Although, contrasting data, with no significant difference in OxA levels between CM patients and controls have also been reported. This study did note an inverse correlation between OxA levels and anxiety, which may have contributed to this discrepancy [38]. In another study, baseline plasma levels of OxA and OxB were lower in episodic migraine (EM) patients than in controls. It was also observed that OxA levels were negatively correlated with weight gain in both groups during treatment with amitriptyline or flunarizine. This observation suggests a disruption in orexinergic pathways in migraine, implying that fluctuations in hypothalamic

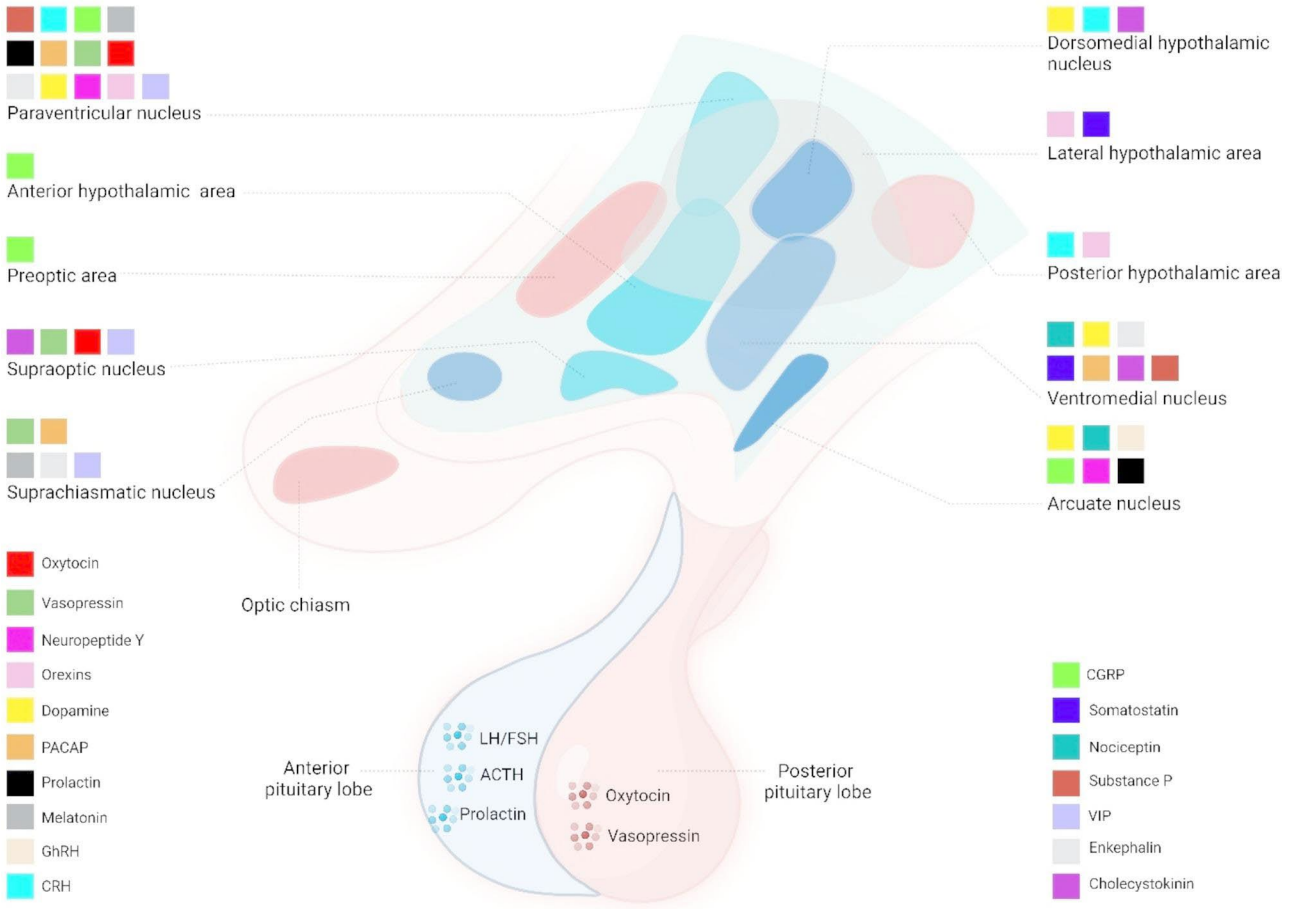

Fig. 2 Overview of hypothalamic nuclei and their associated peptides. A detailed illustration of the primary nuclei of the hypothalamus, with an emphasis on those involved in regulating various physiological functions, with the specific neuropeptides and hormones that mediate these functions highlighted. Together these neurotransmitters are thought to play crucial roles in the hypothalamic contribution to migraine pathogenesis. Created with Biorender.com

orexinergic peptide levels may contribute to weight gain during these prophylactic treatments [39]. A genetic link between orexin and migraine has also been highlighted, with a significant difference in the frequency of rs2271933 polymorphisms in the OX_1 receptor gene between migraine and control groups identified. The A allele was associated with a higher risk of migraine without aura, supporting the idea that OX_1 receptors may be a genetic susceptibility factor for migraine without aura [40, 41].

Preclinical findings also confirm the role of orexins in modulating trigeminal nociception relevant to migraine. OxA, via OX_1 receptor, inhibits dural-evoked meningeal vasodilation and trigeminal neuronal firing [42, 43], in part via a CGRP-dependent mechanism. OxB had no effect in either assay. Furthermore, direct application of OxA or OxB into the posterior hypothalamic area (PH) had differential effects on dural and craniofacial trigeminal nociception, with OxA anti-nociceptive and OxB pronociceptive [44]. A similar outcome of OX_1 receptor-mediated inhibition of migraine-like hyperalgesia was reported through its application into the vlPAG, which receives orexinergic projections from the hypothalamus [45]. Lastly, a dual-orexin receptor antagonist (DORA) was shown to mitigate dural-nociceptive mediated meningeal vasodilation, trigeminal neuronal firing, and reduced the susceptibility to induce cortical spreading depression (CSD), a correlate of migraine aura [46]. It is relevant to note that all the above studies were performed in male rats. It highlights the lack of research on sex-related differences, particularly in light of a male-specific effect noted by Kopruszinski et al. [47] relating to the role of OX_2 receptors in trigeminal nociception. This limits our ability to comprehensively understand the role of the hypothalamic orexinergic system in the context of migraine pathogenesis. That said, these findings support the hypothesis that hypothalamic orexinergic

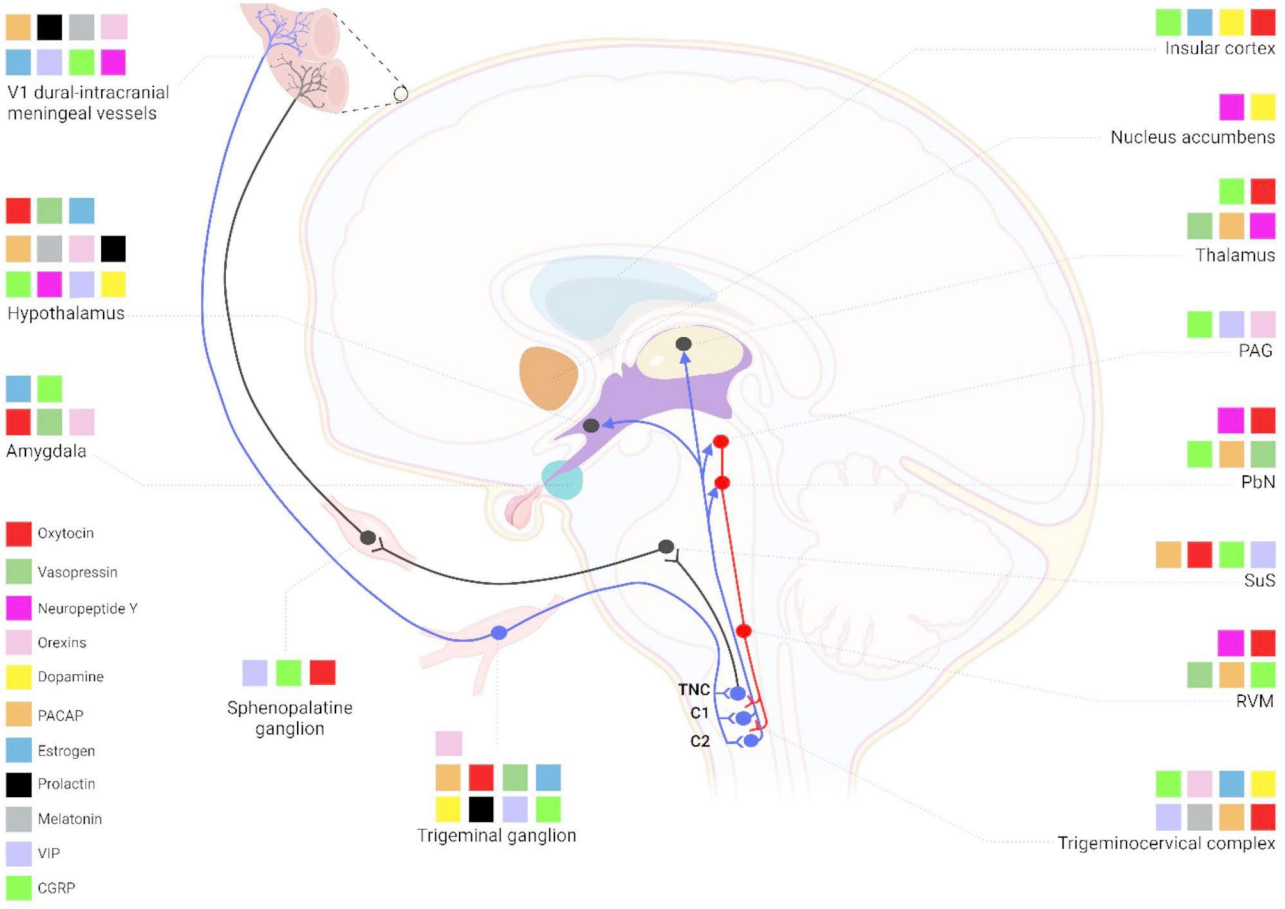

Fig. 3 Illustrative scheme for sites of action, and possible interaction, of hypothalamic-regulated neurotransmitters and hormones in migraine-related structures. This includes peptides synthesized in the hypothalamus, such as oxytocin (red), vasopressin (green), neuropeptide Y (violet), orexins (pink), dopamine (yellow) and pituitary adenylate cyclase-activating polypeptide (PACAP, orange), vasoactive intestinal peptide (VIP, purple), calcitonin gene-related peptide (CGRP, phosphorescent green), as well as hormones regulated by the hypothalamus, such as estrogen (blue), prolactin (black) and melatonin (gray). SuS, superior salivatory nucleus; PAG, periaqueductal gray matter; RVM, rostroventral medulla; PbN, parabrachial nucleus; TNC, trigeminal nucleus caudalis. Created with Biorender.com

mechanisms likely play some role in the central modulation of migraine.

To date, only one clinical trial has been conducted targeting the orexinergic system as a potential therapeutic target in migraine. In a randomized, double-blind, placebo-controlled trial, using the DORA, filorexant (10 mg), nightly for three months, no difference was observed compared to placebo in mean monthly migraine days [48]. These data do not support the effectiveness of antagonizing both orexin receptors, simultaneously, in the prevention of migraine. However, in light of the preclinical data that support a male-specific mechanism of orexins in trigeminal nociception, it is important to note that this clinical trial included 85% females compared to only 15% males [47, 49]. This may explain the lack of effectiveness in this trial and perhaps efforts should be focused on a predominantly male-specific trial population.

Neuropeptide Y (NPY)

Within the CNS, the hypothalamus is the main source of NPY, with significant levels in the PVN, arcuate nucleus, suprachiasmatic nucleus, median eminence, and dorsomedial nucleus. Elevated NPY concentrations are also present in the cerebral cortex [50, 51]. In the peripheral system, NPY is prevalent in the sympathetic nervous system, where it is co-stored and co-released with noradrenaline. NPY functions as a vasoconstrictor and interacts with orexin pathways in the hypothalamus [52]. A subpopulation of parasympathetic neurons also express NPY [51]. Additionally, NPY is found in the intra- and extracranial vasculature, contributing to the regulation of cerebral blood flow [53]. NPY interacts with a family of GPCRs, Y_1-Y_5 receptors, which mediate decrease in intracellular Ca^{2+} levels by $G_{i/o}$ inhibition of adenylate cyclase [52, 53] upon activation. The most well-known are Y_1, Y_5 and the presynaptic Y_2 receptors [54], which

has gained interest in migraine research due to its role in these migraine-related physiological mechanisms.

In clinical studies, migraine patients both with and without aura showed lower plasma NPY levels compared to controls. During attacks, NPY levels increased significantly in patients with aura and moderately in those without. Given the presence of NPY in the sympathetic nervous system, it was suggested that there may be sympathetic dysfunction in migraine patients between the attacks, where levels are low, while elevation during attacks might reflect inefficient sympathetic activation [55]. More recently, it was observed that females with CM had higher levels of NPY compared to EM or healthy controls following a fasting glucose test. Additionally, patients with CM exhibited increased insulin resistance while still having normal beta-cell function during fasting. The heightened levels of fasting NPY in individuals with migraine could potentially initiate mechanisms that raise insulin resistance by affecting energy intake and sympathoadrenal responses [56]. The data together, while not conclusive, do support a possible role of NPY in migraine mechanisms, and therefore a potential endogenous target.

In preclinical studies, NPY modulates migraine-related dural-trigeminovascular nociceptive neurons, likely mediated by Y_1 receptor activation [57], further implicating it in migraine mechanisms. Similarly, it was found that NPY signaling in the medial habenula (dorsal thalamus) induces analgesic and anxiolytic effects via the Y_1 receptor in a mouse model of migraine. Here, galanin and NPY were modulated throughout the natural estrous cycle within trigeminal ganglia (TG), suggesting that ovarian steroids likely play a regulatory role in the modulation of these hypothalamic peptides [58]. They also found that female mice exhibit distinct estrogen-dependent mechanisms that modulate trigeminal nociceptive responses. Consequently, the variations in NPY content within trigeminal neurons during the natural estrous cycle may contribute to the escalation of painful episodes during specific phases of the menstrual cycle [58]. In blood sampling studies after activation of the trigeminovascular system, NPY levels were elevated after acute or repeated TG stimulation in male rats [59]. However, neither TG nor dural electrical stimulation in cats mediated any change in NPY plasma levels [60, 61]. This is similar to observations made during migraine headache attacks [62]. These findings suggest that changes in the TG may rapidly modulate a systemic response originating from the hypothalamus [59]. The collective consideration of these findings may provide innovative insights into potential therapeutic targets for the treatment of migraine via endogenous NPY modulation and indicates that the mechanisms involved in migraine may vary based on estrous cycle/sex.

Pituitary adenylate cyclase-activating polypeptide (PACAP)

PACAP is classified within the glucagon/secretin family of hormones that also includes vasoactive intestinal peptide (VIP). It has two biologically active forms: PACAP38 and PACAP27 [63, 64]. It plays important roles in the processes of hypothalamic control of hormone release, the regulation of circadian rhythms, feeding behavior, and pain circuits [65]. Its biological actions occur through binding and activation of three known GPCRs: PAC_1, $VPAC_1$, and $VPAC_2$. PACAP38 and PACAP27 ($Kd \sim 0.5nM$) bind with high affinity to PAC_1 ($Kd \sim 0.5nM$), $VPAC_1$ and $VPAC_2$ receptors (both $Kd \sim 1nM$). It is noted however that VIP also binds all three receptors, but PAC_1 has much lower (1000-fold less) binding affinity for VIP than PACAP [66–68]. Activation of the PAC_1 receptor is believed to play a crucial role in regulating the synthesis and release of neuroendocrine hormones [64].

In clinical studies, intravenous infusion of PACAP38 elicits mild headache accompanied by sensations of heat in the body or facial area in both healthy volunteers and migraine patients [69, 70], which is followed by delayed migraine-like attacks in the majority (65–70%) of people with migraine [71, 72]. Premonitory symptoms are also identified in a subgroup of patients. PACAP38 also causes vasodilation of the cranial blood vessels [73, 74] and biochemical changes in plasma, which influence the concentrations of VIP and prolactin, but do not alter inflammatory markers such as tumor necrosis factor [75]. Additionally, blood samples taken from people during migraine headache demonstrated elevated serum levels of PACAP38 in adult EM and CM, compared to healthy controls [76]. It is noteworthy that in several studies infusion of VIP was no better than placebo at triggering migraine headache [72, 77]. Collectively, these findings suggest that elevated PACAP levels in individuals with migraine correlate with increased headache severity and frequency, as well as modifications in cranial vascular dynamics.

These data are mirrored preclinically. PACAP38 mediates activation and sensitization of dural-trigeminovascular neurons in rodents, the underlying mechanism in cranial-nociceptive symptoms in migraine, with accompanying somatosensory periorbital hypersensitivity [78–81]. PACAP mechanisms are also likely involved in trigeminal-autonomic functions [82–84]. PACAP38 promotes neuronal activation within the SuS. The SuS receives direct projections from the PVN, which also sends projections to TNC [85]. Microinjection of PACAP38, or a non-selective PAC_1 receptor antagonist, into PVN neurons shifts the responses of dural-trigeminovascular neurons. Furthermore, direct stimulation of the SuS triggers neuronal activation in the TNC via the cranial parasympathetic projection, leading to changes in

lacrimal blood flow, which indicates cranial autonomic symptoms [86]. These responses are specifically inhibited by $VPAC_1$ and PAC_1 receptor antagonists [82]. This evidence reinforces the role of PACAP and, notably, $VPAC_1$ and PAC_1 receptors in migraine mechanisms, broadening the understanding to include areas involving other cranial and central nuclei. While the precise downstream intracellular signaling mechanisms activated by PACAP during migraine remain to be elucidated, clinical and preclinical research has made progress supporting the role of cAMP signaling [87].

There have been several approaches to develop therapeutics to target PACAP and its receptors for the treatment of migraine. The first focused specifically on targeting the PAC_1 receptor with a human monoclonal antibody, (AMG301). In a multicenter, randomized, double-blind, placebo-controlled trial AMG301 showed no efficacy in migraine prevention when compared to placebo [88]. However, it has been suggested that PACAP signaling at more than one receptor may be relevant. Indeed, more recent studies have shown that VIP, when infused for a longer period, 2 h, can trigger migraine in patients [89], supporting the role of multiple PACAP receptors in mediating migraine [87, 90]. Lu AG09222 (previously ALD1910) is a humanized monoclonal antibody that directly targets both isoforms of PACAP (PACAP27 and 38). It therefore impacts PACAP-signaling through all PACAP-binding receptors and isoforms, including PAC_1 and $VPAC_{1/2}$. In a Phase II interventional, randomized, double-blind, parallel-group, placebo-controlled trial, in participants who had previously two-four treatment failures, there was a significant reduction in mean migraine days compared to placebo [91]. These data confirm that targeting PACAP and its receptors may be a relevant treatment approach for migraine, but it also supports that multiple PACAP receptor subtypes are likely relevant to the mechanisms involved.

Oxytocin and vasopressin

Oxytocin (OXT) and vasopressin (AVP) are neurohormones secreted by neurons in the PVN and SON in the hypothalamus and access the blood circulation through the posterior portion of the pituitary gland. The oxytocin (OT) and vasopressin receptors (V_{1A} and V_{1B}) are GPCRs that show cross reactivity, especially at higher levels and are widely expressed in the CNS, where they have been related to regulation of maternal and social behaviors, as well as antinociception at different levels [27, 92–96].

Clinically, intranasal administration of OXT has been reported to inhibit central sensitization, as it relates to trigeminally-related migraine pain and chronicity [97]. Intranasal OXT also decreased the frequency of attacks in CM patients [98] and serum OXT levels between attacks increased, possibly as an adaptive mechanism [99]. AVP levels have been found to be elevated in blood plasma during and after a migraine attack [100, 101]. This could be related to peripheral symptoms i.e. nausea and facial pallor present in patients during severe migraine headache attacks [102], although, contrasting data has been reported in other patients [103].

In preclinical models, OXT is highly distributed in TG and the spinal trigeminal nucleus [104]. OTR are expressed in TCC and TG under normal conditions, with expression significantly increased during the inflammatory process or in response to administration of nitroglycerin [105], supporting a possible role in the regulation of trigeminal sensory processing. OXT decreased TCC neuronal responses to dural electrical stimulation [106], and is effective at reducing mechanical hypersensitivity in models of trigeminal neuropathic pain [107]. Indeed, electrical stimulation of the PVN attenuates dural-intracranial evoked TCC neuronal responses. This inhibition is modulated by local administration of a selective OTR antagonist [18]. While the role of other neuropeptides i.e. PACAP and serotonin [85], cannot be excluded, these data suggest that local release of OXT at the level of the TCC, via PVN projections modulates the response of these migraine-related neurons. Similarly, AVP and its receptors (V_{1A} and V_{1B}) are expressed by Aδ-fibers within TG. They are also detected in PVN and SON suggesting a possible role of AVP modulation on trigeminal sensory inputs [108].

The presence of sex differences in OXT and AVP levels and receptor expression in brain areas has been a topic of interest in sexual, social, and emotional behaviors as well as mental disorders [109–112]. In this context, expression of OTR, V_{1A} and V_{1B} in TG neurons is higher in female rats when compared to males, and OTR expression is reduced in females in the ventromedial hypothalamus and amygdala among other forebrain structures (108). These data point to possible sex-dependent mechanisms of these hypothalamic peptides on trigeminal sensory processing.

The role of the hypothalamus in migraine triggers

Migraine is predominantly regarded as a disorder characterized by altered homeostasis, whereby disturbances in stress responses, sleep, and feeding may trigger and manifest as symptomatic of a migraine attack. Migraine also shows a female-dominant prevalence signaling a possible role of sex hormones. Given that many of these functions are regulated by the hypothalamus, including stress (hypothalamus-pituitary-adrenal axis), food intake (energy homeostasis), sleep (circadian rhythm) and sex behavior (hypothalamus-pituitary-gonadal axis and prolactin secretion), it is plausible that aberrant hypothalamic mechanisms contribute significantly to the pathogenesis of migraine from its early stages and

throughout its progression. Indeed, several imaging studies have demonstrated altered hypothalamic activation in the preictal and premonitory phases of migraine, before any headache occurs [7, 113, 114]. Further, symptoms in the premonitory phase are strongly associated with hypothalamic activation, such as food craving, excessive tiredness, and stress and are often confused as triggers in patients. In a clinical study, nitroglycerin was used to trigger migraine and premonitory phenomena were observed [115]. There was a strong overlap with described premonitory symptoms including altered sleep patterns, food craving, yawning, and irritability (mood change) and perceived patient triggers. These data suggest that these non-headache symptoms, rather than triggers, more likely represent early brain manifestations of a migraine attack that are all linked to the hypothalamus and an indication of hypothalamic changes mediating/triggering the subsequent migraine headache.

Hypothalamus in stress response and migraine

Stress is a natural response of living organisms to environmental disturbances. Normal reactivity to acute stressors and the timely cessation of the stress response are essential for survival and adaptation [116, 117]. In contrast, chronic stressors can have harmful effects, leading to detrimental changes in the brain and other organs [118]. Long-term stressors are associated with the development and/or exacerbation of neurologic disorders, including migraine and other headache disorders. Numerous studies highlight stress as the leading trigger for migraine, responsible for almost 80% of all attacks.

The response to stressors is through two vital mechanisms. First, activation of the hypothalamic-pituitary-adrenocortical (HPA) axis which triggers the release of cortisol and corticosterone from the adrenal cortex into the bloodstream. Second, the sympathetic-adrenergic system activates, releasing adrenaline and noradrenaline from the adrenal medulla and nerve terminals into the circulatory system. This response is a crucial indicator of neuroendocrine and autonomic reactions, demonstrating their innate ability to cope with stress effectively [117, 119–121]. Both responses to stress seem to be altered in migraine patients and animal models and show a clear sexual dimorphism [122–124]. This is relevant, as we know migraine disproportionately affects women [122, 124–126].

In migraine, higher perceived stress is associated with higher migraine frequency [36, 127–129]. Further, elevated levels of endogenous glucocorticoids, particularly cortisol, are linked to migraine [130–133], regardless of age or sex [134]. Elevated cortisol and corticosterone levels in serum and CSF are strongly associated with higher migraine frequency and disability in CM when compared to EM [135]. In addition, in female patients, cyclical premenstrual dysfunction of opioid-mediated hypothalamic control over the HPA axis has been reported [136]. Here, naloxone treatment and corticotropin-releasing hormone infusion significantly increased β-endorphins and cortisol levels in control subjects, regardless of menstrual cycle phase, but in menstrual migraine patients, only during the follicular phases. These data suggest an impairment in this critical adaptive mechanism involved in stress responses and pain regulation, which could establish a causal link between menstrual-related migraine attacks and premenstrual opioid hyposensitivity. There is however data to support the efficacy of glucocorticoids in the treatment of migraine. Dexamethasone, a potent synthetic glucocorticoid, was classified as 'possibly effective' in the acute treatment of migraine, as level C evidence [137]. While further research is required, it is clear, alterations in the levels of important stress-related neurotransmitters can impact migraine outcomes.

In preclinical studies, stress (unpredictable sound or restraint) can mediate migraine-like periorbital hypersensitivity and grimace pain behaviors in mice, with a sexual dimorphic response [138–140]. Female mice exhibited higher levels of mechanical allodynia, pain-related grimacing, and anxiety-like symptoms compared to males after stress induction. Females also had increased plasma levels of inflammatory cytokines (IL-6 and TNF-α) and CGRP [139]. In male mice exposed to prolonged restraint stress, it was demonstrated that elevated corticosterone levels activate the NMDA receptor, triggering microglia proliferation. This response was effectively inhibited by blocking corticosterone synthesis, the glucocorticoid receptor, or the NMDA receptor. These findings suggest that stress and elevated glucocorticoid levels drive a pro-inflammatory microglia response in the CNS, potentially contributing to stress-related inflammatory conditions, including migraine [141]. When restraint stress is used to prime responses to a nitric oxide donor, both acute and primed facial hypersensitivity are blocked by either a corticosterone synthesis inhibitor or a glucocorticoid receptor inhibitor, in both male and female mice. However, repeated corticosterone (CORT) injections, in the absence of stress, only induced facial mechanical hypersensitivity in female mice. These data suggest that while CORT synthesis is crucial for stress-induced behavioral responses in both sexes, it only triggers stress-like hypersensitivity in females [140].

Regarding the sympathetic-adrenergic system, it has been proposed that migraine is linked to chronic sympathetic dysfunction. It is stated that during a migraine headache attack, there is a relative depletion of sympathetic noradrenaline stores. This depletion is accompanied by an increase in the release of other sympathetic transmitters, including dopamine, prostaglandins, ATP, and adenosine. This imbalance in neurotransmitter

activity may contribute to the onset and progression of migraine [142]. Sympathetic dysregulation observed in people with migraine adds support for α-adrenergic agonists and β-adrenergic antagonists in migraine prevention, with their use reducing migraine frequency. Sympathetic postganglionic neurons, activated by stress, play a crucial role in linking immune cells to migraine, as they innervate the dura and contain receptors targeted by triptans. It is further reported that migraine attacks are partly triggered by stress-induced shifts in the balance of pro- and anti-inflammatory mediators in dural immune cells, which activate and sensitize dural afferents. It was demonstrated that stress increases proinflammatory mediators and decreases anti-inflammatory mediators in females, supporting the role of dural immune cells in migraine initiation [123].

Stress also influences sex hormones, and it is notably different between the sexes. Research indicates that acute stress reduces estradiol and testosterone levels in the plasma of female rats, while they remain unchanged in male rats [143]. People with migraine experience neuroendocrine dysregulation as a clinical manifestation of migraine, resulting in increased diurnal cortisol concentration when compared to healthy controls. Also, females with migraine experience decreased estrogen concentrations during the luteal phase of the menstrual cycle [144]. In contrast, testosterone can suppress the activity of the HPA axis, which means higher testosterone levels can lower levels of glucocorticoids and other stress hormones [145, 146].

The role of stress in migraine is almost undeniable, and the impact of sex and sex hormones suggests a dimorphic relationship, to some extent. However, the mechanisms by which stress impacts onset, persistence, frequency, or severity of migraine, and the exact role of sex hormones, remain poorly understood. This uncertainty arises from the complex neurobiological and pathophysiological processes underlying migraine and the role hypothalamic regulation of homeostasis has on this.

Hypothalamus in food disruption and migraine

Skipping meals is one of the most common and long-standing reasons cited as a migraine trigger [147]. Research indicates that both the consumption of specific foods, such as those high in simple sugars or excessive carbohydrates, and the absence of food can precipitate migraine attacks [148]. This section focusses primarily on the significance of fasting or 'skipping meals' as a trigger for headache, including the physiological processes involved, such as hypoglycemia [147], dehydration [149], elevated free fatty acids (FFA) [150], activation of the sympathetic nervous system [151], hypothalamic dysfunction [152], insulin fluctuations [153], and other hormonal changes proposed as potential mechanisms underlying this effect.

The hypothalamus, a critical center for appetite regulation, is activated in specific regions, both prior to and during migraine episodes [8, 113, 154]. Fasting triggers adaptive mechanisms critical for survival, including activating the HPA axis and release of glucocorticoid hormones to mobilize energy reserves [155]. In the first four hours, hormonal and metabolic signals inform the hypothalamus of starvation. The hypothalamus is critical to this process, responding with the synthesis of neuropeptides that promote catabolic activity, a process further amplified by adrenocorticotropic hormone (ACTH), leptin, and adrenal neural activity [155–157]. In this sense, the increase in circulating corticosteroids associated with insulin-induced hypoglycemia is due to adrenocortical activation [154]. An increase in plasma cortisol in response to insulin-induced hypoglycemia indicates the ability of the hypothalamus to secrete corticotropin releasing factor (CRF), which, in turn, stimulates the anterior pituitary to secrete ACTH and an intact adrenal cortex that responds to ACTH. Feeding behaviors and metabolic disorders are clinically correlated with migraine, in which hunger and food cravings often serve as premonitory symptoms in individuals living with migraine [158].

One notable example of this phenomenon is observed among the Muslim population during Ramadan. Several studies have reported a significant increase in the frequency of migraine attacks among individuals with a history of migraine [159–162], particularly during the first week of fasting. Interestingly, the frequency of these attacks tends to decrease after approximately ten days, a pattern that has been partially attributed to physiological changes, including the onset of insulin resistance and the impact of pronounced dehydration [159, 163]. Two studies on insulin regulation in the female population support this point. In one, CM is strongly associated with insulin resistance, suggesting that high insulin levels could play a significant role in CM pathogenesis, supported by the number of insulin receptors in the hypothalamic and brainstem regions [164]. The other study evaluated 83 female migraine patients and examined the relationship between NPY, which is produced in the PVN, insulin resistance, and β-cell insulin secretion, during a glucose tolerance test. Fasting glucose levels were significantly higher in CM and EM, but plasma glucose and insulin levels were similar across CM, EM, and control subjects during the test. CM patients exhibited greater insulin resistance and higher NPY levels than EM and controls. In addition, a positive correlation was found between NPY and fasting glucagon-like peptide-1 levels in CM [56]. Moreover, hyperinsulinemia is associated with migraine and demonstrates a correlation with elevated

nitric oxide stress in both female and male patients [165]. These results suggest CM may maintain normal β-cell function to cope with increased insulin demand. At the same time, elevated NPY could contribute to insulin resistance via altered energy intake and activation of the sympathoadrenal system.

Experimental animal studies demonstrate that dural-inflammatory soup mediates central sensitization of dural-trigeminovascular neurons, activating ascending neuronal pathways that influence parabrachial and ventromedial hypothalamic nuclei. It also leads to suppressed food intake and alterations in feeding behavior [166]. This supports that migraine patients may similarly adjust their food intake in response to trigeminally mediated pain and the resulting activation of specific hypothalamic nuclei. In this context, it has been shown that peptides involved in regulating appetite and glucose, such as insulin, glucagon, and leptin, impact migraine-related nociceptive processing in the trigeminovascular system and hypothalamus. In male rats, insulin and leptin lowered blood glucose, while glucagon raised it, but all three peptides inhibited dural-evoked neuronal firing in the TCC. Moreover, insulin and leptin reduced TCC pERK1/2 expression, but glucagon increased it. Leptin uniquely decreased pERK1/2 expression in the hypothalamic arcuate nucleus, suggesting its specific role in migraine neurobiology [167]. These data support that endocrine peptides involved in feeding regulation can modulate neuronal responses in the TCC following dural nociceptive activation, and these effects appear to be part of a homeostatic feedback mechanism, with disruptions potentially impacting the trigeminovascular system.

Hypothalamus in sleep alterations and migraine

The relationship between migraine and sleep alterations is well established and can be described as bidirectional [168, 169]. Studies show that poor sleep quality can be a trigger of migraine episodes [170–172], while migraine headache attacks can negatively affect sleep patterns causing fatigue and increased day sleepiness [173, 174]. Furthermore, many people with migraine report waking with a migraine headache, whether waking at their natural time with headache or the headache causes them to wake up. While the comorbidity of migraine and sleep disorders is widely described [170, 175, 176], the exact mechanism of the relation between migraine and sleep disturbances has not been elucidated. Here, we will specifically focus on the relationship between the hypothalamic suprachiasmatic nucleus (SCN), melatonin, and orexins.

The hypothalamic SCN is the referent structure in the establishment of daily circadian rhythm. SCN neurons receive inputs from the retina and possess intrinsic circadian regulatory mechanisms that help establish day-night cycle, where their firing rates regulate the activity of other brain areas involved in many circadian behaviors, such as food intake, hormone secretion, autonomic responses, and sleep [177–179]. This regulatory process involves neurotransmitters secreted within the hypothalamus, such as PACAP, AVP, and VIP [179]. In this context, changes in the circadian rhythm have been reported in migraine patients in which circadian misalignment and delayed sleep hours are correlated with higher frequency and intensity of migraine attacks, independent of the sleep hours [180]. The intrinsic circadian rhythm is different in females, tending to be shorter with sleep initiation on a later scale compared to males on the same biological clock [181, 182]. Both androgen and estrogen receptors are expressed in the SCN with significant differences in males and females [183, 184]. Given that the SCN receives trigeminal sensory inputs [12] it is possible that sex-related differences at this level contribute to the prevalence of migraine in females, although this is currently an understudied area. For a detailed review of circadian rhythms and migraine, we suggest the following references [35, 185, 186].

Melatonin, a hormone involved in sleep-wake cycle and released by the pineal gland under hypothalamic regulation [187, 188], is also related to migraine pathophysiology. Studies in animals show that melatonin can modulate TNC neurons [189], induce CGRP downregulation at the spinal level [190], and decrease CGRP release and nitric oxide production in cell cultures obtained from women with menstrual migraine [191]. It is thought that this is through melatonin antioxidant and anti-inflammatory effects. Additionally, melatonin directly affects the activity of hypothalamic nuclei. This is through regulation of local GABAergic activity in SCN and lateral hypothalamus [192, 193], increased synthesis of POMC in the arcuate nucleus [194], regulation of OXT and AVP secretion in the neurohypophysis [195], altering dopamine-glutamate interaction in the anterior hypothalamus [196] and regulation of the hypothalamic-pituitary thyroid and gonadal axis [197–199]. Lastly, melatonin supplements (3 mg) have shown positive results in migraine prevention in comparison with placebo and amitriptyline [200], however, these results were contrasted with little effect when dosing with 2 mg [201]. Indeed, the circadian nature of migraine attacks and decreased levels of melatonin, especially during episodes in patients [202, 203], signal a possible protective mechanism of melatonin in migraine, where its alteration, either by sleep-related or sex-related conditions, could work as a trigger for an attack.

The previously mentioned orexins represent another possible mechanism of interaction between sleep and migraine [204]. Orexinergic neurons are in the lateral and posterior hypothalamus. They send projections to

multiple brain areas that provide a regulatory function over autonomic responses and sleep-wake cycle [205]. While the detailed role of orexins in migraine was discussed earlier, it is worth noting that similar to melatonin, circadian changes in orexin levels [206], increased orexin levels in chronic migraine patients [37], the high prevalence of migraine in narcolepsy patients [207], a disorder known to be related by altered orexinergic transmission [208], and the aforementioned findings of the role of orexins on trigeminal sensory processing, signal a possible role of altered hypothalamic mechanisms that could explain the strong correlation between sleep disorders and migraine.

The role of the hypothalamus in sexual dimorphism and migraine

Sex hormones

It is long established that migraine is more prevalent in women than men, with an often reported 3:1 ratio. This dimorphism is also borne out in various animal models of migraine that are reviewed below. This includes the acute nitroglycerin model. Here, it has been demonstrated that male rats exhibit lower Fos expression levels (indicative of reduced neuronal activation) in the PVN, amygdala and TNC after nitroglycerin compared to freely cycling females [209]. Fundamentally, this suggests that female rodents may be more predisposed to migraine-like neuronal changes. Intuitively, this may suggest that circulating sex hormones may have a role to play in this prevalence. The hypothalamus is crucial to this process. It regulates the secretion of sex hormones by the production of gonadotropin-releasing hormone, which stimulates the anterior pituitary gland to secrete follicular stimulating hormone (FSH) and luteinizing hormone (LH) into the blood stream. These hormones reach the gonads (ovaries or testes) to regulate the development of sex cells and the production of sex hormones (estrogen/progesterone/testosterone), which in turn produces a negative feedback mechanism on both hypothalamic and pituitary gland cells. The high prevalence of migraine in females, especially during their reproductive years, and the incidence of menstrual-associated migraine attacks, signal sex hormones as an active target in understanding migraine pathogenesis and management [210–212].

The International Classification of Headache Disorders-3 (ICHD-3) classifies the presence of migraine attacks with or without aura during the perimenstrual period as pure menstrual migraine, with the presence of these attacks during this period plus other times of the menstrual cycle as menstrual-related migraine [213]. The pathophysiology of menstrual migraine has not been fully elucidated, however, it was initially attributed to low estrogen levels in female patients with migraine [214]. Indeed, an estrogen threshold (45-50pg/mL) below which migraine attacks tend to increase has been described [214, 215] and as a consequence estrogen has been suggested in migraine prevention [216]. This is supported by a combination of hormonal contraceptives with oral replacement therapy decreasing the number of attacks, although this comes with concerns in safety [217, 218]. Finally, studies in rats demonstrate that high estrogen levels potentiate cortical spreading depression (CSD), which was reversed by estrogen withdrawal [219].

Beyond absolute levels of estrogen, some studies have described that physiological fluctuation of estrogen levels could be the possible mechanism of this phenomenon. Decreased estrogen levels are associated with migraine attacks without aura, while elevation of estrogen levels might cause attacks with aura [220–222]. The perimenstrual period is characterized by a drop in estrogen levels coinciding with migraine without aura in menstrual-associated migraine [223]. Females who suffer from migraine show rapid drop in estrogen at the late part of the luteal phase compared to controls, although this did not seem to affect the frequency of headache attacks reported [224]. These observations are not conclusive, therefore other factors, such as previous exposure, hormonal therapy and menstrual variations may also be relevant [212].

Estrogen receptor-α (ER-α) and β (ER-β) are expressed in migraine relevant areas throughout the brain, including the LC, amygdala and many hypothalamic nuclei, such as the SON and PVN, where they are widely present in oxytocinergic neuronal populations [225]. At the trigeminal level, estrogen receptors are expressed in the TCC, TG [226], and at the level of the cranial vasculature [227], supporting its direct role on sensory processing at this level. However, males have lower expression of estrogen receptors in the trigeminal system compared to females [226, 227]. Together, these data suggest that there is some basis for the estrogen withdrawal theory of migraine and the higher prevalence of migraine in females, although it is far from conclusive [210, 228, 229].

The role of progesterone in migraine is more commonly studied in combination with estrogen, following the hypothesis that they have opposing effects in the brain with progesterone inhibiting neurotransmission and estrogen stimulating it [230]. No significant changes in progesterone and allopregnanolone (an endogenous neuro-steroid synthesized from progesterone) levels have been observed in female patients, however its brain levels could vary between sexes and in different phases of the menstrual cycle [230]. Also, levels of allopregnanolone are decreased in menstrual-associated and postmenopausal migraine, even when serum progesterone levels are no different to controls [231]. In rats, progesterone and its receptor are expressed in the TG and hypothalamus with higher expression in females [232]. Interestingly, progesterone enhances the effects of

capsaicin-evoked dural CGRP release and vasodilation exclusively in males [232]. These data signal a possible role of progesterone on trigeminal sensory processing that might illustrate sexual dimorphism.

The lower prevalence of migraine in males could also be considered in the context of higher levels of testosterone. Indeed, males suffering from CM showed decreased levels of testosterone [233], and use of androgens decreased headache attacks in females with menstrual migraine [234, 235]. A neuroprotective effect of testosterone was observed in familial hemiplegic migraine 1 (FHM1) mice, which demonstrated a decreased susceptibility to CSD development [236]. The potentially protective effect of testosterone in migraine [237] could be attributed to modulation of serotoninergic transmission through restoration of 5-HT_{1A} receptor expression in stress-related conditions [238], regulation of blood flow [239], and inhibition of nociceptive signaling [240] as observed in temporomandibular joint pain [241], which is a commonly comorbid in migraine patients [242]. Together, these may contribute to higher levels of testosterone making it less likely that migraine is triggered.

Prolactin

Prolactin (PRL) is a 199-amino-acid polypeptide hormone, primarily produced by lactotrophic cells in the anterior pituitary gland, with additional synthesis in various extra-pituitary tissues, including the placenta, uterus, ovaries, prostate, and immune system [243–245]. There are three different circulating PRL forms: monomer, dimer and multimer, which exert their biological actions through the prolactin receptor (PRLR), a membrane-bound protein belonging to the cytokine receptor superfamily. PRL is unique among pituitary hormones because its secretion is controlled by dopamine via D_2 receptors within the hypothalamic arcuate nucleus, not hypothalamic-releasing hormones [246, 247]. However, PRL secretion can be stimulated by estrogen, thyrotropin-releasing hormone, and vasoactive intestinal peptide [247]. PRL participates in diverse cellular signaling pathways, and emerging evidence indicates its involvement in mechanisms underlying migraine. Indeed, in patients with hyperprolactinemia, 65.2% showed migraine-like symptoms regardless of the cause. Treatment with a dopamine agonist alleviated headache in 75% of cases [248]. Also, in patients with prolactinomas, headache improved or resolved after one year of dopamine agonist treatment, coinciding with a 47% tumor size reduction. Together, it indicates that headaches linked to hyperprolactinemia are resolved upon the resolution of PRL levels [249].

Many studies have looked at prolactin levels in serum of females with migraine and linked this with migraine prevalence. In a systematic review of clinical studies, the main findings are that serum prolactin levels are higher in females with migraine compared to healthy controls [250]. Further, PRL levels should be viewed as a potential factor in worsening migraine symptoms [251], with increased serum PRL indicative of a higher frequency of migraine attacks in CM and EM patients [252], and a reduction in PRL levels correlating with an improvement, linking the normalization of these levels to decreased headache severity in follow-ups. Indeed, individuals diagnosed with pituitary microadenomas and hyperprolactinemia, hyperprolactinemia seems to play a contributory role in the onset of pain within specific subgroups of patients with migraine [253]. While these data are compelling, there is also some contradictory data. A decrease in serum prolactin levels has also been observed during migraine headache attacks. Here, the authors propose that this may be attributed to heightened activity within the dopaminergic system [254].

The role of prolactin and its receptors in the sexual dimorphism of pain and migraine is also supported by preclinical studies. Indeed, spinal application of PRL, taken from suckled lactating rats attenuated the nociceptive firing of wide dynamic range spinal dorsal horn neurons in male rats, while PRL from non-suckled lactating rats increased responses of nociceptive neurons in males. The data indicate that nociceptive responses of spinal dorsal horn cells is dependent on the physiological state of the rats [255]. The important interaction between CGRP and PRL in the meninges has also been studied. Direct administration of PRL onto the dura mater caused prolonged migraine-like behaviors in cycling and ovariectomized female rodents, while males showed no such responses. Further, PRLR was expressed on dural afferent nerves in females, with little expression in males. PRL increased neuronal excitability in female TG neurons innervating the dura mater and sensitized CGRP release in only female ex vivo dura. Deletion of PRLR from sensory neurons in these studies significantly reduced migraine-related responses to dural CGRP [256]. Together, these data support that bidirectional CGRP and PRL interactions in the meninges may lead to female-specific responses, contributing to the higher prevalence of migraine in women. This mechanism was confirmed in a restraint stress migraine model. Stress increased serum PRL in both female and male mice, but more so in females. Bromocriptine (PRL-release inhibitor) significantly reduced serum PRL in both sexes but was only able to attenuate stress-induced nociceptive behaviors in female mice [257]. These results suggest that PRL acts in a female-specific way on stress-induced behaviors in this migraine model and therefore represents a potentially novel therapeutic target, specifically in females with migraine. Furthermore, a sexually dimorphic neuroendocrine mechanism is also demonstrated in the sumatriptan

medication overuse headache (MOH) model. Here, sumatriptan MOH only caused down-regulation of the PRLR in the TG of female mice, and only in female mice did MOH periorbital allodynia respond to cabergoline, which inhibits circulating PRL, and prevented the down-regulation of PRLR [258].

These data link hypothalamic migraine mechanisms via prolactin release and a potential sexual dimorphism. In another study, restraint stress activated the kappa opioid receptor (κ receptors) on tuberoinfundibular dopaminergic neurons, resulting in an increase in circulating prolactin in female mice [259]. The authors argue that this represents the first mechanistic link between stress-induced hypothalamic activation and female-specific trigeminal nociceptors giving rise to trigeminal sensitization and migraine-like pain, through the dysregulation of prolactin receptor isoforms. They also reported that repeated use of κ receptor agonists leads to trigeminal sensitization in response to normally innocuous stimuli, but only in females is this mechanism dependent on PRL/PRLR mechanisms [260]. Together, these studies reveal a previously unrecognized neuroendocrine mechanism linking the hypothalamus to nociceptor sensitization that increases the risk of migraine pain in females and suggests opportunities for novel sex-specific therapies.

Concluding remarks and future perspectives

Migraine is a complex neurovascular disorder, and while we do not fully understand its pathogenesis, growing evidence supports the role of the hypothalamus in migraine mechanisms and the generation of specific migraine symptoms, including headache. The importance of the hypothalamus in normal human function is perhaps crucial to understanding why it may be so integral to migraine pathogenesis. It has neural connections with a complex array of structures in the brain involved in migraine symptoms, with the release and modulation of a huge number of endogenous neurotransmitters and hormones. It is believed to regulate the control of homeostasis related to feeding, sleep/wake, autonomic function, and our response to stress, and possible sexual dimorphism in disease, amongst many other human behaviors, but all linked to possible triggers of migraine. It is also specifically activated as a response to environmental, dietary, hormonal, and sensory factors. This review has highlighted the complex ways the hypothalamus is likely involved in regulating endogenous migraine mechanisms, ictally, preictal, and interictally, through many hypothalamic-related molecules.

While it is perhaps too simplistic to say that it 'triggers' or 'mediates' migraine and migraine headache, or its activation is a cause of specific symptoms, it seems to be an appropriate way to assess hypothalamic involvement in migraine. Firstly, the large number of nociceptive projections of TCC neurons to hypothalamic nuclei and neurons that directly regulate many of the common migraine symptoms outlines a pathway for pain signals processed through the TCC to be transmitted to the hypothalamus to mediate these symptoms. This contributes to affective, autonomic, endocrine and physiological responses that patients identify as migraine associated. Both ascending and descending hypothalamic projections, via the release of many neurotransmitters (orexins, NPY, leptin, oxytocin, PACAP) likely contribute to the craniofacial nociceptive experience in migraine. Secondly, it is known that the hypothalamus has increased activity preictal and indeed fluctuating activity during the interictal period [7, 261]. It suggests that the homeostatic balance can shift and the threshold for the onset of a migraine attack reduces, such that established migraine triggers (feeding disruption, sleep/wake changes, stress) that directly affect hypothalamic homeostatic regulation change the brain state, so it becomes more likely to mediate migraine symptoms. Activation of hypothalamic nuclei during the premonitory phase and the presentation of symptoms during the pre-headache phase, confirms a mechanistic rationale for the role of the hypothalamus in migraine attack generation taking place prior to the engagement of trigeminovascular mechanisms and the onset of headache. Instead, it supports that it can directly initiate many associated symptoms, not just as the consequence of ascending nociceptive processing that can result in these symptoms.

The role of the hypothalamus in the regulation of sex hormones also goes someway to potentially implicate the hypothalamus in migraine sexual dimorphism. The curious cases of PRL and OX_2 receptors appearing to be either female [258, 259] or male-specific [47], respectively, and as potential novel targets for migraine in a sex-dependent manner, adds support to the role of the hypothalamus in these mechanisms. While this does not fully explain the genetic prevalence of migraine in females, the important role of the hypothalamus in the regulation of sex hormones and their potential role in migraine mechanisms supports that the hypothalamus may be crucial to our understanding. The greatest weakness in our understanding of these sex-related mechanisms is that up until 2014, sex was not fully acknowledged as an important biological variable in preclinical research supported by many funding bodies, and therefore it was not standard to include both male and female rodents in preclinical studies. Therefore, many gaps in our understanding exist. In the coming years it is hoped that research and its funding sources maintain their commitment to using both males and females, enabling us to learn more about where differences do occur, and also where both sexes are aligned.

In summary, it is believed that targeting endogenous hypothalamus-related molecules represents a potentially

promising strategy to both understand migraine mechanisms, but also for the development of therapeutics that might offer personalized treatment approaches. Current preclinical studies have already identified several sex-related mechanisms, via endogenous hypothalamic neurotransmitters that could lead to sex-specific treatments. It is likely that with more research additional novel and precision targets may be identified that might modulate endogenous hypothalamic mechanisms that can benefit specific migraine phenotypes.

Abbreviations

ACTH	Adrenocorticotropic hormone
AVP	Vasopressin
CM	Chronic migraine
CSD	Cortical spreading depression
DMH	Dorsomedial hypothalamus
EM	Episodic migraine
ER1	Estrogen receptors type 1
ER2	Estrogen receptors type 2
GPCR	G-protein-coupled receptors
HPA	Hypothalamic-pituitary-adrenocortical
MOH	Medication-overuse headache
NPY	Neuropeptide Y
OT	Oxytocin
OTR	Oxytocin receptors
OxA	Orexin A
OxB	Orexin B
PACAP	Pituitary adenylate cyclase-activating peptide
PAG	Periaqueductal grey matter
PH	Posterior hypothalamic area
PRL	Prolactin
PRLR	Prolactin receptor
PVN	Paraventricular hypothalamic nucleus
RVM	Rostral ventromedial medulla
SCN	Suprachiasmatic nucleus
SON	Supraoptic hypothalamic nucleus
SuS	Superior salivatory nucleus
TCC	Trigeminocervical complex
TG	Trigeminal ganglia
TNC	Trigeminal nucleus caudalis

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