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REVIEW

Potential Roles of G Protein-Coupled Receptor 30 (GPR30) in Migraine Pathophysiology

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Abstract: Migraine is a highly prevalent and disabling neurological disorder with multiple hypotheses regarding its pathogenesis. G protein-coupled receptor 30 (GPR30), a member of the G protein-coupled receptor family, was once considered a membrane estrogen receptor. GPR30 is highly expressed in migraine-associated core tissues such as the trigeminal ganglion and exerts an indirect regulatory effect on the pathophysiological processes of migraine, yet there remain controversies over its specific molecular mechanisms and whether it is involved in estrogen-mediated regulation. This review systematically summarizes the latest research advances in the effects of GPR30 on the pathogenesis of migraine, with a focus on the molecular structure, ligand profile, distribution characteristics in the nervous system, related signal transduction pathways of GPR30, as well as its regulatory effects on migraine-associated neural functions. Existing studies have mainly reported the impacts of GPR30 on migraine-related signal pathways and neural functions in neurological diseases, but only verified the correlation between GPR30 and these signal pathways, with contradictory conclusions regarding its regulation of neurovascular functions. In clinical research, there is a lack of evidence from migraine-specific therapeutic clinical trials targeting GPR30, and no estrogen-related evidence chain has been established. Overall, GPR30 may serve as a potential novel target for the prevention and treatment of migraine, and the existing challenges also provide new research perspectives for the development of GPR30-targeted migraine-specific therapies.

Keywords: G protein-coupled receptor 30, GPR30, G protein-coupled estrogen receptor, GPER, migraine

Introduction

Migraine ranks as the second leading cause of disability among neurological disorders and the third most prevalent disease globally.[1] A distinct gender predilection is observed in migraine, with the female-to-male prevalence ratio ranging from 2:1 to 3:1. Moreover, 50% to 60% of female migraineurs suffer from menstrually related migraine,[2] which underscores a close correlation between migraine onset and estrogen levels.

The pathophysiological mechanisms underlying migraine remain incompletely understood. The trigeminovascular theory serves as the mainstream hypothesis, encompassing neurotransmitter imbalance, neuroinflammation, and neurovascular interactions.[3] Based on the gender predilection of migraine, the estrogen withdrawal hypothesis was proposed.[4,5] This hypothesis has been extensively investigated but remains a subject of controversy. Current preventive and therapeutic strategies primarily target imbalances of neurotransmitters, including calcitonin gene-related peptide (CGRP) and 5-hydroxytryptamine (5-HT).[6–9] Nevertheless, existing medications fail to provide benefits to all patients11. Clinical application of estrogen for migraine treatment has demonstrated preliminary efficacy, yet improper use may trigger migraine attacks. Such attacks are associated with fluctuations in hormone levels, dosage, and rate of change,[10–12] thereby limiting the clinical utility of estrogen. Consequently, there is an urgent need to explore alternative regulatory targets to resolve the clinical dilemmas associated with direct estrogen administration. Recent advancements in biological

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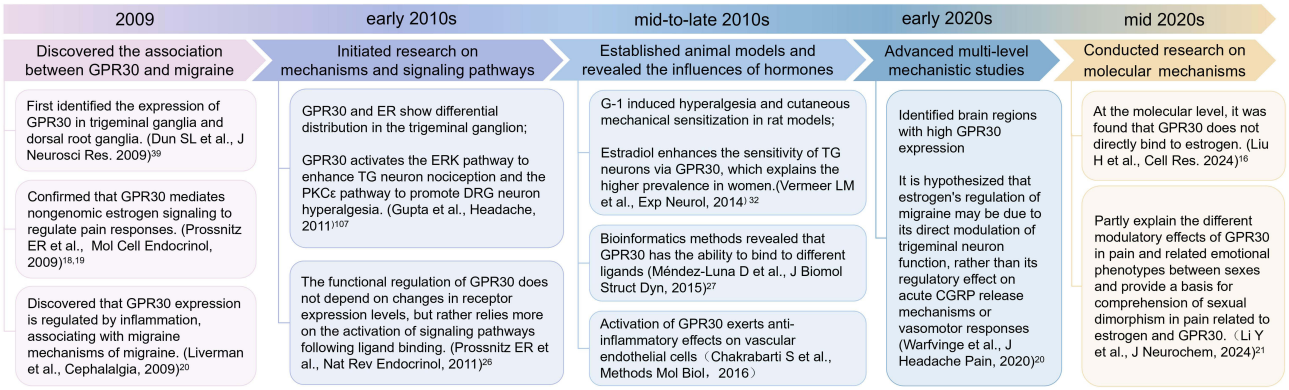

Figure 1 Key studies on the role of GPR30 in migraine.

agents for migraine treatment, including real-world evidence, have offered new insights into therapeutic development.[13,14] Novel biological agents targeting migraine pathophysiology have exhibited promising efficacy in real-world settings, which supports the value of exploring new therapeutic targets.[15,16]

Estrogen exerts its biological effects primarily through two canonical nuclear estrogen receptors, ERα and ERβ.[17] These receptors act as ligand-dependent transcription factors to regulate gene expression over a time frame of hours to days. G protein-coupled receptor 30 (GPR30), also known as GPER, is a G protein-coupled receptor frequently described as a membrane estrogen receptor.[18,19] However, the assertion that it is the only membrane estrogen receptor remains controversial. In addition, the structural characteristics of GPR30 are debated; inconsistencies exist in research regarding its transmembrane domain organization and ligand-binding pocket structure, and these inconsistencies hinder the understanding of its functional mechanisms. Since the association between GPR30 and migraine pathogenesis was first proposed in 2009,[20] research in this field has advanced steadily.[21] Studies have confirmed that GPR30 regulates neuroinflammatory responses,[22,23] mediates the release of various neurotransmitters,[5] modulates bioelectrical signals,[24] and inhibits central nociceptive sensitization[25] (Figure 1). It is important to emphasize that GPR30 should not be simply considered an alternative to classical estrogen receptors. Its unique regulatory role in migraine, which is either independent of or complementary to ERα and ERβ, deserves in-depth exploration. Summarizing the effects of GPR30 on migraine not only deepens our understanding of the disease's pathophysiology but also provides research ideas and a theoretical foundation for the development of novel therapeutic strategies.

Molecular Structure, Ligand Profile, and Tissue Distribution of GPR30

The human GPR30 gene is located on human chromosome 7p22.3 and encodes a 375-amino-acid G protein-coupled receptor with a seven-transmembrane domain.[15] Cryo-electron microscopy studies have resolved the high-resolution structure of GPR30.[16] Conformational changes in its transmembrane helices are critical for ligand binding.[26–29] Unlike the generic structural description of traditional G protein-coupled receptors (GPCRs), The short N-terminus without glycosylation modification and the rich serine/threonine phosphorylation site at the C-terminus of GPR30 are the molecular basis for its ligand binding specificity and signaling bias,[30,31] which is closely related to the regulation of pain signaling related to migraine.

The endogenous ligand profile of GPR30 and its binding relationship with estrogen remain a key controversy in current research, which is critical for elucidating its role in migraine pathogenesis. Early preclinical studies have identified a diverse range of ligands for GPR30, including endogenous hormones represented by 17β-estradiol (E2),[32] bisphenol A (BPA),[33] synthetic ligands such as G1 and G15,[34] natural plant components including quercetin and curcumin, selective estrogen receptor modulators (SERMs) and selective estrogen receptor downregulators (SERDs).[35] However, recent structural biological analyses using high-resolution cryo-electron microscopy have directly challenged this classical view by demonstrating that GPR30 does not bind to estrogen in a direct ligand-receptor manner.[16] This groundbreaking conclusion subverts the long-standing understanding of GPR30 as a direct estrogen receptor and

redefines the nature of its interaction with the estrogen signaling pathway. Collectively, this key contradiction indicates that the association between GPR30 and estrogen signaling in migraine regulation is unlikely to rely on direct ligand-receptor binding, but rather may be mediated through indirect regulatory mechanisms or synergistic effects with other estrogen receptors. This also suggests that the functional link between GPR30 and migraine may involve estrogen-independent regulatory pathways that require further in-depth investigation.

In the nervous system, GPR30 is highly expressed in the core regulatory regions of migraine such as trigeminal ganglion (TG) and trigeminal spinal nucleus, which provides an anatomical basis for its involvement in migraine pain signal transduction.[36–39] In addition, GPR30 is expressed in the trigeminal spinal tract nucleus (TNC), trigeminal cortical projection areas, dorsal raphe nucleus of the brainstem, locus coeruleus, and ventral posteromedial nucleus (VPM) of the thalamus, all of which are involved in the relay and transmission of headache signals.[19] In the prefrontal cortex, insular cortex, and hippocampus, GPR30 is mainly expressed in neurons and glial cells, participating in the regulation of cognitive functions and pain-related emotional responses, which may be closely associated with cognitive impairment and anxiety commonly observed in migraine patients.[40–42] These findings suggest that GPR30 may be closely associated with cognitive impairment and anxiety symptoms that are commonly observed in migraine patients. However, it should be clearly noted that the current research data on the distribution characteristics of GPR30 in neural tissues are all derived from rodent models and reporter gene models, and there is a lack of direct verification evidence from human autopsy samples or in vivo imaging techniques. Therefore, the relationship between GPR30 distribution and migraine pathogenesis is still only speculative at the level of functional research, and requires further verification in human-related research models.

At the subcellular level, GPR30 is primarily localized to the plasma membrane and presynaptic membrane of neurons, with a small fraction present in the endoplasmic reticulum and Golgi apparatus.[20,43] GPR30 on the plasma membrane senses extracellular ligand signals and initiates rapid responses to external stimuli through nongenomic effects.[20] In contrast, GPR30 in the endoplasmic reticulum may be involved in the regulation of intracellular calcium signaling.[44] This dual localization allows GPR30 to regulate cellular functions from both intracellular and extracellular perspectives, further enhancing the flexibility of signal modulation (Figure 2).

Regulation of Migraine-Related Signal Transduction and Neural Functions by GPR30

GPR30 is generally recognized as a membrane receptor that mediates estrogen-dependent rapid nongenomic signaling. Its regulation of migraine is primarily exerted through G protein-dependent and β-arrestin-dependent pathways, modulating neural functions such as trigeminovascular system activity, neural signal transduction, neuroinflammation, and neuroprotection. The effects of GPR30 on migraine are characterized by multidimensionality and bidirectionality, with significant differences in functional outcomes depending on the target region, cell type, and pathological state. This complexity not only reflects the diversity of migraine pathophysiological mechanisms but also provides subdivided directions for precision targeted therapy (Figure 2). However, the research data come from ischemia, anxiety, subarachnoid hemorrhage or general pain models, and the association between GPR30 and migraine is mostly circumstantial. In addition, some pathways have conditional bidirectional effects, so it is necessary to combine with specific physiological conditions to clarify their functional guidance.

G Protein-Dependent Pathways

Upon activation, GPR30 can stimulate different types of G proteins, Gq and Gs, initiating downstream cascades that mediate peripheral pain induction, central analgesia, and neuroprotective effects, respectively. These pathways represent the core mechanisms underlying the bidirectional regulation of migraine by GPR30.

PLC-PKC Pathway

Estrogen withdrawal affects GPR30 activity and thus participates in the pathogenesis of migraine by regulating PLC-PKC pathway, which is the core hypothesis to explain the involvement of GPR30 in menstrual migraine. However, this pathway has not been directly verified by experiments.[45] When E2 levels decrease rapidly, GPR30 undergoes

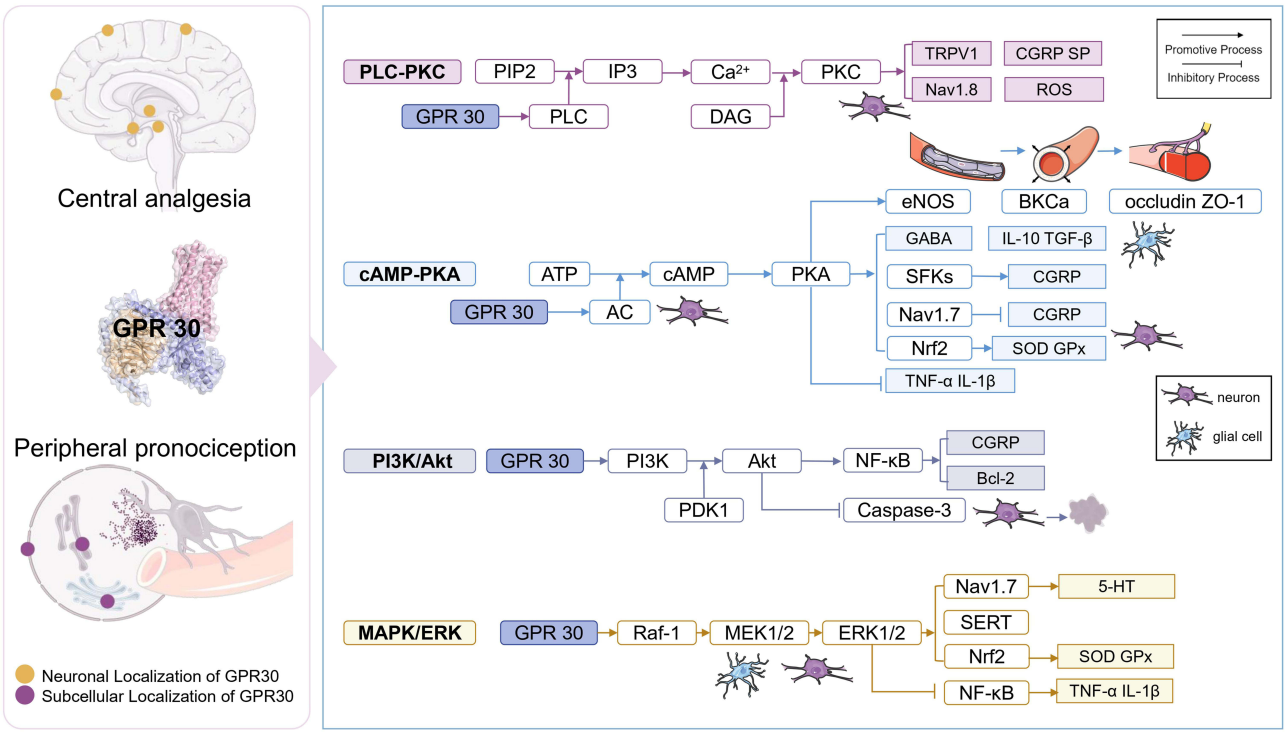

Figure 2 Localization of GPR30 and its related signaling pathways. The figure depicts the neuronal and subcellular localization of GPR30, and its promotive (peripheral pronociception) and inhibitory (central analgesia) signaling cascades with key molecular mediators and downstream effects. GPR30 activates multiple axes (PLC-PKC, cAMP-PKA, PI3K/Akt, MAPK/ERK) to regulate ion channels (TRPV1, Nav1.7/1.8), neuropeptides (CGRP, SP), inflammatory cytokines (TNF-α, IL-1β/IL-10), antioxidant factors (Nrf2, SOD, GPx), tight junction proteins (occludin, ZO-1) and other effectors (GABA, TGF-β, 5-HT/SERT, eNOS, BKCa). It modulates apoptosis (Bcl-2, Caspase-3), oxidative stress (ROS) and cellular barrier function, with NF-κB as a key transcriptional regulator of inflammatory responses. Promotive Process: Signaling events enhancing peripheral nociceptor activation and pro-inflammatory/pro-nociceptive outputs. Inhibitory Process: Signaling events mediating central pain suppression, anti-nociceptive/anti-inflammatory effects and cellular barrier protection.

Abbreviations: AC, adenylyl cyclase; BKCa, large-conductance calcium-activated potassium channel; CGRP, calcitonin gene-related peptide; DAG, diacylglycerol; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; GABA, gamma-aminobutyric acid; GPx, glutathione peroxidase; IL, interleukin; IP3, inositol 1,4,5-trisphosphate; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; Nav, voltage-gated sodium channel; PKA, protein kinase A; PKC, protein kinase C; PDK1, 3-phosphoinositide-dependent protein kinase 1; PI3K, phosphoinositide 3-kinase; PLC, phospholipase C; PIP2, phosphatidylinositol 4,5-bisphosphate; ROS, reactive oxygen species; SFKs, Src family kinases; SERT, serotonin transporter; SOD, superoxide dismutase; SP, substance P; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; TRPV1, transient receptor potential vanilloid 1; ZO-1, zonula occludens-1.

conformational changes and activates Gq proteins, which in turn activate phospholipase C (PLC) to hydrolyze phosphatidylinositol bisphosphate (PIP2) on the plasma membrane. The resulting inositol trisphosphate (IP3) binds to IP3 receptors on the endoplasmic reticulum, increasing intracellular calcium concentration; diacylglycerol (DAG) then cooperates with calcium to activate protein kinase C (PKC), which subsequently phosphorylates downstream target proteins.[46] PKC-mediated phosphorylation of TRPV1 significantly reduces its activation threshold, enhancing neuronal sensitivity to noxious stimuli and promoting the release of neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P (SP).[47]

Although SP was previously dismissed as a potential therapeutic target for migraine, the recent success of peptide-based migraine therapies has renewed academic interest in its role in migraine pathogenesis. While GPR30 may be involved in the regulation of SP release, direct evidence supporting this link in migraine is still limited and requires further verification. In addition, PKC can activate its downstream subtype PKCε to phosphorylate the Nav1.8 sodium channel, which enhances the excitability of trigeminal ganglion neurons and accelerates the conduction of peripheral pain signals.[48] Persistent activation of the Gq/11-PLC-PKC pathway can also increase the production of mitochondrial reactive oxygen species (ROS) in trigeminal ganglion neurons, induce oxidative stress, and further amplify pain signals, forming a vicious cycle of pain sensitization.[49]

cAMP-PKA Pathway

The cAMP-PKA pathway is one of the major mechanisms through which GPR30 exerts analgesic, anti-inflammatory, and vascular homeostasis-regulating effects in the central nervous system.[50]

In the central nervous system, GPR30-mediated activation of Gs proteins triggers the activation of adenylate cyclase (AC) by the α subunit of Gs, which promotes the conversion of ATP to cyclic adenosine monophosphate (cAMP). Elevated intracellular cAMP further activates protein kinase A (PKA),[51,52] which regulates a variety of downstream biological processes to exert anti-nociceptive and anti-inflammatory effects. In the trigeminal ganglion, PKA promotes the phosphorylation of Src family kinases (SFKs),[53] which then undergo autophosphorylation to enhance CGRP/CGRP receptor signal transduction, thereby promoting trigeminal ganglion sensitization.[54,55] Concurrently, in the central sensory nerve terminals of the trigeminal system, PKA-mediated phosphorylation of the Nav1.7 sodium channel can reduce the release of CGRP,[56–58] which exerts an analgesic effect by inhibiting the central transmission of pain signals. In the anterior cingulate cortex (ACC), a key brain region involved in pain perception and emotional regulation, PKA can promote the release of gamma-aminobutyric acid (GABA) from GABAergic neurons, thereby enhancing the inhibitory effect on cortical nociceptive neurons and alleviating the subjective perception of pain and associated anxiety symptoms.[59,60] In addition, PKA can also mediate the expression of anti-inflammatory factors such as IL-10 and TGF-β in astrocytes, and inhibit the release of pro-inflammatory factors including TNF-α and IL-1β, thereby effectively suppressing neuroinflammation in migraine-related brain regions.[61]

In contrast to its protective effects in the central nervous system, activation of the cAMP-PKA pathway in cerebrovascular tissues can promote migraine attack by regulating vascular tone and permeability. In cerebrovascular endothelial cells, cAMP-activated PKA phosphorylates endothelial nitric oxide synthase (eNOS) and promotes the synthesis and release of nitric oxide (NO), which leads to intracranial vasodilation—a key pathological mechanism of the throbbing headache characteristic of migraine.[62–64] In dural vascular endothelial cells, PKA can phosphorylate serine residues of tight junction proteins (occludin and ZO-1), enhance their membrane localization, reduce vascular permeability, inhibit the adhesion of neutrophils to endothelial cells, and block the infiltration of inflammatory cells into brain tissue,[65–67] which may represent a compensatory protective effect against neuroinflammation. In vascular smooth muscle cells, PKA activates large-conductance calcium-activated potassium (BKCa) channels and promotes potassium efflux, leading to vascular smooth muscle relaxation and further exacerbating intracranial vasodilation, thus participating in the onset of migraine.[68,69]

PI3K/Akt Pathway

The PI3K/Akt pathway is the main signaling pathway through which GPR30 exerts its neuroprotective effects, and it primarily acts on neurons and microglia in various brain regions including migraine-related core tissues.[70,71] This pathway exhibits distinct functional roles in different phases of migraine, with bidirectional regulatory effects closely related to the pathological state of the disease. During acute migraine attacks, activated PI3K/Akt can promote CGRP gene transcription through the NF-κB pathway, thereby driving the neurogenic inflammatory cycle and amplifying migraine pain.[72,73]

In contrast, during the interictal phase of migraine, GPR30 may activate the PI3K/Akt pathway to inhibit the activation of Caspase-3, a key executor of apoptosis, thereby blocking the execution of neuronal apoptosis.[74,75] In addition, the PI3K/Akt pathway can also enhance the expression of anti-apoptotic genes such as Bcl-2 via the NF-κB pathway,[76–78] exerting a neuroprotective effect by inhibiting neuronal apoptosis and reducing brain tissue damage caused by repeated migraine attacks.

β-Arrestin-Dependent Pathway

At present, there is almost no migraine-specific research evidence to support the role of the β-arrestin-dependent pathway in migraine pathogenesis, and its specific regulatory mechanism in migraine is still in the theoretical exploration stage. The only relevant research data are derived from general pain model studies, which have shown that GPR30 can recruit β-arrestin1/2 proteins through the phosphorylation sites in its intracellular domain upon activation.[79,80] The β-arrestin-dependent pathway not only participates in GPR30 receptor desensitization and endocytosis but also activates the

downstream MAPK/ERK pathway, which is hypothesized to play important roles in long-term analgesia, neuroprotection, and neuroinflammation regulation in migraine.

Receptor Desensitization and Endocytosis

β-arrestin-mediated endocytosis of GPR30 is a key negative regulatory mechanism to prevent excessive receptor signal activation, which is critical for maintaining the homeostasis of GPR30 signal transduction.[81] The specific regulatory process is as follows: following GPR30 activation, the serine/threonine residues in its intracellular C-terminus are phosphorylated by G protein-coupled receptor kinases (GRK2/5), and the phosphorylated C-terminus then binds to the N-terminal domain of β-arrestin1/2.[82] β-arrestin mediates the specific interaction between GPR30, clathrin, and adaptor protein AP-2, forming endocytic vesicles that transport the activated GPR30 from the plasma membrane to intracellular endosomes.[83,84] The internalized GPR30 can be dephosphorylated in early endosomes and recycled back to the plasma membrane, which achieves short-term receptor desensitization and signal resetting.[85,86] If the extracellular ligand signal is persistently activated, the internalized GPR30 is transported to late endosomes and degraded through fusion with lysosomes, which reduces the expression of GPR30 on the plasma membrane and exerts a long-term signal inhibition effect.[87]

MAPK/ERK Pathway

While mediating GPR30 receptor endocytosis, β-arrestin1/2 can recruit key signaling molecules such as Raf-1 and MEK1/2 through its scaffolding function, forming a specific signaling complex that activates the downstream MAPK/ERK pathway. This pathway primarily acts on central neurons and glial cells, and is hypothesized to exert multiple protective effects in migraine.[88] Activation of the MAPK/ERK pathway may produce central analgesic effects through two main mechanisms: on the one hand, ERK can reduce the current activity of the Nav1.7 sodium channel, decrease the firing frequency of nociceptive neurons, and inhibit the transmission of pain signals to the cerebral cortex; on the other hand, ERK can promote the phosphorylation of the 5-HT transporter (SERT), reduce the reuptake of 5-HT in the synaptic cleft, increase the extracellular 5-HT concentration, and thus enhance the analgesic effects mediated by 5-HT1B/1D receptors.[89–91] In addition, the β-arrestin2-ERK pathway can regulate the activity of key transcription factors and participate in the regulation of neuroinflammation. It can influence the nuclear translocation of NF-κB, promote the polarization of microglia from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype,[92] and also directly inhibit the nuclear translocation of NF-κB to reduce the release of pro-inflammatory factors such as TNF-α and IL-1β,[18,93] thereby exerting an anti-inflammatory effect in migraine-related brain regions.

Regulation of Oxidative Stress

Oxidative stress is an early pathophysiological process in migraine attacks.[94,95] GPR30 can alleviate oxidative stress damage through the synergistic effects of G protein-dependent and β-arrestin-dependent pathways.[18,96] The Nrf2 pathway can be activated by the cAMP-PKA and MAPK/ERK pathway, promoting the translocation of Nrf2 from the cytoplasm to the nucleus, where it binds to antioxidant response elements (AREs) to enhance the expression and activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx).[97–100] GPR30 can reduce ROS production by inhibiting the activity of mitochondrial respiratory chain complex;[101,102] it also regulates endoplasmic reticulum calcium homeostasis, avoiding endoplasmic reticulum stress induced by calcium overload and further reducing ROS levels.[103–105] Notably, no direct clinical proof-of-concept currently supports a causal role for GPR30-dependent oxidative stress regulation in migraine patients.

Indirect Clinical Evidence and Limitations of GPR30-Targeted Migraine Therapy

Clinical research has shown that the E2 can reduce the frequency of migraine attacks.[106] In a series of clinical studies investigating the efficacy of raloxifene for the treatment of endometriosis, migraine was monitored as a secondary adverse event, and the results indicated that raloxifene treatment significantly reduced the proportion of migraine patients in the overall study population.[107–109] However, raloxifene, as a selective estrogen receptor modulator, can act on ERα, ERβ and GPR30 simultaneously. The clinical effects observed in the treatment of migraine cannot be completely or

specifically attributed to the regulation of GPR30, which is only theoretical.[110] No human clinical trials have been conducted for GPR30 specific ligands,such as G-1, in migraine. All the evidence for the association between GPR30 and migraine treatment is indirect evidence, and there are core problems of unclear target specificity.

Discussion and Conclusion

This review systematically clarifies the association among migraine, estrogen, and GPR30, as well as the regulatory role of GPR30 in the pathogenesis of migraine. It is confirmed that estrogen serves as a core gender-related regulatory factor for migraine onset, while GPR30, a key membrane estrogen receptor mediating estrogenic effects, is highly expressed in migraine-associated core tissues such as the trigeminal ganglion. Through G protein-dependent and β-arrestin-dependent signaling pathways, GPR30 rapidly mediates nongenomic responses to estrogen fluctuations and modulates core pathological processes of migraine including trigeminovascular system activation, neuroinflammation, oxidative stress, and nociceptive sensitization. Thus, GPR30 acts as a crucial molecular mediator of estrogen-regulated migraine pathogenesis and a highly promising therapeutic target for migraine prevention and treatment.

Existing studies do not refute the core functional association among migraine, estrogen, and GPR30,[111–113] instead, they dialectically falsify the hypothesis of a simple linear direct causal relationship between the three based on multi-level research evidence. High-resolution cryo-electron microscopy structural studies provide direct and convincing evidence confirming that GPR30 does not bind to estrogen directly,[16] which overturns the fundamental premise that estrogen regulates migraine by directly binding to GPR30 and suggests the existence of a sophisticated and complex indirect regulatory cascade between GPR30 and estrogen signaling in migraine. Studies on the activity characteristics of GPR30 provide indirect evidence indicating that GPR30 activation is not entirely dependent on estrogen, which demonstrates that estrogen is merely one of its upstream regulatory factors, and GPR30 can independently participate in migraine pathogenesis through estrogen-independent pathways. Supporting clinical and pathological evidence further reveals that GPR30 lacks subtype-specific expression and regulatory patterns in different migraine phenotypes, and its alterations in expression and activity are not unique to the pathological process of migraine but may also represent secondary changes to neuronal damage and inflammatory responses in other neurological disorders. These findings collectively confirm that GPR30 is not an independent primary pathogenic factor for migraine, but a co-pathogenic factor that amplifies pathological effects under specific physiological and pathological conditions such as estrogen level fluctuation and enhanced oxidative stress. In summary, the current research evidence clearly illustrates that migraine, estrogen, and GPR30 form a complex regulatory system involving multiple signaling pathways and functional links, rather than a simple linear causal relationship.[114]

Current research on GPR30 and migraine still faces numerous unresolved challenges and open scientific questions. First, the indirect regulatory mechanism between GPR30 and estrogen in migraine remains largely unelucidated, and the key intermediate signaling molecules and upstream-downstream regulatory cascades between the two await further in-depth investigation. Second, the expression characteristics and regulatory effects of GPR30 in different migraine subtypes and different disease stages have not been clearly defined, with a serious lack of subtype-specific targeted research data. Third, most existing GPR30 ligands are only tool compounds used in preclinical research, which have significant limitations including low bioavailability, poor tissue selectivity, and rapid in vivo metabolism, and there is a dearth of highly specific and clinically applicable GPR30-targeted ligands. Fourth, the downstream crosstalk mechanisms between GPR30 and classic migraine therapeutic targets such as CGRP and 5-HT receptors have not been fully clarified, and the cell-specific functional differences of GPR30 in different migraine-related tissues remain unknown, which are likely to induce off-target effects in subsequent drug intervention studies. Fifth, there is a complete lack of migraine-specific clinical trials for GPR30-targeted therapy; the applicable population, effective dosage window, and long-term safety of such therapy have not been determined, and the impact of individual differences such as gender, age, and hormone levels on GPR30 expression and drug response remains to be verified in clinical studies.

In-depth elucidation of the complex association among migraine, estrogen, and GPR30 and overcoming the aforementioned research challenges hold significant clinical and practical value. Mechanistically, it perfects the molecular basis of gender predilection in migraine, fills the gap in the downstream regulation of migraine induced by estrogen fluctuations, and provides a comprehensive theoretical framework for explaining the high incidence of migraine in

women of childbearing age. Therapeutically, it breaks through the clinical limitations of direct estrogen supplementation for migraine treatment, circumvents the risk of migraine attacks caused by hormone level fluctuations, and establishes a novel clinical intervention strategy of "regulating key downstream estrogen receptors" to achieve precise targeted modulation of migraine. From the perspective of drug development, the characteristic of GPR30 in rapidly regulating the acute pathological processes of migraine makes up for the limitation that existing drugs targeting a single neurotransmitter can only benefit a subset of migraine patients, thus providing a highly targeted direction for the development of novel anti-migraine drugs.

Future research in this field should focus on two goals: elucidating the molecular regulatory network among migraine, estrogen and GPR30, and translating preclinical findings into clinical therapeutic applications. To this end, priority should be given to mechanistic and translational research efforts: on the one hand, to deeply investigate the indirect regulatory mechanisms between estrogen and GPR30 in migraine, identify key intermediate signaling molecules and pathways, and refine the upstream-downstream regulatory cascades of the three; meanwhile, to carry out subtype-specific research on GPR30 across different migraine phenotypes and disease stages, and clarify population-specific differences in its expression and activity in combination with estrogen level changes, laying a foundation for stratified precision therapy.

On the other hand, it is critical to advance the development and clinical translation of GPR30-targeted drugs: optimize the design and synthesis of GPR30 ligands with high specificity, favorable bioavailability and tissue selectivity via modern pharmaceutical technologies, and develop multi-target drugs acting on both GPR30 and classic migraine therapeutic targets to enhance efficacy and reduce off-target effects; explore innovative administration routes and drug delivery systems to achieve efficient blood-brain barrier penetration, increase drug concentration in migraine-associated target tissues and minimize systemic adverse reactions.

In addition, rigorous stratified clinical trials should be designed with estrogen levels and GPR30 expression as key molecular biomarkers for patient selection, and long-term follow-up conducted in populations with different genders,[115] menstrual statuses and migraine subtypes to define the clinical application scope, optimal dosage window and long-term safety of GPR30 modulators. Novel combination therapy regimens of GPR30 modulators with first-line anti-migraine drugs such as triptans and CGRP antagonists[6–9] should also be actively explored, so as to provide effective treatment options for patients with refractory migraine who respond poorly to conventional therapy.

In summary, as a key molecular target of estrogen-regulated migraine, GPR30 forms a tight and complex regulatory system with estrogen and migraine. Existing studies have dialectically falsified the simple linear causal relationship among the three, opening up a new perspective for the mechanistic research of migraine. Although the current elucidation of this regulatory network, development of targeted ligands, and clinical translation still face multiple challenges, in-depth research on migraine-estrogen-GPR30 is bound to drive new breakthroughs in the field of precise migraine prevention and treatment, and provide important theoretical support and practical solutions for addressing the clinical challenges of this highly prevalent and disabling neurological disorder.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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