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# NEUROVASCULAR AND NEUROINFLAMMATORY PATHWAYS IN MIGRAINE: COMPREHENSIVE REVIEW

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## ABSTRACT

Migraine is a complex neurobiological disorder characterized by recurrent headache attacks and associated neurological symptoms. Increasing evidence supports the involvement of both neurovascular and neuroinflammatory mechanisms in migraine pathophysiology. The neurovascular hypothesis emphasizes the interaction between neuronal activity and cerebral blood vessels, particularly the activation of the trigeminovascular system. Release of vasoactive neuropeptides such as calcitonin gene–related peptide (CGRP), substance P, and neurokinin A leads to vasodilation of meningeal vessels and sensitization of peripheral and central nociceptive pathways. Concurrently, neuroinflammatory processes play a critical role in migraine initiation and progression. Activation of trigeminal afferents induces sterile inflammation within the meninges, characterized by mast cell degranulation, cytokine release, and increased vascular permeability. Pro-inflammatory mediators, including interleukins, tumour necrosis factor-α, and nitric oxide, contribute to neuronal sensitization and sustained pain signalling. Crosstalk between vascular, immune, and neuronal components amplifies migraine attacks and may underlie central sensitization and chronic migraine development. Understanding the interplay between neurovascular and neuroinflammatory pathways has led to novel therapeutic strategies, particularly CGRP-targeted treatments, highlighting their importance in migraine management and future drug development.[1]

**KEYWORDS:** Neuroprotective, Trigeminovascular system, CGRP-targeted therapy, Tumour necrosis factor-α (TNF-α), Oxidative Stress.

## INTRODUCTION

CGRP-targeted therapies represent a major neuropharmacological breakthrough Migraine is a chronic, episodic, and often disabling neurological disorder characterized by recurrent attacks of headache of moderate to severe intensity.[2]

The pain is typically unilateral, throbbing or pulsatile in nature, and is frequently associated with nausea, vomiting, photophobia, and phonophobia. Migraine affects individuals across all age groups, with a higher prevalence among women, suggesting a strong hormonal and genetic influence. According to global health estimates, migraine is one of the leading causes of years lived with disability, highlighting its significant clinical and socioeconomic burden. Migraine attacks are classically divided into four phases: prodrome, aura (in some patients), headache phase, and postdrome. The prodromal phase includes mood changes, food cravings, and fatigue, while aura consists of transient focal neurological symptoms such as visual disturbances or sensory abnormalities. The headache phase represents the most debilitating period, followed by postdrome, characterized by exhaustion and cognitive difficulty. From a neuropharmacological standpoint, migraine is now recognized as a complex neurovascular disorder involving dysfunction of both central and peripheral nervous systems. The trigeminovascular system plays a pivotal role, wherein activation of trigeminal sensory afferents innervating the meninges leads to the release of vasoactive neuropeptides. These neuropeptides promote vasodilation, plasma protein extravasation, and neurogenic inflammation, ultimately resulting in pain perception. Several neurotransmitters are implicated in

migraine pathophysiology. Serotonin (5-hydroxytryptamine, 5-HT) has been extensively studied, as decreased serotonergic transmission is observed during migraine attacks. This understanding has formed the basis for the development of triptans, which are selective 5-HT1B/1D receptor agonists. Dopamine hypersensitivity explains premonitory symptoms such as yawning and nausea, while glutamate-mediated excitatory neurotransmission contributes to cortical hyperexcitability. Impaired inhibitory gamma-aminobutyric acid (GABA) signalling further enhances neuronal susceptibility. Migraine is a chronic neurovascular disorder with significant global impact Trigeminovascular activation is central to migraine pain generation Key neurotransmitters include serotonin, dopamine, glutamate, and GABA.[3]

**Role of CGRP, Nitric Oxide & Oxidative Stress in Migraine**

CGRP, Nitric Oxide (NO), and oxidative stress are central to migraine, forming a vicious cycle where trigeminal nerve activation releases CGRP, triggering NO release, causing vasodilation and sensitizing nerves; this neuroinflammation generates Reactive Oxygen Species (ROS) (oxidative stress), impairing brain function, leading to increased CGRP/NO production, and perpetuating the migraine attack, with CGRP targeting drugs highlighting this pathway's importance.

Calcitonin gene-related peptide (CGRP) is a 37–amino acid neuropeptide abundantly expressed in trigeminal sensory neurons. During migraine attacks, CGRP is released from peripheral and central trigeminal terminals, leading to potent vasodilation of intracranial blood vessels. Elevated CGRP levels have been consistently detected in the external jugular vein during spontaneous migraine attacks, and normalization of these levels correlates with headache relief. CGRP facilitates nociceptive transmission by sensitizing second-order neurons in the trigeminal nucleus caudalis and enhancing synaptic transmission. Its pivotal role is further supported by the efficacy of CGRP antagonists and monoclonal antibodies in both acute and preventive migraine therapy. Stimulates mast cells, increases blood flow, and sensitizes trigeminal neurons, contributing to both peripheral and central sensitization. Infusion can trigger migraines, and CGRP-blocking drugs are highly effective, proving its central role. Nitric oxide (NO) is a gaseous signalling molecule that plays a significant role in migraine initiation and maintenance. Administration of nitric oxide donors such as nitroglycerin can reliably induce migraine-like headaches in susceptible individuals. NO promotes vasodilation, activates trigeminal nociceptors, and stimulates CGRP release, thereby amplifying migraine pathways. Increased expression of nitric oxide synthase (NOS), particularly inducible NOS, has been reported in migraine conditions Increases cyclic GMP (cGMP), opening potassium channels and stimulating neurons, contributing to pain signalling and vasodilation. Nitroglycerin (an NO donor) triggers migraines, and NO pathway components are upregulated in migraine, making NOS inhibitors potential treatments. It represents another important contributor to migraine pathophysiology. Excessive production of reactive oxygen species (ROS) leads to mitochondrial dysfunction, lipid peroxidation, and neuronal damage. Migraine patients often exhibit reduced levels of endogenous antioxidants such as superoxide dismutase, catalase, and glutathione. Oxidative stress not only sensitizes nociceptive pathways but also interacts with inflammatory mediators, thereby exacerbating migraine severity and frequency. ROS (like superoxide) can damage cells, increase inflammation, and disrupt mitochondrial function, lowering the migraine threshold .Impaired oxidative-antioxidative balance is seen in migraine, and CGRP/NO loops can induce ROS, linking these pathways. Trigger like Stress, diet (nitrates), or other factors activate the trigeminal nerve. CGRP Release is Trigeminal neurons release CGRP. CGRP promotes nitric oxide synthesis. Vasodilation & Sensitization is NO and CGRP cause dural vasodilation and sensitize pain-sensing nerves (peripheral sensitization). This cascade activates inflammatory pathways and generates ROS, increasing oxidative stress. Sensitized peripheral nerves lead to central sensitization, amplifying pain signals. Increased CGRP/NO further fuels ROS production, perpetuating the cycle and progressing episodic to chronic migraine.

**Experimental Models of Migraine in Laboratory Animals**

It play a crucial role in elucidating migraine mechanisms and evaluating novel therapeutic agents. Since migraine is a complex human disorder, animal models aim to replicate specific pathophysiological features rather than the complete clinical syndrome. The nitroglycerin-induced migraine model is widely used, as nitroglycerin releases nitric oxide and produces migraine-like symptoms such as hyperalgesia and photophobia. Cortical spreading depression (CSD) models mimic the neurophysiological basis of migraine aura and involve a wave of neuronal depolarization followed by suppression of cortical activity. Another commonly employed model involves the application of inflammatory mediators, known as inflammatory soup, onto the dura mater to activate trigeminal nociceptors. **Common Animal Models for Migraine Nitroglycerin (NTG) Model:** Systemic injection (IV or IP) of NTG, a nitric oxide donor, induces a migraine-like attack in rodents, causing periorbital mechanical allodynia (pain from light touch) and other behaviours like increased grooming and anxiety (fig 1). This model allows testing of anti-migraine drugs like triptans, which reverse the NTG-induced pain. **Trigeminal Nerve Stimulation (Electrical/Chemical):** Direct electrical stimulation of the trigeminal ganglion or meningeal nerve endings (e.g., superior sagittal sinus) activates the trigeminovascular system (TVS). Activates neuropeptide release (like CGRP) and induces pain behaviours, mapping central pain pathways. **Cortical Spreading Depression (CSD)**

**Model:** Inducing CSD, the wave of neural depression underlying migraine aura, through various stimuli. CSD in rodents, a key feature of migraine aura, can cause spontaneous pain behaviours reversed by CGRP antagonists. **Genetic Models:** Studying specific gene mutations linked to rare, severe migraines (e.g., familial hemiplegic migraine). These models help understand genetic predispositions and mechanisms of rare migraine forms.[4]

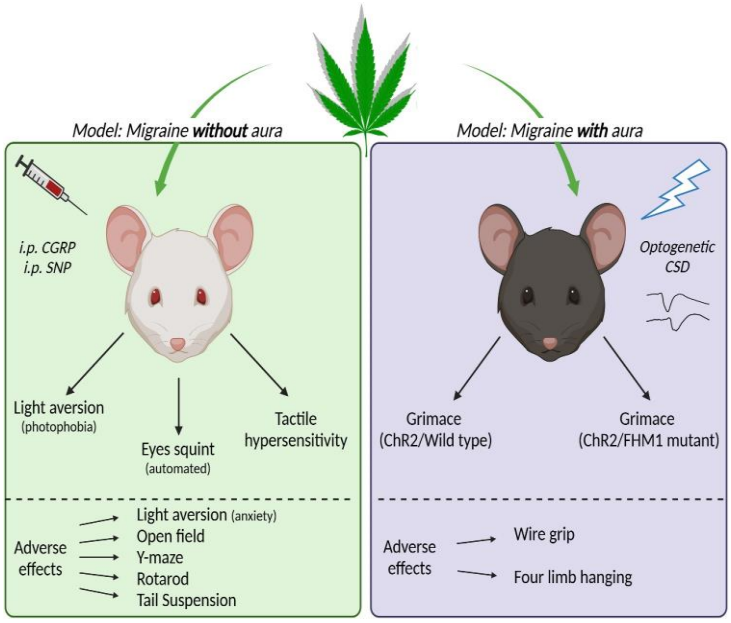


**Fig. 1. Experimental models of migraine in laboratory animal.**

**Mechanistic Basis in Neurological Modulation**

The observed neurological benefits are explained by a multi-pathway mechanism of action, as demonstrated by experimental evidence from preclinical studies. Experimental findings indicate that administration of the extract elevates levels of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) while modifying the activity of key enzymes involved in its metabolism, including L-glutamic acid decarboxylase (L-GAD) and GABA-transaminase (GABA-T), particularly within the hippocampal region. Certain flavonoid compounds are believed to interact with the benzodiazepine binding site of the GABA-A receptor, thereby strengthening inhibitory synaptic transmission and producing central nervous system depressant as well as anxiolytic effects. **Antioxidant activity** is the Neurological disorders such as epilepsy and neurodegenerative conditions are frequently associated with elevated oxidative stress. Treatment with the extract has been shown to significantly counteract this imbalance by reducing the generation of reactive oxygen species (ROS) and enhancing endogenous antioxidant defense systems, thereby protecting neural tissue from oxidative damage. **Anti-Neuroinflammatory Effects is** the extract demonstrates pronounced anti-inflammatory properties within the central nervous system, leading to reduced neuroinflammatory responses in brain regions such as the hippocampus. This effect is particularly important, as sustained neuroinflammation is a key contributor to neuronal injury and cognitive dysfunction in various neurological disorders. Through the combined actions of neurotransmitter regulation, oxidative stress reduction, and suppression of inflammation, the extract provides a neuroprotective effect. This protection limits neuronal degeneration and cell loss in the hippocampus, as observed in experimental seizure models.[5]

**Evidence on Anti-inflammatory & Anti-oxidant Activities**

Anti-inflammatory and antioxidant mechanisms play a crucial role in migraine management, as migraine is increasingly recognized as a neurovascular disorder associated with oxidative stress. Clinical studies have shown that migraine patients exhibit elevated oxidative stress markers such as malondialdehyde and nitric oxide, along with a reduction in total antioxidant capacity and endogenous antioxidant enzymes. This imbalance promotes mitochondrial dysfunction and neuronal hyperexcitability, which are central to migraine pathophysiology. Inflammation significantly contributes to the initiation and progression of migraine attacks through the release of pro-inflammatory mediators such as calcitonin gene-related peptide (CGRP), tumour necrosis factor-α, and interleukins. Oxidative stress further aggravates this inflammatory cascade, leading to neurogenic inflammation, vasodilation, and sensitization of trigeminal pain pathways. The interaction between oxidative stress and inflammation creates a self-perpetuating cycle that increases migraine frequency and severity. Evidence supports the therapeutic potential of antioxidant and anti-inflammatory strategies as adjuncts in migraine prevention. By reducing reactive oxygen species and modulating inflammatory pathways, these agents may improve mitochondrial energy metabolism

and decrease neuronal sensitization. Such mechanisms contribute to a reduction in migraine intensity and attack frequency, supporting their role as complementary approaches alongside conventional antimigraine therapy.[6]

**Behavioural & Biochemical Assessment Parameters in Migraine Studies**

**They are** essential to understand both the subjective experience and objective biological mechanisms of the disorder. **Behavioural assessments** typically include standardized clinical tools such as the *Visual Analog Scale (VAS)* for pain intensity, *Headache Impact Test (HIT-6)*, *Migraine Disability Assessment (MIDAS)*, and questionnaires measuring quality of life, anxiety, and depression. These tools quantify headache severity, attack frequency, impact on daily functioning, and psychological burden, providing clinicians and researchers with validated measures of how migraines affect patient behaviour and well-being over time. Such parameters help in evaluating treatment responses, comparing patient subgroups (e.g., episodic vs. chronic migraine), and linking symptoms with underlying mechanisms. **Biochemical assessments** involve laboratory analysis of blood markers linked to migraine pathophysiology,(fig 2) especially those reflecting oxidative stress and inflammation. Common biomarkers include **proinflammatory cytokines** such as interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and IL-1β, as well as adipokines like high-molecular-weight adiponectin and leptin. These molecules can be measured using assays such as enzyme-linked immunosorbent assay (ELISA) and are often compared between migraine patients and healthy controls to identify dysregulated immune signalling. Elevated levels of specific cytokines and adipokines have been correlated with higher headache frequency, increased disability scores such as MIDAS, and physiological changes, suggesting that neuroinflammation and metabolic factors contribute to migraine progression and chronification. The **integration of behavioural and biochemical parameters** enhances our understanding of migraine as a multifactorial neurological disorder. By correlating subjective measures (e.g., pain severity, disability, psychological distress) with objective biomarkers (e.g., IL-6, adiponectin), studies can reveal how physiological processes such as inflammation and oxidative stress influence patient experiences. This dual approach supports the identification of potential biomarkers for diagnosis, prognosis, and treatment response, and helps tailor both pharmacological and lifestyle interventions to individual migraine phenotypes.[7]

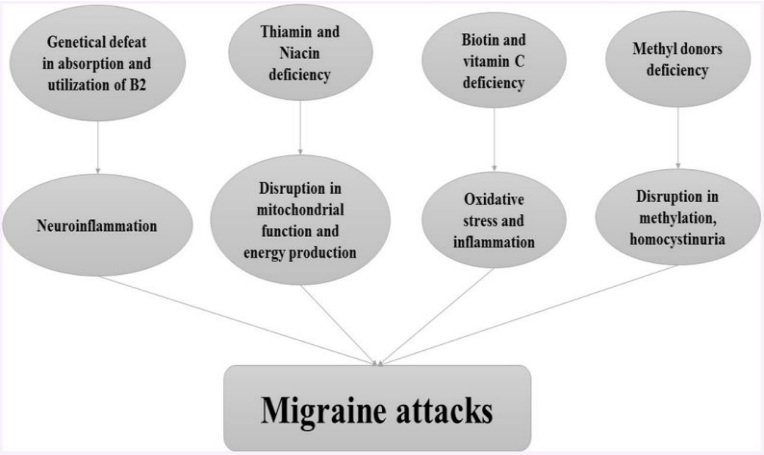


**Fig.2 Migraine attacks.**

**Neuroprotective mechanisms in migraine management**

**It** refer to biological processes and therapeutic strategies that protect neural tissue from damage associated with migraine pathology. One proposed mechanism involves **modulating oxidative stress and inflammatory pathways** in the central nervous system. Oxidative stress can exacerbate neuronal hypersensitivity and promote neurogenic inflammation, which contributes to migraine attacks. Neuroprotective strategies aim to **reduce reactive oxygen species (ROS)**, enhance endogenous antioxidant defenses (e.g., via upregulation of Nrf2 pathways), and stabilize neuronal energy metabolism, thereby limiting neuronal excitability and protecting against chronic functional changes in pain pathways. Another neuroprotective facet relates to **endogenous neuropeptides and growth factors**, which, beyond their roles in pain signalling, may support neuronal survival and repair. For example, calcitonin gene-related peptide (CGRP), a key mediator in migraine, has been shown to participate in **neuroprotective processes** under stress conditions by buffering intracellular calcium, activating anti-apoptotic signalling, and upregulating neurotrophic factors in experimental models, suggesting a dual role in both migraine pathophysiology and neuronal homeostasis. These mechanisms indicate that treatments should balance **inhibiting pathological pain signalling** while preserving or enhancing **intrinsic neuroprotective responses**. Clinically, some **pharmacologic agents used in migraine prevention**—such as topiramate—may exert neuroprotective effects by **modulating oxidative stress and neurogenic inflammation** in addition to their

primary actions on neuronal excitability. These effects include reducing pro-inflammatory cytokines and mitigating oxidative damage, which may help stabilize neuronal membranes, prevent central sensitization, and decrease the frequency and severity of migraine attacks. Such mechanisms support the rationale for targeting **oxidative and inflammatory pathways** as part of an integrated migraine management strategy that includes neuroprotection.

**Comparative Analysis with Standard Anti-migraine Therapies**

Triptans (e.g., eletriptan, rizatriptan, sumatriptan, zolmitriptan): Most effective for acute migraine treatment, with eletriptan showing the best overall profile (37% pain-free at 2 hours) NSAIDs (e.g., ibuprofen, diclofenac): Next most effective group, but less potent than triptans Gepants (e.g., rimegepant, ubrogepant): Less effective than triptans, but with fewer side effects .Lasmiditan is More effective than gepants, but with higher risk of dizziness and fatigue .CGRP monoclonal antibodies (e.g., erenumab, fremanezumab, galcanezumab, eptinezumab): Most effective and tolerated treatment for migraine prophylaxis, with fremanezumab showing the highest efficacy Topiramate is Less effective than CGRP monoclonal antibodies, with higher risk of adverse events Beta-blockers: Moderate efficacy, with common side effects like fatigue and dizziness .Rimegepant and atogepant show promise for migraine prevention, with efficacy cmparable to CGRP monoclonal antibodies. Non-invasive neuromodulation techniques: Emerging evidence supports their use as adjunctive therapies.

**Phytochemical Profile & Active Constituents**

They are bioactive compounds derived from medicinal plants and have gained increasing attention in migraine research due to their multi-targeted pharmacological actions and favourable safety profiles. Traditional medicinal systems have long utilized herbal remedies for headache disorders, and modern research has begun to validate their therapeutic potential. Major classes of phytochemicals relevant to migraine include flavonoids, alkaloids, terpenoids, phenolic acids, and glycosides. Flavonoids such as quercetin, rutin, kaempferol, and luteolin possess strong antioxidant and anti-inflammatory properties. These compounds scavenge free radicals, inhibit lipid peroxidation, and suppress pro-inflammatory cytokines involved in migraine pathogenesis. Alkaloids can modulate neurotransmitter release and receptor activity, thereby influencing pain perception. Terpenoids have been shown to inhibit nitric oxide synthesis and reduce CGRP release. Phenolic compounds further contribute to neuroprotection by stabilizing neuronal membranes and enhancing endogenous antioxidant defenses. The synergistic interaction of these constituents enhances the overall therapeutic efficacy of phytochemical-based interventions.[8]

**CONCLUSION**

Migraine is no longer viewed solely as a vascular disorder but is now recognized as a complex neurobiological disease involving tightly interconnected neurovascular and neuroinflammatory mechanisms. Activation of the trigeminovascular system represents a central event in migraine pathophysiology, linking neuronal hyperexcitability with the release of vasoactive and pro-inflammatory mediators such as calcitonin gene-related peptide (CGRP), substance P, and pituitary adenylate cyclase–activating polypeptide (PACAP). These mediators drive meningeal vasodilation, plasma protein extravasation, and sensitization of peripheral and central nociceptive pathways. Neuroinflammation further amplifies migraine signalling through the activation of glial cells, mast cells, and immune pathways, leading to the release of cytokines, chemokines, and nitric oxide(9). This inflammatory milieu contributes to sustained trigeminal sensitization and may underlie the transition from episodic to chronic migraine. Importantly, cortical spreading depolarization, particularly in migraine with aura, provides a mechanistic link between neuronal dysfunction and downstream neurovascular and inflammatory responses(10) .Advances in molecular and imaging studies have significantly refined our understanding of these pathways and directly informed therapeutic innovation. The clinical success of CGRP-targeted monoclonal antibodies and small-molecule antagonists underscores the translational relevance of the neurovascular–neuroinflammatory interface in migraine. Nevertheless, unresolved questions remain regarding individual susceptibility, sex differences, and the long-term impact of immune and glial modulation. Future research should focus on integrating neuroimmune signalling, vascular biology, and central nervous system plasticity to identify novel biomarkers and therapeutic targets. A more comprehensive understanding of neurovascular and neuroinflammatory interactions holds promise for precision medicine approaches and improved outcomes for patients with migraine.[11]

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