REVIEW ARTICLE

Unraveling Migraine: Inflammation, Genetics, and Emerging Therapeutic Targets

S. Lakshmi Manideep Royal[1], Prasanthi Samathoti[2], C. SaiSukeerthan Reddy[3], S. Sudhesh Sreepathi[3], B. Akhil Naik[3], M. Sai Deepa[3], N. Sree Lekha[1], V. Sarovar Reddy[4]

[1]Department of Pharmacy Practice, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India, [2]Department of Pharmaceutics, Mohan Babu University (Erstwhile SreeVidyanikethan College of Pharmacy), Tirupati Andhra Pradesh, India, [3]Department of Pharmacy Practice, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India, [4]Department of Pharmaceutics, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India

Abstract

Migraine is a profoundly disabling neurological disorder, long misunderstood and trivialized as a simple headache. Its true nature, however, is that of a complex brain state, rooted in genetic susceptibility and manifested through a cascade of inflammatory and neurovascular events. This review article seeks to unravel the intricate threads of migraine pathophysiology, charting the scientific journey that has transformed our understanding. We begin by deconstructing the historical "vascular theory," replacing it with the modern neurovascular model, which places the brain at the center of the disorder. We then provide a deep dive into the inflammatory cascade of an attack, detailing the pivotal role of the trigeminovascular system and the neuropeptide Calcitonin Gene-Related Peptide (CGRP) – a target whose inhibition has revolutionized treatment. The article then explores the genetic architecture of migraine, from the rare, illuminating channelopathies of Familial Hemiplegic Migraine that provided the first molecular clues, to the large-scale genomic studies that have painted a picture of a polygenic, hyperexcitable "migraine brain." Finally, building on this foundation of knowledge, we survey the exciting horizon of emerging therapeutic targets that lie beyond CGRP, including the PACAP pathway, novel ion channel modulators, and next-generation serotonin agonists. By weaving together the strands of inflammation and genetics, we present a holistic view of migraine and look toward a future of increasingly precise and personalized medicine.

Key words: Calcitonin gene-related peptide, cortical spreading depression, familial hemiplegic migraine, genetics, genome-wide association studies, migraine, neuroinflammation, personalized medicine, pituitary adenylate cyclase-activating polypeptide, therapeutic targets

INTRODUCTION: MORE THAN A HEADACHE, A GLOBAL NEUROLOGICAL BURDEN

For the hundreds of millions of people worldwide who live with it, a migraine is not "just a bad headache." It is a multi-sensory, immersive, and profoundly disabling neurological event. The experience is often a symphony of suffering: A throbbing, unilateral head pain that builds to a crescendo, accompanied by a visceral intolerance to light (photophobia), sound (phonophobia), and often smell (osmophobia). Nausea and vomiting are frequent companions, and for about a third of individuals, the pain is preceded or accompanied by a transient neurological disturbance known as an aura – most commonly shimmering lights, blind spots, or zigzagging lines that drift across the visual field.[1] The Global Burden of Disease studies have consistently ranked migraine as the second leading cause of disability worldwide, and the primary cause among women

Address for correspondence:
S. Lakshmi Manideep Royal, Department of Pharmacy Practice, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India. Mobile: +91-7032386194.
E-mail: manideeproyal1999@gmail.com

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under 50, stealing countless days from work, family, and life itself.[2]

For much of the 20th century, migraine was conceptualized through the simplistic lens of the vascular theory: That a primary vasoconstriction of cranial blood vessels (causing the aura) was followed by a rebound, painful vasodilation (causing the headache). This theory, while intuitive, failed to explain rich neurological tapestry of symptoms. The paradigm has now decisively shifted. We now understand migraine as a primary disorder of brain function – a neurovascular disorder where aberrant neural activity is the inciting event, and the subsequent vascular changes are important, but secondary, phenomena.[3]

The key to truly unraveling migraine lies at the fascinating intersection of two core concepts: An inherited, genetic predisposition that creates a hyperexcitable brain, and the dynamic neuro-inflammatory cascade that constitutes the attack itself. It is a story of a sensitive brain's overreaction to internal or external triggers – be it stress, hormonal shifts, or a sleepless night. Decades of painstaking research into these pathways have not only illuminated the biology of an attack but have also led to the first-ever mechanism-based, disease-specific treatments, fundamentally changing the therapeutic landscape. This review will delve into the inflammatory biology of a migraine attack, explore the genetic blueprint that confers susceptibility, and survey the exciting array of new therapeutic targets that are emerging from this integrated understanding.

THE INFLAMMATORY CASCADE: THE BIOLOGY OF A MIGRAINE ATTACK

The pain of a migraine does not originate within the brain tissue itself, which lacks pain receptors. Instead, it arises from the activation and sensitization of the trigeminovascular system (TVS), a network of nerves that richly innervate the pain-sensitive protective membranes surrounding the brain (the meninges) and their blood vessels.[4]

The initiating spark: Cortical spreading depression (CSD)

In migraine with aura, the neurological prelude is strongly believed to be caused by a phenomenon known as CSD. CSD is a slow-moving, self-propagating wave of intense neuronal and glial depolarization that creeps across the cerebral cortex at a rate of 2–5 mm/min, followed by a prolonged period of neural suppression.[5] This wave of activity directly correlates with the slow march of aura symptoms. For example, a wave moving across the visual cortex would produce a visual aura. While its exact trigger in spontaneous migraine remains elusive, CSD is not a benign event. It is a potent activator of trigeminal nerve endings in the meninges, likely through the release of signaling molecules such as potassium ions, nitric oxide, and arachidonic acid into the perivascular space.[6] CSD thus serves as the crucial link between the cortical events of aura and the subsequent activation of the pain-producing TVS, igniting the headache phase. Even in migraine without aura, a similar, but clinically silent, CSD-like event in non-eloquent brain regions is hypothesized to be the trigger.

The star player: Calcitonin gene-related peptide (CGRP)

Once the trigeminal nerves are activated, they release a cocktail of inflammatory neuropeptides. Among these, one has emerged as the undisputed star player in migraine pathophysiology: CGRP. The evidence for its central role is overwhelming and represents a triumph of translational science:

- The clinical evidence: Landmark studies by Goadsby *et al*. in the 1990s demonstrated that levels of CGRP are elevated in the jugular venous blood draining the head during a migraine attack, and that these levels normalize upon successful treatment with sumatriptan[7]
- The provocation model: Intravenous infusion of CGRP can reliably trigger a migraine-like headache in individuals with a history of migraine, but not in healthy controls, proving its causal role[8]
- The mechanism of action: CGRP is a potent vasodilator of the meningeal arteries, contributing to the throbbing quality of the pain. More importantly, its release initiates what is termed sterile neurogenic inflammation. It causes plasma proteins to leak out of dural blood vessels and activates nearby immune cells, creating an inflammatory soup that further sensitizes the trigeminal nerve endings.[9] CGRP also acts at both peripheral (trigeminal ganglion) and central (e.g., trigeminal nucleus caudalis) sites to enhance the transmission of pain signals to the brain. It essentially turns up the volume on the pain pathway, a process known as sensitization, which explains why a normally non-painful stimulus, like a pulse of blood through an artery, becomes excruciatingly painful during an attack
- The therapeutic revolution: The ultimate validation of the CGRP hypothesis has been the unprecedented success of two new classes of migraine-specific drugs. The first are injectable monoclonal antibodies (e.g., erenumab, fremanezumab, galcanezumab, eptinezumab) that either bind to the CGRP molecule itself or block its receptor. The second are small molecule CGRP receptor antagonists, known as "gepants" (e.g., ubrogepant, rimegepant, atogepant), which can be taken orally.[10] The remarkable efficacy of these drugs in both preventing and treating migraine attacks has transformed the lives of millions and stands as a testament to mechanism-based drug discovery.

The supporting cast: Other inflammatory mediators

While CGRP holds the spotlight, it does not act alone. The inflammatory milieu of a migraine attack is complex.

- Pituitary adenylate cyclase-activating polypeptide (PACAP): This neuropeptide has emerged as another key player. Like CGRP, PACAP is found in the trigeminal ganglion and is a potent vasodilator. Crucially, infusion of PACAP-38 can also trigger migraine attacks in susceptible individuals, and it does so even in the presence of CGRP blockade.[11] This suggests that PACAP acts via a parallel, at least partially independent, pathway, making it a highly attractive target for new therapies.
- Other molecules: Substance P and Neurokinin A are also released from trigeminal nerve endings and contribute to plasma extravasation. Nitric oxide (NO), a gaseous signaling molecule, is a well-known migraine trigger (e.g., the headaches caused by nitroglycerin) and plays a key role in vasodilation and the sensitization of the trigeminal system.[12]

THE GENETIC BLUEPRINT: THE "MIGRAINE BRAIN"

A fundamental question in migraine is why only certain individuals are susceptible to these attacks. The answer lies overwhelmingly in genetics. Migraine is a highly heritable disorder, and research has followed two main streams: Studying rare, single-gene forms of the disorder and hunting for common genetic variants in the general population.

Lessons from the rare: Familial hemiplegic migraine (FHM)

FHM is a severe but rare subtype of migraine with aura that includes transient motor weakness on one side of the body. Its study has been a "Rosetta Stone" for understanding migraine, as it has allowed researchers to pinpoint specific, high-impact gene mutations. To date, three main genes have been identified:

- FHM1 is caused by mutations in the *CACNA1A* gene, which encodes the α1A subunit of the P/Q-type voltage-gated calcium channel. These channels are critical for regulating neurotransmitter release at synapses[13]
- FHM2 is caused by mutations in the *ATP1A2* gene, which encodes a subunit of the Na+/K+ pump, the enzyme responsible for maintaining the electrochemical gradients essential for neuronal excitability[14]
- FHM3 is caused by mutations in the *SCN1A* gene, which encodes the Nav1.1 voltage-gated sodium channel, crucial for initiating action potentials.[15]

The unifying theme of FHM is profound: it is a channelopathy or, more broadly, an ion-transporter-opathy. These genetic defects lead to a state of cortical neuronal hyperexcitability. This means the neurons have a lower threshold for firing, making the brain a tinderbox, ready to ignite a wave of CSD in response to a minor spark. This provided the first direct molecular evidence that migraine is a disorder of brain excitability.

Decoding the common: Genome-wide association studies (GWAS)

For the vast majority of people with common migraine (with and without aura), the genetic picture is polygenic. The risk is not from one faulty gene, but from the cumulative effect of hundreds of common genetic variants, or single-nucleotide polymorphisms, each conferring a tiny amount of risk. Identifying these has required enormous GWAS, which compare the genomes of hundreds of thousands of migraine sufferers with those of healthy controls.

These massive studies have been incredibly fruitful, identifying well over 100 distinct genetic loci associated with migraine risk.[16,17] While the function of every gene is not yet known, the identified loci are not random. They show significant enrichment – or thematic clustering – in highly plausible biological pathways:

- Vascular regulation: Genes involved in smooth muscle function, endothelial integrity, and vascular tone
- Synaptic function: A large number of hits are in or near genes related to neurotransmission, particularly the glutamatergic system, which is the brain's primary excitatory pathway
- Ion homeostasis: Genes encoding various ion channels and transporters, echoing the lessons learned from FHM
- Pain signaling and metalloproteinases: Genes directly involved in pain pathways and tissue remodeling.

The GWAS findings powerfully corroborate the neurovascular model of migraine. They paint a picture of a "migraine brain" that is built, from the ground up, with a lower threshold for activation, a more reactive vascular system, and heightened pain sensitivity.

THE NEW HORIZON: THERAPEUTIC TARGETS BEYOND CGRP

The triumphant success of CGRP-targeted therapies has invigorated the field, proving that a deep understanding of pathophysiology can lead to revolutionary treatments. Researchers are now leveraging this knowledge to explore the next wave of therapeutic targets.

Targeting the PACAP pathway

As discussed, PACAP represents a parallel signaling pathway to CGRP. Its receptor, PAC1, is highly expressed in the trigeminal ganglion and other key structures of the trigeminal

pain pathway. The fact that PACAP can trigger migraines even in patients on CGRP blockers makes the PAC1 receptor an extremely high-value target.[18] It offers the potential for a new class of drugs that could be effective for patients who do not respond adequately to CGRP inhibitors, or could even be used in combination for difficult-to-treat cases. Several pharmaceutical companies are actively developing small-molecule PAC1 receptor antagonists, with some now in clinical trials.

Modulating ion channels for neuronal stability

The genetic discoveries in FHM and GWAS have pointed directly to ion channels as fundamental players in migraine susceptibility. This opens up a rational design strategy: developing drugs that can stabilize neuronal excitability.

- Potassium channels (TRESK): The discovery that a loss-of-function mutation in the *KCNK18* gene, which codes for the TRESK potassium channel, causes a familial form of migraine with aura was a major breakthrough.[19] TRESK is a "leak" channel, meaning it is open at rest and helps to keep neurons in a quiet, non-excited state. It acts as a natural brake on neuronal firing. A faulty TRESK channel removes this brake. Therefore, developing small-molecule TRESK channel activators is a highly promising therapeutic strategy aimed at restoring this braking mechanism and dampening the hyperexcitability that initiates attacks
- Sodium channels: Specific sodium channel subtypes, like Nav1.7, are heavily involved in pain transmission and represent another area of active investigation for new, non-addictive pain therapies that could be applied to migraine.

The glutamatergic system

Given that glutamate is the brain's primary excitatory neurotransmitter and a key driver of CSD, its receptors has long been a target of interest. However, broadly blocking glutamate receptors like AMPA and NMDA with systemic drugs has been plagued by significant psychiatric and cognitive side effects, limiting their development.[20] The future may lie in developing more subtle modulators of the glutamatergic synapse that can dial down hyperactivity without causing global disruption.

Revisiting serotonin with precision: The ditans

The triptans, which are serotonin 5-HT${1B/1D}$ receptor agonists, were the first migraine-specific acute therapy. However, their action at the 5-HT${1B}$ receptor causes vasoconstriction, precluding their use in patients with cardiovascular disease. The identification of the 5-HT$_{1F}$ receptor offered a brilliant solution. This receptor is located on trigeminal neurons but is absent from cranial blood vessels. Agonizing this receptor inhibits the release of CGRP and reduces pain signaling without causing vasoconstriction. This led to the development of the "ditans," with lasmiditan being the first-in-class.[21] It represents a significant advance, decoupling effective pain relief from cardiovascular risk.

THE INDIAN CONTEXT: AN IMMENSE BURDEN AND A VAST TREATMENT GAP

While the scientific progress is astounding, its translation to clinical practice faces significant hurdles, particularly in a country like India. The burden of migraine here is immense, affecting tens of millions of people, yet it is often culturally dismissed or endured in silence, leading to chronic underdiagnosis and undertreatment.[22]

The arrival of the new mechanism-based therapies highlights a stark reality of global healthcare inequity. As of July 2025, in cities like Hyderabad, the revolutionary CGRP monoclonal antibodies remain prohibitively expensive, costing orders of magnitude more than traditional generic therapies. Their use is confined to a very small segment of the urban affluent population, leaving the vast majority of sufferers reliant on older medications like NSAIDs and triptans.[23] This creates a vast treatment gap, where the best available science is inaccessible to most.

The path forward for India requires a multi-pronged approach. There is a critical need for large-scale epidemiological and genetic studies within the diverse Indian population to understand local nuances of the disease. Furthermore, a focus on developing affordable diagnostics, scaling up telehealth services for neurological care, and advocating for policies that can improve access to newer medications will be essential to bridge this gap and lessen the burden of migraine on a national scale.

CONCLUSION: A NEW DAWN IN MIGRAINE CARE

The journey to understand migraine has been a long and winding one, leading us from a simplistic model of blood vessels to a sophisticated understanding of a complex genetic brain disorder. We now know that migraine is not a character flaw or a psychological weakness, but a tangible neurobiological disease with identifiable pathways and specific molecular players. The unraveling of the CGRP pathway is a landmark achievement in neuroscience, a case study in how decades of basic research can culminate in life-altering therapies.

We are now standing at the dawn of an even more exciting era. The knowledge gained from genetics and the continued exploration of inflammatory pathways are revealing a host

of new targets – PAC1, TRESK, and beyond. The future of migraine care will not be one-size-fits-all. It will be one of increasing precision and personalization, where a deeper understanding of an individual patient's biology, perhaps informed by their genetic profile or specific biomarkers, will guide the choice of the most effective therapy. The work is far from over, but for the first time in the long history of this ancient affliction; the path towards truly conquering the burden of migraine is clearly illuminated.

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