Inflammation in Migraine Headaches: From Pathophysiological Mechanisms to Emerging Therapeutic Targets-An Updated Review

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Abstract:
Background: Migraine is a highly prevalent neurological disorder and one of the leading causes of disability worldwide. Increasing evidence indicates that inflammation and neuroinflammation play fundamental roles in migraine pathogenesis through complex interactions involving immune mediators, neurotransmitters, and neurovascular signaling pathways. These inflammatory mechanisms also contribute to the high prevalence of psychiatric comorbidities, particularly depression, thereby increasing disease burden and complicating clinical management.
Aim: This review aims to comprehensively examine the role of inflammation and neuroinflammation in migraine pathophysiology, with particular emphasis on inflammatory cytokines, nitric oxide, glutamate, calcitonin gene-related peptide (CGRP), and their therapeutic implications.
Methods: A narrative review of the current literature was conducted using published experimental, clinical, and epidemiological studies focusing on migraine pathogenesis, inflammatory biomarkers, neurotransmitter dysregulation, neuroimmune mechanisms, and emerging targeted therapies.
Results: Evidence demonstrates that activation of the trigeminovascular system, microglial activation, and neurogenic inflammation initiate the release of pro-inflammatory cytokines, nitric oxide, glutamate, and CGRP, resulting in cortical spreading depression, peripheral and central sensitization, and persistent nociceptive signaling. Dysregulation of these inflammatory pathways contributes to migraine chronification, increased pain sensitivity, and the frequent coexistence of depression. Recent therapeutic advances targeting CGRP signaling and inflammatory mediators have significantly improved migraine prevention and treatment, although considerable interindividual variability in treatment response remains.
Conclusion: Inflammation represents a central mechanism underlying migraine initiation, progression, and chronicity. A better understanding of neuroimmune interactions and inflammatory signaling pathways may facilitate the development of personalized therapeutic strategies and novel disease-modifying interventions that improve clinical outcomes in patients with migraine.

Keywords: Migraine; Neuroinflammation; Inflammation; Calcitonin Gene-Related Peptide; CGRP; Cytokines; Nitric Oxide; Glutamate; Trigeminovascular System; Cortical Spreading Depression; Depression; Neuroimmune Mechanisms.

Introduction

Migraine is a highly prevalent and debilitating neurological disorder characterized by recurrent episodes of moderate-to-severe headache accompanied by a constellation of neurological, gastrointestinal, and autonomic symptoms. Unlike primary headaches that arise solely from peripheral nociceptive mechanisms, migraine is increasingly recognized as a complex neurovascular disorder involving intricate interactions among the central and peripheral nervous systems, cerebral vasculature, and immune-inflammatory pathways. Clinically, migraine attacks are typically manifested by

unilateral, pulsating headache of varying intensity and duration and are frequently associated with nausea, vomiting, photophobia, phonophobia, and, in many individuals, transient neurological disturbances collectively referred to as aura. These aura symptoms may include visual impairment, sensory disturbances, speech dysfunction, or other transient neurological manifestations preceding or accompanying the headache phase [1]. Although substantial advances have been achieved in understanding migraine biology during the past several decades, its precise pathophysiological mechanisms remain incompletely elucidated, reflecting the multifactorial nature of this disorder and the complex interplay between genetic susceptibility, environmental influences, neuronal excitability, vascular alterations, and immune-mediated inflammatory responses [1]. Headache disorders collectively represent one of the most common neurological conditions affecting populations worldwide and constitute a substantial public health challenge because of their high prevalence and significant socioeconomic consequences. Epidemiological evidence indicates that headache disorders affect approximately 52% of the global population, with migraine accounting for nearly 14% of all headache disorders [2, 3]. The widespread occurrence of migraine contributes substantially to reduced quality of life, impaired occupational productivity, diminished educational performance, and increased healthcare utilization. Beyond the immediate burden imposed by recurrent pain episodes, migraine frequently leads to persistent functional impairment that adversely affects social relationships, emotional well-being, and daily activities. Consequently, migraine has emerged as one of the leading contributors to disability worldwide. According to the Global Burden of Disease study, migraine ranked as the second leading cause of disability-adjusted life years (DALYs) attributable to neurological disorders in 2016, underscoring its profound impact on both individual health and global healthcare systems [4].

The burden of migraine extends beyond physical pain and neurological dysfunction, as this disorder exhibits a strong association with several psychiatric comorbidities, particularly depressive disorders. Depression represents another major contributor to global disability, with its prevalence increasing considerably following the COVID-19 pandemic. Recent estimates have demonstrated an approximately 27.6% increase in major depressive disorders during the pandemic period, reflecting the substantial psychological, social, and economic consequences experienced worldwide [5]. Depression affects individuals across all age groups, although its prevalence varies according to demographic characteristics. Older adults have demonstrated an estimated prevalence of depressive disorders approaching 35.1%, while depression remains among the leading causes of disease burden in children and adolescents, ranking second among young females and fifth among young males [6, 7]. Population-based investigations further illustrate the widespread nature of depressive disorders across different geographical regions. For example, a 2022 study conducted in South Africa reported that the estimated prevalence of depression ranged between 14.7% and 38.8%, with depression and anxiety occurring more frequently among retired individuals and adults older than 65 years. These findings also highlighted the important contribution of social, psychosocial, and economic stressors to the development and persistence of mood disorders within vulnerable populations [8]. An increasing body of evidence has demonstrated that migraine and depression frequently coexist, suggesting the presence of shared biological mechanisms rather than a simple coincidental association. A systematic review and meta-analysis published in 2023 revealed that children and adolescents younger than 19 years who experience migraine exhibit considerably higher rates of depression compared with individuals without migraine, with reported prevalence estimates ranging from approximately 20% to 50% [9]. The frequent coexistence of these disorders suggests the existence of bidirectional interactions in which migraine may predispose individuals to depressive symptoms while depression itself may increase the susceptibility to recurrent migraine attacks. This reciprocal relationship is believed to arise from overlapping neurobiological pathways involving alterations in neurotransmitter systems, neuronal hyperexcitability, genetic susceptibility, hypothalamic dysfunction, and inflammatory signaling pathways [9]. Dysregulation of serotonin and dopamine neurotransmission has long been implicated in both migraine pathophysiology and mood disorders, while persistent inflammatory activation further amplifies neuronal sensitization and emotional disturbances. These interconnected mechanisms not only increase vulnerability to depressive disorders but also contribute to greater migraine frequency, enhanced pain perception, prolonged disease duration, and poorer therapeutic outcomes [9].

Among the various mechanisms implicated in migraine pathogenesis, neuroinflammation has emerged as one of the most extensively investigated and clinically relevant processes. Neuroinflammation refers to the inflammatory response occurring within the central nervous system, encompassing both the brain and spinal cord, and involves the activation of resident immune cells together with the release of numerous inflammatory mediators [10]. Under physiological conditions, neuroinflammatory responses serve protective functions by maintaining tissue homeostasis and facilitating repair following injury. However, persistent or excessive activation of these inflammatory pathways may result in neuronal dysfunction, central sensitization, and chronic pain development. The neuroinflammatory cascade is characterized by the production of pro-inflammatory cytokines, chemokines, reactive oxygen species (ROS), nitric oxide, and various intracellular signaling molecules that collectively amplify inflammatory responses and influence neuronal communication [10]. The intensity and progression of neuroinflammation are determined by multiple factors, including the magnitude of inflammatory stimuli, the duration of immune activation, genetic predisposition, and the presence of underlying neurological disorders that may further exacerbate neuronal injury and dysfunction [11]. Current understanding increasingly recognizes migraine as a disorder involving activation of the trigeminovascular system accompanied by neurogenic inflammation within intracranial pain-sensitive structures. Inflammatory mediators released from activated trigeminal nerve endings contribute to vasodilation, plasma protein

extravasation, mast cell degranulation, and sensitization of peripheral and central nociceptive pathways. These events collectively promote the initiation and maintenance of migraine attacks while facilitating the transition from episodic to chronic migraine in susceptible individuals. Hall described headaches as manifestations of neuroinflammation involving pain originating from deep cranial structures and transmitted to pain-sensitive tissues located both within the cranial cavity and in extracranial regions [1]. This conceptual framework has shifted the traditional vascular hypothesis toward a more comprehensive neurovascular-inflammatory model, emphasizing the central role of inflammatory signaling in migraine generation and progression.

The management of migraine encompasses both pharmacological and non-pharmacological approaches designed to reduce attack frequency, alleviate symptom severity, improve functional capacity, and enhance overall quality of life. Lifestyle modifications, including optimization of sleep hygiene, dietary regulation, stress management, hydration, and avoidance of individual migraine triggers, remain fundamental components of comprehensive migraine management. Pharmacological interventions are generally categorized into first-, second-, and third-line therapeutic options according to clinical indications, efficacy, and patient characteristics [12]. Commonly prescribed medications include nonsteroidal anti-inflammatory drugs (NSAIDs), triptans, ergots, and the more recently introduced ditans, each targeting different aspects of migraine pathophysiology [12]. In parallel with conventional pharmacotherapy, growing interest has focused on medicinal plants and naturally derived bioactive compounds possessing anti-inflammatory properties. Traditional herbal therapies such as *Tanacetum parthenium* (Feverfew) and *Curcuma longa* (Turmeric) have demonstrated potential benefits in migraine prevention through modulation of inflammatory pathways. Furthermore, emerging experimental evidence has suggested that hot-water extracts derived from psilocybin-containing mushrooms exhibit anti-inflammatory activity by suppressing lipopolysaccharide (LPS)-induced cyclooxygenase-2 (COX-2) expression and reducing pro-inflammatory cytokine production, thereby highlighting their potential therapeutic value in inflammation-associated disorders, including migraine [13, 14, 15]. Despite substantial progress in elucidating migraine pathophysiology and expanding available therapeutic options, many patients continue to experience inadequate symptom control, recurrent attacks, or treatment-related adverse effects that limit long-term adherence and effectiveness [16]. Considerable heterogeneity exists in treatment response owing to differences in genetic background, disease phenotype, inflammatory status, comorbid conditions, and individual pharmacodynamic variability. Consequently, there is an increasing emphasis on developing personalized therapeutic strategies capable of targeting the underlying biological mechanisms specific to individual patients [16]. An additional clinical concern involves medication overuse, which may contribute to medication-overuse headache while simultaneously increasing the risk of mood disturbances and depressive symptoms. Moreover, certain antidepressant therapies have also been implicated in influencing migraine susceptibility, further complicating the management of patients with coexisting neurological and psychiatric disorders [17].

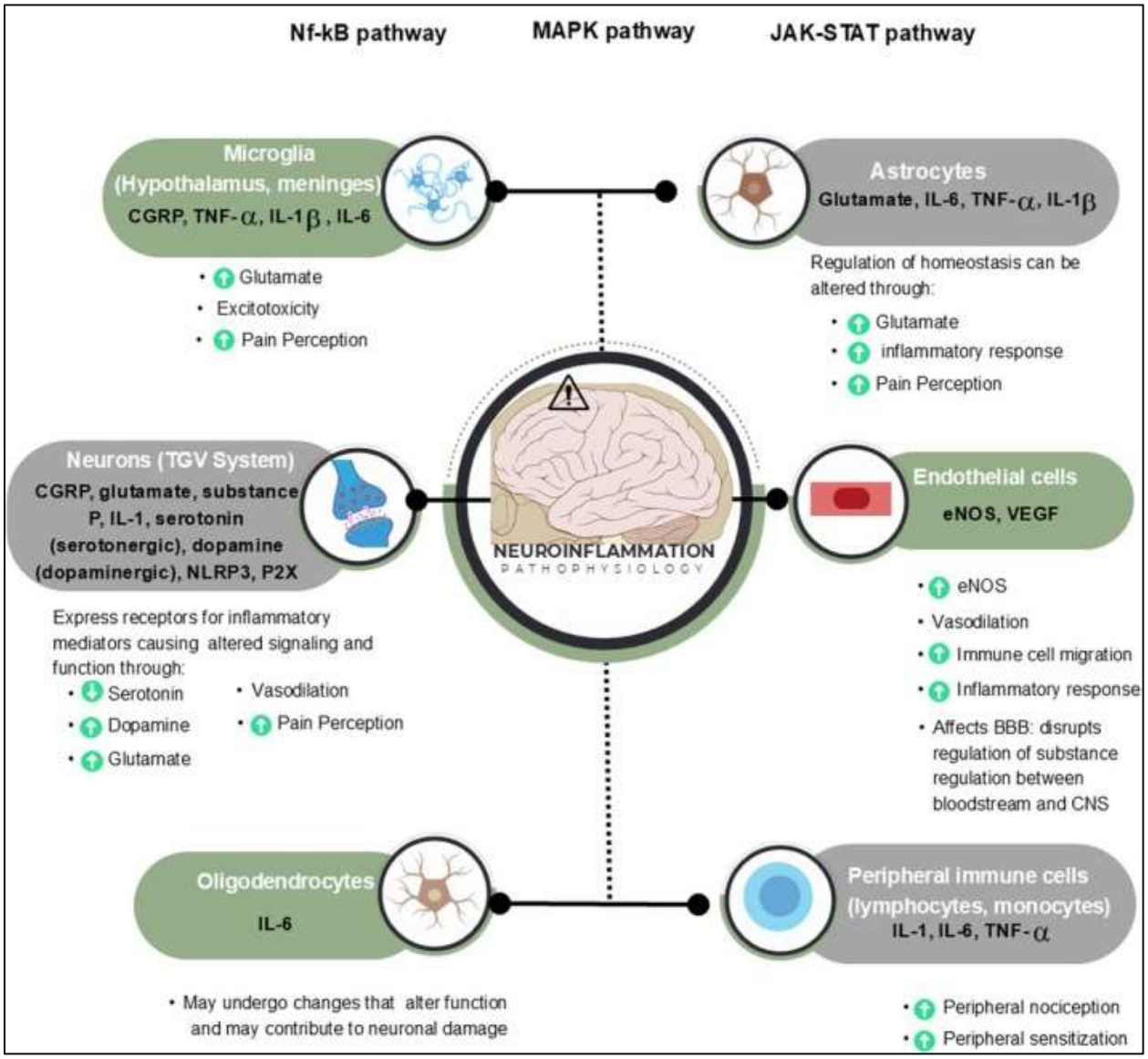

Fig. 1: Inflammation and Migraine.

Recent investigations have further highlighted the importance of excitatory neurotransmission in migraine pathogenesis, particularly the role of glutamate, which represents the principal excitatory neurotransmitter within the central nervous system. Dysregulation of glutamatergic signaling contributes significantly to cortical hyperexcitability, cortical spreading depression, trigeminal activation, central sensitization, and persistent nociceptive transmission associated with migraine attacks. The complexity of glutamate receptor subtypes, intracellular signaling pathways, and interactions with inflammatory mediators has presented significant challenges in the development of effective targeted therapies. Nevertheless, accumulating evidence suggests that modulation of glutamatergic neurotransmission may provide promising therapeutic opportunities for both acute and chronic migraine management [18, 19]. A comprehensive understanding of the intricate relationships among systemic inflammation, neuroinflammation, neurotransmitter dysregulation, and neuronal sensitization is therefore essential for identifying novel therapeutic targets. Advancing knowledge in these interconnected mechanisms may ultimately facilitate the development of more effective, mechanism-based interventions capable of addressing the substantial unmet clinical needs of individuals affected by migraine while improving long-term neurological and psychological outcomes [18, 19].

Migraine, Neuroinflammation, and Associated Neuropsychiatric Comorbidities

Migraine is a chronic neurological disorder that represents one of the most prevalent forms of primary headache and remains a major contributor to global morbidity and disability. It is currently recognized as the second most common headache disorder worldwide and one of the leading causes of years lived with disability, particularly among individuals during their most productive years of life [20]. Beyond the recurrent episodes of severe headache, migraine is increasingly acknowledged as a multifaceted neurobiological disorder characterized by disturbances in neuronal excitability, neurovascular regulation, immune activation, and inflammatory signaling. The considerable burden imposed by migraine extends beyond physical suffering, affecting cognitive performance, occupational productivity,

academic achievement, psychological well-being, and overall quality of life. Consequently, migraine has become a major public health concern that imposes substantial economic and healthcare burdens across both developed and developing countries [20]. The epidemiological burden of migraine continues to increase globally, with prevalence varying across geographical regions, socioeconomic backgrounds, and demographic characteristics. In South Africa, for example, Tucker [21] estimated that approximately 20% of the population, representing more than 11.8 million individuals, will experience migraine during their lifetime regardless of race, geographical location, lifestyle, or socioeconomic status [21]. These findings emphasize that migraine is a universal neurological disorder affecting diverse populations and highlight the need for equitable healthcare strategies aimed at improving diagnosis, treatment accessibility, and long-term disease management. Similar epidemiological patterns have been observed worldwide, demonstrating that migraine remains consistently underdiagnosed and undertreated despite its high prevalence and profound impact on functional capacity.

An important aspect of migraine pathophysiology is its strong association with psychiatric disorders, particularly depression. Accumulating clinical and epidemiological evidence has demonstrated that individuals with migraine exhibit a significantly greater risk of developing depressive disorders compared with the general population. Likewise, patients diagnosed with depression possess an increased susceptibility to recurrent migraine attacks, indicating a bidirectional relationship between these two conditions [22]. Rather than representing independent disorders that merely coexist, migraine and depression appear to share common biological pathways, genetic predispositions, and environmental risk factors that collectively contribute to their frequent comorbidity. Several investigations have demonstrated that migraine chronicity is closely associated with depressive symptoms through overlapping neurobiological mechanisms involving neurotransmitter dysregulation, neuroendocrine dysfunction, inflammatory activation, and altered neuronal plasticity [22]. This growing body of evidence suggests that understanding the biological interactions between migraine and depression may facilitate earlier diagnosis and the development of integrated therapeutic strategies capable of addressing both neurological and psychiatric manifestations simultaneously. Genetic susceptibility has emerged as another critical determinant influencing migraine development and disease progression. Advances in molecular genetics have identified numerous genes and polygenic variants that contribute to migraine susceptibility, providing valuable insight into the heritable nature of this neurological disorder [23, 24]. Although migraine is widely regarded as a complex polygenic disease rather than a single-gene disorder, multiple susceptibility loci have been implicated in regulating neuronal excitability, vascular function, inflammatory responses, and neurotransmitter signaling. These genetic influences contribute not only to migraine occurrence but also to disease severity, attack frequency, treatment responsiveness, and associated comorbidities. Studies involving twins and siblings have further strengthened the evidence supporting genetic contributions to both migraine and depression, demonstrating that shared hereditary factors may increase vulnerability to developing depressive disorders among individuals affected by migraine [25]. These findings reinforce the concept that migraine and depression possess overlapping genetic architectures that influence common neurobiological pathways.

The clinical relationship between migraine and depression extends beyond simple coexistence and significantly influences disease prognosis and patient outcomes. Individuals experiencing either episodic or chronic migraine demonstrate a substantially increased likelihood of developing depressive symptoms, while depression itself represents an independent risk factor for migraine chronification. Global estimates indicate that the prevalence of depression among individuals with migraine ranges from approximately 8.6% to 47.9%, reflecting differences in study populations, diagnostic criteria, and disease severity [22, 26]. The coexistence of depression often worsens migraine-related disability by increasing headache frequency, prolonging attack duration, reducing treatment responsiveness, and impairing overall quality of life. Furthermore, depression has been associated with increased psychosocial dysfunction, diminished social participation, reduced occupational performance, elevated healthcare utilization, and an increased risk of suicidal ideation and behavior among migraine sufferers [27]. These observations underscore the importance of comprehensive patient assessment that includes routine screening for psychiatric comorbidities as part of migraine management. Lifestyle factors also contribute substantially to migraine susceptibility and disease progression through their influence on neurochemical homeostasis and inflammatory regulation. Sleep disturbances, irregular dietary habits, psychological stress, and disruptions in circadian rhythms have all been identified as important triggers capable of precipitating migraine attacks. Alterations in normal sleep architecture and eating behavior may disrupt cognitive function and interfere with the synthesis, release, and metabolism of several neurotransmitters implicated in migraine pathophysiology, including serotonin, dopamine, glutamate, and numerous pro-inflammatory cytokines [27, 28]. These neurotransmitters originate from distinct anatomical regions, including the brainstem, hypothalamus, and peripheral nervous system, where they coordinate pain transmission, autonomic regulation, emotional processing, and vascular function [28]. Dysregulation within these interconnected neurochemical systems contributes not only to migraine initiation but also to the development of associated mood disorders, thereby reinforcing the complex bidirectional interactions between neurological and psychiatric disease processes.

Neuroimaging studies have provided additional evidence supporting shared neurobiological mechanisms between migraine and depression. Functional and structural imaging investigations have consistently demonstrated abnormalities in several brain regions involved in pain processing, emotional regulation, cognitive function, and sensory integration. Altered activity within cortical and subcortical structures has been observed in patients with migraine, particularly among individuals experiencing migraine without aura, suggesting that these neuroanatomical alterations may contribute to both headache generation and depressive symptomatology [22, 26]. The identification

of overlapping neural circuits involved in nociception, affective regulation, and cognitive processing further supports the hypothesis that migraine and depression represent interconnected neurological conditions arising from common disturbances within central nervous system networks. Pharmacological management of migraine-associated depression presents additional clinical challenges because medication overuse may paradoxically worsen headache frequency and contribute to disease progression. Excessive or prolonged use of antidepressants and opioid analgesics has been associated with an increased likelihood of recurrent migraine attacks and the development of medication-overuse headache [18, 29]. This phenomenon illustrates the complexity of managing patients with concurrent migraine and depression, as therapies intended to alleviate one condition may inadvertently exacerbate the other. The shared neurochemical pathways underlying both disorders further complicate treatment selection, emphasizing the importance of individualized therapeutic approaches that consider each patient's neurological, psychological, and pharmacological profile. Neuroinflammation has become a central concept in understanding the biological basis of migraine and numerous other neurological disorders. The term neuroinflammation refers to inflammatory processes occurring within the central nervous system (CNS) that involve interactions among immune cells, neurons, glial cells, and vascular structures, ultimately contributing to neuronal dysfunction and persistent neurological disease [30]. Headache disorders represent one of the most prevalent clinical manifestations associated with neuroinflammatory activation. A comprehensive systematic assessment involving 357 publications estimated that active headache disorders affected approximately 52% of the global population in 2022, highlighting the enormous worldwide burden of neuroinflammatory conditions [2]. Regional epidemiological investigations have similarly demonstrated high prevalence rates of primary headache disorders. A study examining headache prevalence across the Middle East, Asia, and Africa reported that approximately 23.4% of individuals experienced primary headache disorders, with overall headache prevalence reaching 53.29%, 27.44%, and 30.52% within these respective regions [31]. These findings emphasize the widespread nature of headache disorders across diverse populations and reinforce the urgent need for improved prevention and treatment strategies.

The neuroinflammatory response underlying migraine involves a highly coordinated interaction among peripheral immune cells, endothelial cells, astrocytes, microglia, and other neuroglial populations residing within the central nervous system [10, 30]. Activation of these cellular components initiates the release of numerous neurotransmitters and inflammatory mediators that collectively regulate neuronal excitability, synaptic transmission, and pain perception. Key mediators implicated in migraine pathophysiology include glutamate, dopamine, gamma-aminobutyric acid (GABA), interleukins such as IL-1α, IL-1β, and IL-16, tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), chemokines including CCL2, and complement proteins such as C1q [10, 30]. These molecules function within complex signaling networks that influence immune activation, neuronal sensitization, vascular permeability, and central pain processing. Cytokines, in particular, possess dual biological functions, acting as either pro-inflammatory or anti-inflammatory mediators depending on the physiological context and stage of disease progression. This dual functionality enables cytokines to either amplify inflammatory responses and neuronal injury or promote inflammation resolution and tissue repair, illustrating the dynamic nature of neuroimmune regulation during migraine attacks [30]. The expanding understanding of inflammatory signaling has directly influenced the development of contemporary migraine therapeutics. Current pharmacological strategies increasingly target specific inflammatory mediators and neurotransmitter systems responsible for migraine initiation and propagation. Both agonistic and antagonistic therapeutic approaches have been developed to modulate pathways involving calcitonin gene-related peptide (CGRP), serotonin (5-hydroxytryptamine; 5-HT) receptors, and multiple inflammatory cytokines [19, 32]. These targeted interventions aim to suppress neurogenic inflammation, inhibit nociceptive transmission, reduce central sensitization, and prevent recurrent migraine episodes. Conventional pharmacological therapies continue to include triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), and ergot derivatives, each acting through distinct mechanisms to interrupt inflammatory and pain signaling pathways [19]. Continued investigation into the molecular mechanisms governing neuroinflammation is expected to further improve therapeutic precision by identifying novel pharmacological targets capable of enhancing treatment efficacy while minimizing adverse effects. Such advances will contribute significantly to optimizing clinical management and improving long-term outcomes for patients suffering from migraine and its associated neurological complications.

Headaches, Migraine, and Depression

Headache disorders are among the most common neurological conditions worldwide, accounting for approximately 96% of benign neurological complaints and nearly 3% of emergency department presentations [33]. They are broadly classified into primary and secondary headache disorders according to the International Classification of Headache Disorders, Third Edition (ICHD-III). Primary headaches, including migraine, tension-type headache, and trigeminal autonomic cephalalgias, occur independently without an identifiable underlying structural or systemic disorder. In contrast, secondary headaches arise as a consequence of another medical condition, such as traumatic brain injury, cranial or cervical vascular diseases, nonvascular intracranial disorders, or cranial neuropathies including trigeminal neuralgia [34]. Primary headache disorders represent a significant public health concern because of their high prevalence, chronicity, and disabling nature, with medication-overuse headache constituting an additional clinical challenge that further complicates disease management [35]. Although headache epidemiology has expanded considerably in recent years, substantial variations remain across populations owing to differences in geographical regions, study methodologies, diagnostic criteria, and demographic characteristics [2]. The absence of pain-sensitive

nociceptors within the brain parenchyma suggests that headache pain primarily originates from surrounding pain-sensitive structures, including the meninges, cerebral and extracranial blood vessels, cranial and spinal nerves, facial tissues, and pericranial muscles [33]. Migraine is one of the most prevalent primary headache disorders and is characterized by recurrent attacks of moderate-to-severe unilateral, pulsating headache that may occur either with or without aura [36]. Migraine without aura, commonly referred to as common migraine, typically presents with headache episodes lasting between 4 and 72 hours and is frequently accompanied by nausea, vomiting, photophobia, and phonophobia in the absence of preceding neurological symptoms [32]. Conversely, migraine with aura affects approximately 8% of the general population and is characterized by transient, fully reversible neurological disturbances involving visual, sensory, or language functions that usually precede headache onset by 30 to 60 minutes [37]. Visual aura is by far the most common manifestation, occurring in approximately 98–99% of aura episodes, whereas sensory and language disturbances occur in nearly 36% and 10% of cases, respectively [37, 38]. Although migraine with and without aura share several pathophysiological mechanisms, they also exhibit distinct neurochemical profiles, biomarkers, and patterns of neuronal activation. Clinically, migraine attacks are generally divided into five phases, namely the prodrome, aura, headache, postdrome, and interictal phases, although not every patient experiences all stages during each attack [39].

Migraine pathophysiology involves a complex interaction among neuronal, vascular, inflammatory, and neurochemical mechanisms. Various endogenous and environmental triggers can initiate migraine attacks through alterations in receptor signaling and neurotransmitter release, including catecholaminergic pathways [32]. Psychosocial stress, disturbances in serotonergic and glutamatergic neurotransmission, and dysfunction of central pain-modulating systems further contribute to disease initiation and progression [28, 29]. These triggers activate interconnected brain regions, particularly the hypothalamus, brainstem, and limbic system, producing characteristic premonitory symptoms such as fatigue, excessive yawning, mood changes, and heightened sensitivity to light and sound before headache onset [39]. Activation of the trigeminovascular system represents a hallmark event in migraine pathogenesis. Stimulation of the trigeminal nerve (cranial nerve V) induces the release of vasoactive neuropeptides, including calcitonin gene-related peptide (CGRP), substance P, and vasoactive intestinal peptide (VIP), leading to neurogenic inflammation within the meningeal vasculature [10]. This inflammatory response promotes mast cell degranulation, plasma protein extravasation, vasodilation, and activation of peripheral nociceptors, collectively amplifying pain transmission and central sensitization during migraine attacks [10, 28, 29]. In addition, growing evidence implicates the purinergic P2X7 receptor in migraine pathogenesis, with elevated receptor expression observed in individuals with migraine, suggesting its potential role as a therapeutic target [40, 41, 42]. Migraine imposes a substantial global health burden by causing persistent disability, impaired daily functioning, reduced quality of life, and significant economic costs related to healthcare utilization and productivity loss [43]. Despite considerable advances in pharmacological management, a substantial proportion of patients with chronic migraine continue to exhibit inadequate responses to conventional therapies, emphasizing the need for novel treatment strategies that target the underlying inflammatory and neurobiological mechanisms of the disease [43]. Continued investigation into the interactions among neuroinflammation, immune signaling, and nociceptive pathways is therefore essential for improving therapeutic outcomes and developing more effective mechanism-based interventions.

Depression is among the leading causes of disability worldwide and represents one of the most common psychiatric comorbidities associated with migraine [44]. According to the Global Burden of Diseases, Injuries, and Risk Factors Study 2019, depressive and anxiety disorders were identified as the two most disabling mental health conditions globally and ranked among the top 25 causes of disease burden worldwide [45]. Epidemiological studies have consistently demonstrated that individuals with migraine are three to six times more likely to develop depression than individuals without a history of severe headaches [46, 47, 48]. Furthermore, evidence supports a bidirectional relationship in which migraine increases the risk of developing major depressive disorder, while depression independently increases the likelihood of subsequent migraine attacks [47, 48]. Interestingly, this reciprocal association appears to be specific to migraine rather than other severe headache disorders, suggesting the presence of unique shared biological mechanisms linking these two conditions [47, 48]. The coexistence of migraine and depression reflects overlapping genetic, neurochemical, and neurobiological pathways rather than independent disease processes. Depression is characterized by persistent disturbances in mood, emotional regulation, and cognitive function resulting from complex interactions among genetic susceptibility, environmental stressors, and alterations in central nervous system function [49]. While migraine was traditionally considered primarily a peripheral disorder involving sensitization of trigeminal nociceptors and depression was viewed as a disorder of central neurotransmission, contemporary evidence indicates substantial overlap between the two conditions. Neuroimaging studies have demonstrated abnormal cortical sensory processing and altered central pain modulation in patients with migraine, further supporting the involvement of central nervous system dysfunction in migraine pathogenesis [50]. Dysregulation of neurotransmitters including serotonin, dopamine, and norepinephrine, together with altered neuropeptide signaling, hormonal imbalance, and chronic inflammatory activation, contributes to both migraine and depression by affecting brain regions responsible for pain perception, emotional regulation, and stress responses. Consequently, accumulating evidence indicates that migraine and depression frequently coexist because they share interconnected neurological and inflammatory pathways capable of promoting the onset and progression of each disorder [51].

Inflammation, Neuroinflammation, and Key Inflammatory Mediators in Migraine

Inflammation is a fundamental physiological response that protects tissues against injury, infection, and cellular damage while maintaining tissue homeostasis. Within the central nervous system (CNS), this process is referred to as neuroinflammation and is primarily mediated by activated microglia and astrocytes together with the release of pro-inflammatory cytokines and other immune mediators that initially serve protective functions [36]. However, persistent or dysregulated inflammatory responses disrupt normal neuronal function and contribute to the development of neurological disorders, including migraine. Both neurogenic inflammation and neuroinflammation have been consistently implicated in the pathogenesis of migraine with aura, migraine without aura, and chronic migraine [52, 53]. Neurogenic inflammation represents a sterile inflammatory response initiated by peripheral release of neuropeptides from activated nociceptive fibers, leading to vasodilation, plasma protein extravasation, and activation of the trigeminovascular system within the dura mater [11, 53]. In contrast, neuroinflammation involves activation of resident immune cells within the CNS, particularly microglia and astrocytes, which release cytokines, chemokines, reactive oxygen species (ROS), and secondary messengers that amplify neuronal sensitization and pain transmission [10, 11]. Chronic or maladaptive activation of these inflammatory pathways has been recognized as a major contributor to persistent neurological dysfunction and migraine chronification [10]. Among the inflammatory mediators implicated in migraine, cytokines have emerged as important biomarkers of disease activity and progression. Activation of microglia, the NOD-like receptor pyrin domain-containing-3 (NLRP3) inflammasome, and cyclooxygenase-2 (COX-2) stimulates the production of numerous cytokines and chemokines, including interleukin (IL)-1β, IL-6, tumor necrosis factor-alpha (TNF-α), inducible nitric oxide synthase (iNOS), matrix metalloproteinases, and chemokines that promote neurogenic inflammation [50, 56–58]. Elevated concentrations of IL-1α, IL-1β, IL-6, IL-8, IL-10, TNF-α, homocysteine, and matrix metalloproteinase-9 (MMP-9) have been detected during migraine attacks, indicating that inflammatory activation accompanies both the onset and progression of migraine episodes [16]. Cytokines also contribute to cortical spreading depression (CSD), particularly in migraine with aura, while enhanced parasympathetic activation sensitizes meningeal nociceptors and promotes premonitory symptoms such as nausea, mood alterations, and nasal congestion [10, 58]. Furthermore, inflammatory signaling mediated through nuclear factor-kappa B (NF-κB), activation of P2X7 receptors, NLRP3 inflammasome assembly, and intracellular pathways involving mitogen-activated protein kinase (MAPK), cyclic adenosine monophosphate (cAMP), cAMP-response element-binding protein (CREB), and extracellular signal-regulated kinase (ERK) collectively enhance peripheral and central sensitization, thereby increasing susceptibility to chronic migraine and persistent pain [36, 56, 59, 60, 61, 62].

Nitric oxide (NO) is another critical mediator in migraine pathophysiology because of its dual physiological and pathological functions. Under normal conditions, NO regulates vascular homeostasis, cerebral blood flow, neurotransmission, and immune responses. These functions are mediated by three nitric oxide synthase (NOS) isoforms, namely endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS) [63–65]. While eNOS and nNOS generate physiological concentrations of NO that support vascular function and neuronal communication, iNOS is induced during inflammatory conditions and produces excessive NO that promotes oxidative stress, vascular inflammation, and neuronal injury [63, 64]. Increased iNOS activity within cranial tissues contributes to vasodilation, activation of trigeminal nociceptive pathways, and heightened pain perception during migraine attacks [63, 65]. Nitroglycerin, an NO donor, is well known to induce migraine-like headaches through excessive NO production and activation of purinergic receptors and the NLRP3 inflammasome [56, 63]. Sustained elevations in NO further impair inhibitory feedback mechanisms, promote calcium influx, oxidative stress, altered neuroplasticity, and depressive symptoms, thereby linking nitrosative stress to both migraine and psychiatric comorbidities [56, 63–65]. Glutamate, the principal excitatory neurotransmitter in the CNS, also plays a central role in migraine pathogenesis. Through activation of N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors, glutamate regulates excitatory neurotransmission, cortical spreading depression, pain modulation, and central sensitization [39]. During migraine attacks, excessive glutamate release produces neuronal hyperexcitability and excitotoxicity, activating microglia and stimulating production of inflammatory cytokines that further amplify neuroinflammation [66, 68]. Astrocytes normally regulate extracellular glutamate concentrations by converting excess glutamate into glutamine, thereby preserving neuronal homeostasis and blood-brain barrier integrity [51]. However, impaired glutamate clearance contributes to sustained neuronal activation and inflammatory signaling. Magnesium deficiency, frequently observed during migraine attacks, further enhances NMDA receptor activation and calcium influx, facilitating cortical spreading depression and increasing migraine susceptibility [69]. Chronic glutamatergic dysregulation promotes persistent central sensitization and has also been implicated in depressive disorders through excitotoxic injury affecting the prefrontal cortex, amygdala, and hippocampus [32, 70].

Calcitonin gene-related peptide (CGRP) has emerged as one of the most important mediators linking neurogenic inflammation and migraine. CGRP is a 37-amino acid neuropeptide widely distributed throughout the peripheral nervous system and CNS, where both CGRP-α and CGRP-β isoforms contribute to peripheral and central sensitization [50]. Activation of trigeminal afferents during migraine results in CGRP release, producing dilation of meningeal and cortical blood vessels, increased cerebral blood flow, and amplification of inflammatory signaling [10, 28, 50]. Experimental evidence further suggests that CGRP contributes to depressive-like behaviors and photophobia while increased expression of receptor activity-modifying protein-1 (RAMP-1) enhances CGRP receptor signaling during migraine attacks [28, 29]. Current evidence indicates that migraine develops through activation of meningeal nociceptors and the trigeminovascular system following exposure to intrinsic or extrinsic triggers such as hormonal

fluctuations, stress, dietary factors, sensory stimuli, and environmental changes [2, 61, 70]. These stimuli alter neurotransmitter homeostasis, promote calcium influx, and induce release of CGRP, glutamate, cytokines, nitric oxide, and inflammasome mediators, resulting in neurogenic inflammation, peripheral nociceptor sensitization, cortical spreading depression, and persistent pain transmission [10, 59, 71]. Collectively, advances in migraine research have established inflammation, neuroimmune activation, glutamatergic signaling, nitric oxide metabolism, and CGRP-mediated pathways as interconnected mechanisms that provide important therapeutic targets for the prevention and treatment of both episodic and chronic migraine [19, 32].

Conclusion

Migraine is a multifactorial neurovascular disorder in which inflammation and neuroinflammation play central roles in disease initiation, progression, and chronification. The coordinated activation of the trigeminovascular system, inflammatory cytokines, nitric oxide, glutamate, CGRP, and microglial cells contributes to neuronal sensitization and persistent pain transmission. These pathways also explain the frequent coexistence of migraine with depression and other neuropsychiatric disorders. Advances in understanding neuroimmune mechanisms have led to targeted therapeutic approaches, particularly CGRP-based therapies. Continued research into inflammatory biomarkers and individualized treatment strategies is essential for improving therapeutic efficacy, reducing disability, and enhancing the quality of life of patients with migraine.

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