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Glia Signaling and Brain Microenvironment in Migraine

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Abstract

Migraine is a complicated neurological disorder affecting 6% of men and 18% of women worldwide. Various mechanisms, including neuroinflammation, oxidative stress, altered mitochondrial function, neurotransmitter disturbances, cortical hyperexcitability, genetic factors, and endocrine system problems, are responsible for migraine. However, these mechanisms have not completely delineated the pathophysiology behind migraine, and they should be further studied. The brain microenvironment comprises neurons, glial cells, and vascular structures with complex interactions. Disruption of the brain microenvironment is the main culprit behind various neurological disorders. Neuron-glia crosstalk contributes to hyperalgesia in migraine. In the brain, microenvironment and related peripheral regulatory circuits, microglia, astrocytes, and satellite cells are necessary for proper function. These are the most important cells that could induce migraine headaches by disturbing the balance of the neurotransmitters in the nervous system. Neuroinflammation and oxidative stress are the prominent reactions glial cells drive during migraine. Understanding the role of cellular and molecular components of the brain microenvironment on the major neurotransmitters engaged in migraine pathophysiology facilitates the development of new therapeutic approaches with higher effectiveness for migraine headaches. Investigating the role of the brain microenvironment and neuroinflammation in migraine may help decipher its pathophysiology and provide an opportunity to develop novel therapeutic approaches for its management. This review aims to discuss the neuron-glia interactions in the brain microenvironment during migraine and their potential role as a therapeutic target for the treatment of migraine.

Keywords Migraine · Neuroinflammation · Blood–brain barrier · Cytokines · Neurotransmitters · Oxidative stress · Glial cells

Abbreviations

CNS	Central nervous system
BBB	Blood-brain barrier
IgE	Immunoglobulin
TNF- α	Tumor necrosis factor- α
IL	Interleukin
CGRP	Calcitonin gene-related peptide
NMDA	N-methyl-D-aspartate
SGC	Satellite glial cells
PICs	Proinflammatory cytokines
TNC	Trigeminal nucleus caudalis
PAG	Periaqueductal gray
LC	Locus coeruleus
RN	Raphe nuclei
PI3K	Phosphatidylinositol-3-kinase
CSD	Cortical spreading depolarization
TRPA1	Transient receptor potential ankyrin 1
NO	Nitric oxide
TG	Trigeminal ganglion
FHM	Familial hemiplegic migraine

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DRG	Dorsal root ganglion
TRP	Transient receptor potential
CRLR/CGRPR1	Calcitonin receptor-like receptor/CGRP receptor 1
ROS	Reactive oxygen species
TGF- β	Transforming growth factor- β
BDNF	Brain-derived neurotrophic factor
NLRP3	NLR family pyrin domain containing 3
TLR	Toll-like receptor
NF-K β	Nuclear factor kappa B
STAT	Signal transducer and activator of transcription
IFN	Interferon
iNOS	Inducible nitric oxide synthase
P2XR	P2X purinergic receptor
ATP	Adenosine triphosphate
AMPA	α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
GABAA	Gamma-aminobutyric acid A
GLT1	Glutamate transporter 1
GluR1	Glutamate receptor 1
Kir	Inwardly rectifying potassium channels
EAAT2	Excitatory amino acid transporters 2
EPK	Eukaryotic protein kinase
RAMP	Receptor activity modifying proteins
CASK	Calmodulin-dependent serine protein kinase
GFAP	Glial fibrillary acidic protein
Iba1	Ionized calcium-binding adaptor molecule 1
SNAP-25	Synaptosomal-associated protein, 25 kDa
HK-1	Hemokinin-1
pERK	Extracellular signal-regulated kinase
PRR	Pattern recognition receptors
JAK	Janus kinase
CCL	Chemokine ligand
A7 nAChR	α 7 Nicotinic acetylcholine receptor
P-JNK	Phosphorylated c-Jun N-terminal kinase
MAPK	Mitogen-activated protein kinase
SFRP1	Secreted frizzled-related protein 1
PACAP	Pituitary adenylate cyclase-activating polypeptide
VIP	Vasoactive intestinal peptide
Th	T helper cells
PGI2	Prostaglandin I2
GABA	Gamma-aminobutyric acid
TRPV1	Transient receptor potential cation channel subfamily V member 1
PAC1	PACAP type I
AEG-1	Astrocyte elevated gene-1
5-HT	5-Hydroxytryptamine

nVNS	Non-invasive vagus nerve stimulation
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
HERNS	Hereditary endotheliopathy with retinopathy, nephropathy, and stroke
GDNF	Glial cell line-derived neurotrophic factor
GFR α 3	Growth family receptor α 3
NSAIDs	Nonsteroidal anti-inflammatory drugs
FDA	US Food and Drug Administration

Introduction

Migraine is a throbbing unilateral headache that lasts 4–72 h, with symptoms such as nausea and vomiting, sensory and cognitive dysfunctions, and photophobia with or without aura. It occurs in episodic (less than 15 days per month) or chronic type headaches (15 or more days per month) [1–4]. Altered mitochondrial function, neuroinflammation, oxidative stress, neurotransmitter disturbances, cortical hyperexcitability, genetic factors, and endocrine system disorders are among the various etiologies for migraine. None of the above can thoroughly delineate the pathophysiology behind it alone, and current medications are not entirely effective in all patients [5, 6].

Migraine as a multi-etiological disorder has direct and indirect interaction with neurons, brain glial cells, and other environmental and genetic components [7]. Glial cells, including microglia, astrocytes, oligodendrocytes, and ependymal cells, regulate central nervous system (CNS) homeostasis. They supply nutrients, provide physical support for neural development, and modify the interneural synaptic activity through neuroglial signaling and specific neurotransmitters, namely glutamate, adenosine triphosphate, serine, and gamma-aminobutyric acid [8, 9]. Astrocytes are pivotal in blood–brain barrier (BBB) integrity, cell metabolism, neural plasticity, and glutamate uptake in the synaptic space. On the other hand, they can cause several neurologic disorders through inflammatory reactions, apoptosis, and oxidative stress [10, 11]. Studies reported that the release of calcitonin gene-related peptide (CGRP) from sensory neurons and their interaction with satellite glial cells (SGCs) via gap junctions and paracrine signaling results in hyperalgesia during migraine episodes [8, 12, 13]. Released CGRP and substance P (trigeminal ganglia neuropeptides) from primary afferents activate second-order neurons for subsequent allodynia [14, 15].

In recent years, the role of neuromodulators and their interactions with the immune system in the trigeminal ganglia microenvironment have been investigated. Microglia and astrocyte pedicles at the basal lamina regulate tight

junction integrity in BBB [16]. In the nociceptive-activated trigeminal system, microglia release IL-6 and TNF- α proinflammatory cytokines (PICs), increasing vascular permeability in migraine [17–21]. Higher levels of immunoglobulin E (IgE), tumor necrosis factor- α (TNF- α), histamine, and interleukin-1 β (IL-1 β) and lower phagocytosis of polymorphonuclear leukocytes are associated with migraine [14, 22–24]. TNF- α acts on trigeminal nociceptive afferents to increase neural predisposition to noxious stimuli [14, 15].

The exact mechanisms involved in the initiation and progression of migraine have not been thoroughly understood. The precise role of glial cells and their mediators, ion channels, and sex differences mechanisms during the attacks should be determined by further studies [25–27]. The present review aims to explain the role of glial cells, neuron-glia interactions, and inflammatory reactions in migraine pathophysiology. Moreover, potential therapeutic targets of migraine associated with the brain microenvironment will be discussed.

Brain Microenvironment

Definition and Structure

Brain microenvironment is a term used to describe the complex dynamic neuron-glia interactions and brain vasculature involved in physiological and pathological processes in the CNS [28]. During migraine episodes, trigeminal afferents in the trigeminal ganglion transmit impulses to the trigeminal nucleus caudalis (TNC), located in the brainstem. Neurons from TNC project to the thalamus, hypothalamus, and rostral brain areas for pain perception. TNC also receives modulatory inputs from periaqueductal gray (PAG), locus coeruleus (LC), and the raphe nuclei (RN)—all of them are involved in attacks [15, 29]. Dura matter vessels take parasympathetic reflexes from the trigeminal nucleus through the salivary nucleus and sphenopalatine ganglia to dilate the vessels and promote inflammation, leading to initiation of the headache [30, 31].

Neuron-Glia Crosstalk

Neuron-glia crosstalk is responsible for various pain mechanisms [32]. Astrocytes are one of the most critical modulators of neurons in the brain microenvironment among all glial cells participating in the migraine mechanism. They control extracellular components and neurotransmitter concentration in the synaptic cleft [33]. Familial hemiplegic migraine (FHM) mutations, subsequent disrupted excitatory-inhibitory cell balance, and pannexin 1 mega channel activated by NMDA glutamate receptor are responsible for the inflammatory cascade in astrocytes [34–36]. Astrocytes

with CKI δ mutations augment calcium signaling and alter the sleep pattern in migraine [37]. Astrocytes and microglia participate in chronic trigeminal sensitivity.

Recently, the glial-associated lymphatic system, also known as the glymphatic system, as an essential part of the CNS microenvironment, has attracted attention in the pathophysiology of neurological diseases [38]. Neurotransmitters are also an indispensable component of neuron-glia interaction. The primary suggested etiology for lifetime changes in migraine attacks is serotonin, which decreases with aging [39].

Cortical Spreading Depolarization and Brain Microenvironment

Cortical spreading depolarization (CSD) is a slow propagated partial neuron-astrocyte depolarization leading to consequences, including out-of-balance ion flux, inflammatory reactions, and neural activity suppression. CSD is the primary event that triggers aura and activates trigeminal afferents nearby meningeal vessels through modification of intracellular Ca²⁺ + [40–42]. Various triggers may activate the CSD and increase the extracellular potassium and glutamate, leading to a slow propagated neuroglial electrophysiological wave in the gray matter of migraine with aura. As a consequence, inflammatory reactions start to increase immediately following the event [43]. The CSD-inflammation theory was confirmed through the observation of increased neuroglial activation in several brain regions as traced by PET/MRI scans, which was found to be more concentrated in individuals experiencing frequent episodes and was specifically related to migraine pain [44].

In migraine with aura, CSD stimulates meningeal inflammation and excitation of trigeminovascular neurons. Frequent neuroinflammatory reactions lead to BBB breakdown; hence neuropeptides, namely CGRP and pituitary adenylate-cyclase-activating polypeptide (PACAP), get through the brain tissue to instigate migraine attacks [45]. In the acute stage of inflammatory reactions in the brain, BBB disruption and trigeminal hypersensitivity could be observed [16]. After CSD, long-term vasoconstriction with sustained intracellular calcium release in capillary pericytes results in apoptosis and BBB integrity disruption [46]. Hyperexcitation of neurons and glial cells reduces the trigeminal signaling threshold through some known mutations. Higher calcium currents seen in CACNA1A gene mutation (encoding CaV2.1 Channels) boost the glutamate release and activate NMDA receptors to facilitate the CSD. Activated TRP ankyrin1 (TRPA1) receptors in trigeminal ganglion (TG) contribute to the secretion of CGRP and nitric oxide (NO), stimulating IL-1 β production in glia. IL-1 β increases cyclooxygenase activity and subsequently augments prostaglandin E2 production, which can sensitize TG [47].

A summary of general events in the migraine and the role of microglia has been demonstrated in Fig. 1.

Glial Cells and Oxidative Stress in Migraine

Oxidative Stress and Channelopathies

Oxidative imbalance contributes to pain sensitization and glial cell activation processes in migraine, specifically when the aura is also present [48, 49]. CSD triggers oxidative spreading to trigeminal nociceptive and activates CGRP release [50]. During sensitization, oxidative stress stimulates transient receptor potential (TRP) channels to mediate Ca^{2+} influx across the cell membrane [51]. TRPA1 ion channels in C fiber neurons are involved in CGRP release, subsequent

inflammation, and oxidative environment. Selenium inhibits the TRP channel activation in the DRG and prevents peripheral pain sensitization [52, 53]. Therefore, oxidative stress and channelopathies are responsible for inflammatory conditions exist through the trigeminal ganglia in migraine disease.

Mitochondrial Dysfunction in the Migraine

The central nervous system (CNS) is highly dependent on blood oxygen, making neural cells susceptible to damage in the event of mitochondrial dysfunction. Longitudinal and cohort studies suggest that the mitochondrial oxidative process may contribute to the pathophysiology of migraines. Several studies have documented a higher incidence of migraines in individuals with various forms of mitochondrial

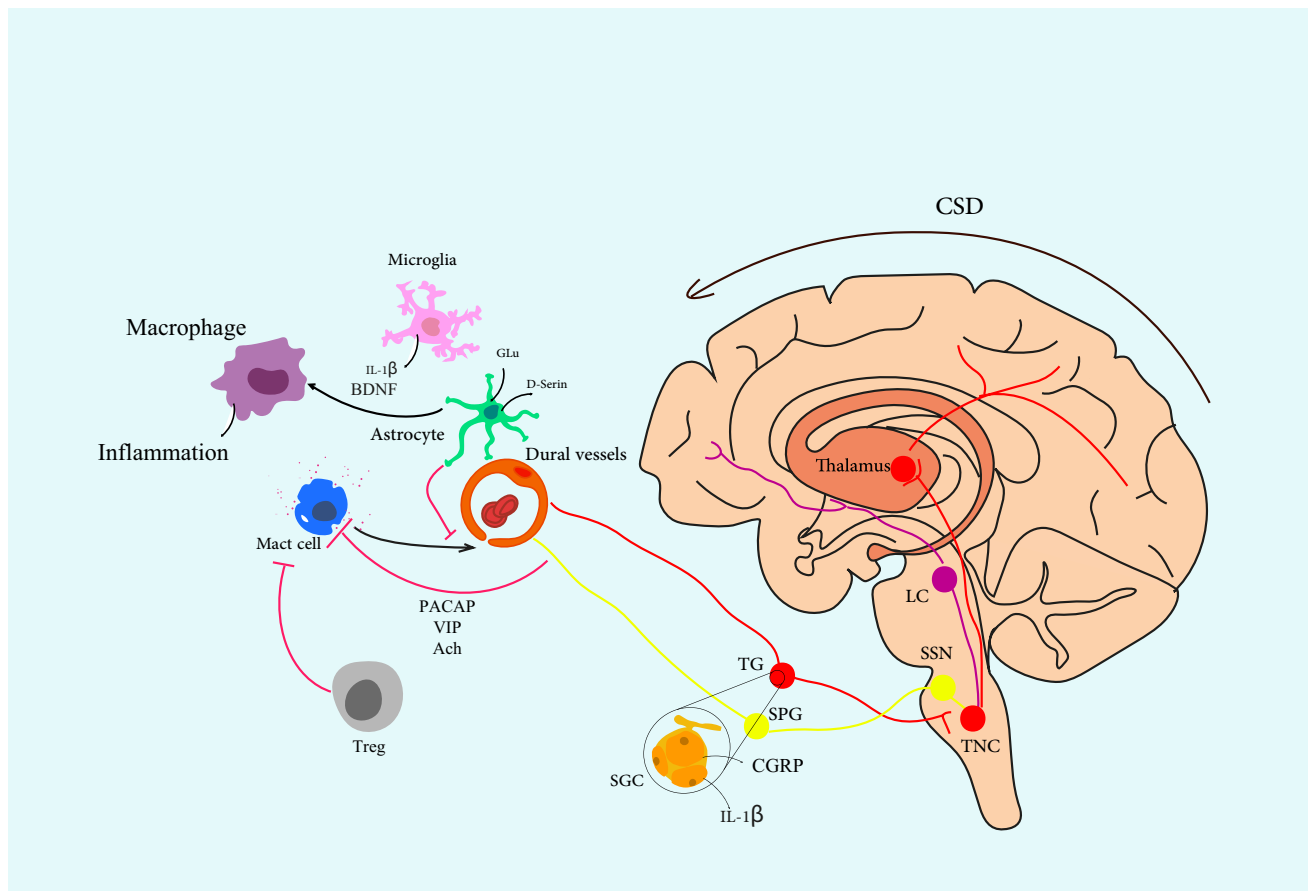


Fig. 1 Summary of glia involvement in migraine. The central and peripheral nervous systems interact with each other during migraine pathophysiology. In neurogenic inflammation, CSD stimulates peripheral nerves to release substance P and CGRP from TG, leading to further vascular leakage and mast cell degranulation. Neuroglial signaling at peripheral sites induces inflammation and nociception, which start an inflammation-allodynia positive loop in TG. Moreover, glial-glia and neuron-glia interactions, in addition to inflammatory reactions, play a significant role in migraine induction within the

brain. Abbreviations: CSD, cortical spreading depolarization; LC, locus coeruleus; SSN, superior salivatory nucleus; TNC, trigeminal nucleus caudalis; TG, trigeminal ganglion; SPG, sphenopalatine ganglion; CGRP, calcitonin gene-related peptide; IL-1 β , interleukin-1 β ; SGC, satellite glial cell; PACAP, pituitary adenylate-cyclase-activating polypeptide; VIP, vasoactive intestinal peptide; Ach, acetylcholine; Treg, regulatory T cells; Glu, glutamine; BDNF, brain-derived neurotrophic factor

diseases [54–56]. Deficiency in the mitochondrial oxidative phosphorylation process, higher brain oxygen demands, and several mitochondrial-related triggers are involved in the early stages of the migraine. Decreased activity in complex I of the electron transport chain has been observed in non-H mitochondrial haplotype patients with migraine. Nuclear DNA mutations, impaired superoxide dismutase, and cytochrome-c oxidase dysfunction could increase reactive oxygen and nitrogen products [57–60]. The vascular changes that occur during CSD and subsequent hypoxia result in longer NADH usage and a decreased ability of the mitochondrial redox system to generate ATP [61]. Further studies are necessary to fully understand the role of mitochondria in the progression of migraines.

Oxidative Markers in Migraine Episodes

Oxidative stress may arise from mitochondrial overactivity, membrane destruction, microglial activation, and higher neuronal NADPH oxidase activity [52]. Togha et al. reported higher oxidative markers (NO and malondialdehyde) and lower amounts of antioxidants (catalase and superoxide dismutase) in chronic migraine patients [62]. NO produce reactive free radicals that have apoptotic effects on cells and enhance inflammatory signaling in TG, leading to augmented reactive oxygen species (ROS) production [26, 63, 64]. Aral et al. showed that glyceryl trinitrate with NO groups altered calcitonin receptor-like receptor/CGRP receptor 1 (CRLR/CGRPR1) expression in astrocytes, microglia, and meningeal cells in migraine and caused cellular iron mislocalization. These iron free radicals participate in oxidative stress-related cellular damage [65]. Studies found a correlation between other oxidative markers in migraineurs' blood. Dini et al. observed higher oxidation protein products and lower ferric-reducing antioxidant power and thiolic groups in chronic migraine patients. Onabotulinumtoxin A reduced oxidative stress and improved antioxidative reactions in these patients [66]. Tripathi et al. found significantly reduced glutathione, glutathione-S-transferase, and total antioxidant activity in migraineurs. Treatment with amitriptyline resulted in improved glutathione-S-transferase and total antioxidant activity [67].

Glia Cells' Roles in the Brain Microenvironment in Migraine

Microglia

Microglia in CNS Disorders

Microglia are a population of macrophage-like cells in the brain whose functional state and proliferation are closely

controlled by the local microenvironment and surrounding cells [68]. Microglia have multiple roles and contribute to the development of CNS and its appropriate function; hence their disturbances can be seen in different CNS disorders. In the prenatal brain, microglia act through phagocytosis of neural progenitors, modulation of molecular signaling, and degradation of growing axons, thus regulating brain development. In the postnatal brain, proper oligodendrogenesis and myelinogenesis depend on microglia function in neural network organization. Synaptic plasticity via brain-derived neurotrophic factor (BDNF) release and fractalkine pathway and synaptic pruning via complement signaling are parts of microglia's function in brain development and learning process [69].

Microglia Phenotyping and Its Role in Inflammation

Microglial cells and non-parenchymal macrophages in the choroid plexus and perivascular areas are the main contributors to innate immune reactions in the brain [70]. TLR activates microglia to secrete TNF- α , chemokine ligand-2 (CCL-2), IL-1 β , and IL-6. Activated microglia also secrete BDNF, which is necessary for synaptic plasticity. Non-parenchymal macrophages perform phagocytosis and release proinflammatory substances, matrix metalloproteinases, and free radicals, therefore instigating inflammation and neurodegeneration [70–72]. An in vitro study demonstrated that activated macrophages increase neural stimulation by hyperstimulating pain transducer P2X3 receptors on neurons [73]. Microglia polarization imbalance can cause excessive M1 macrophages and initiate neurodegenerative disease. M1 macrophage phenotype activation results in neural injury. On the other hand, the M2 macrophages have anti-inflammatory effects through the expression of neuroprotective elements, including IL-10, arginase, mannose receptor C type 1, and insulin-like growth factor-1 [74].

Microglia can switch between two opposite subtypes in different conditions: the M1 phenotype with the potential to produce ROS, TNF- α , IL-1 β , and IL-12 in the proinflammatory environment and the M2 phenotype with the capacity to release transforming growth factor- β (TGF- β) and BDNF in the anti-inflammatory environment [75, 76]. M1 microglia play an essential role in CSD by ROS and TNF- α production and suppression of inhibitory synapses. Environmental enrichment and nasal IL-11 could polarize the M2 phenotype and decrease attack frequencies in rats [77]. M1 microglial cell is the brain's primary source of inducible NO synthase (iNOS). Pusic et al. showed that nasal administration of exosomes derived from interferon (IFN)- γ dendritic cells decreased M1 polarization of microglia, leading to lower oxidative processes in the hippocampus and increased CSD threshold in both in vitro and in vivo settings [78]. This switching pattern between M1 and M2 phenotypes in

microglia-associated disorders makes it a promising pharmaceutical target for drug development. Gaojian et al. found that parthenolide, the significant ingredient of feverfew leaves, can shift microglia to the M2 phenotype, therefore inhibiting nuclear factor kappa B (NF- κ B) and signal transducer and activator of transcription (STAT)1/3 inflammatory pathways in spinal cord injury patients [79]. Wen et al. demonstrated that inhibiting miR-155-5p diminishes allodynia by downregulating the SIRT1 gene in activated macrophages and decreasing the expression of involved microglial inflammatory markers, such as TNF- α and myeloperoxidase, CGRP, and c-Fos [80].

Microglia's Role in CSD Propagation and Migraine Attacks

The P2X7 receptor (P2X7R) of microglia in TNC is involved in hyperalgesia, microglial autophagia suppression, and induced inflammatory status in chronic migraine [81]. Inhibition of the P2X7 increases the CSD threshold and CGRP expression in the trigeminovascular system and decreases IL-1 β , NO, and cyclooxygenase-2 production [82]. Autophagy dysfunction has a role in migraine through P2X7R. The inhibited P2X7R decreases CGRP and c-Fos levels in TNC, activates autophagic flux, lessens microglial activation, and reduces the activity of NLRP3 inflammasome [83].

Macroglia involvement in migraine has suggested sex-specific mechanisms for its pathophysiology. In female rats, microglia and BDNF are not obligatory for pain sensitization and allodynia [84]. Karkhaneh et al. evaluated the connection between 17 β -estradiol and patients with menstrual migraine. 17 β -estradiol decreased CGRP, IL-1 β , and iNOS activity in physiologic doses but with the opposite effects in the pharmacologic doses [85]. There are still unanswered questions about the microglial function and its interaction with other glial cell types in migraine attacks that should be addressed in further studies.

Astrocytes

Astrocytes in CNS Disorders

Astrocytes regulate synaptogenesis, calcium signaling, potassium ion uptake, neurotransmitter reuptake, and energy delivery to neurons through the lactate shuttle [86–89]. Astrocytes take part in almost all CNS disorders. Reactive astrocytes disturb glutamate transporter 1 (GLT1)–mediated homeostasis and Ca²⁺ signaling creating a neurotoxic inflammatory environment in Huntington's disease [90]. Glutamate receptor 1 (GluR1), a subunit of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, is highly expressed in epilepsy and results in a higher influx of sodium and calcium ions through the cells

and induces hyperexcitability. The reuptake of potassium ions via inwardly rectifying potassium (Kir) channels is also blocked [91, 92]. Malfunctioning astrocytes' glutamate transporter with a further extracellular accumulation of glutamate and higher intracellular calcium levels through NMDA receptor overexpression is seen in ischemic stroke [93–95]. Astrocytes proliferate and turn into a reactive state to form glial scars by producing neuroprotective factors and cytokines, including IL-1 β , IL-6, IL-10, TGF- β , and IFN- γ in ischemic areas. Released cytokines induce NO synthesis, neural death, and neurogenesis [94, 96].

Astrocytes' Role in CSD Propagation and Migraine Attacks

CSD reactive astrogliosis correlates with inflammatory conditions [97]. CSD propagates throughout astrocyte gap junctions. In migraine with aura, cortical astrocytes sensitize dural afferents using calcium-independent pathways. CSD is associated with meningeal vasodilation and trigeminal nociceptive activation in migraine with aura and increased extracellular concentrations of K⁺, Ca²⁺, and Na⁺ when astrocytes are inhibited [98]. Na⁺/K⁺-ATPase is highly expressed in astrocytes and is essential in glutamate and K⁺ reuptake mutation in the Na⁺/K⁺-ATPase α_2 subunit of causes FHM type 2 (FHM2), which is associated with decreased CSD threshold. It is demonstrated that haploinsufficient mice for α_2 subunit isoform Na⁺/K⁺-ATPase pump channels have lower inflammatory reactions in response to lipopolysaccharide (LPS) in the hippocampus. This isoform is also required for LPS-induced upregulation of the toll-like receptor 4 (TLR4) [99, 100].

Astrocytes' excitatory amino acid transporters 2 (EAAT2) in chronic migraine reduce CGRP production in TNC and suppress central hyperalgesia [101]. TNF- α and ATP release by astrocytes increases the presynaptic glutamate secretion in the pain circuit. Postsynaptic increase of the AMPA receptors and decrease of gamma-aminobutyric acid A (GABA_A) receptors happen via TNF- α signaling [102].

The essential energy source for glutamate and potassium elimination in the synaptic process is stored as glycogen in the astrocytes' endfeet. The synaptic metabolic stress due to insufficient glycogen causes excessive extracellular K⁺, leading to decreased CSD threshold through pannexin 1 activation [103]. Due to mitochondrial dysfunction, lower glucose concentrations induce astrocytes to release ROS substances, IL-6, and IL-1 β [104]. Future studies on these cells are recommended to decipher the pathophysiology behind migraine and develop novel therapeutic approaches for its treatment. PACAP type I (PAC1) receptors in astrocytes are upregulated in brain injuries for protection and repair. PACAP has a proinflammatory role by increasing the expression of IL-6 and MIP-1 α in astrocytes [105]. Astrocytes are activated

longer by intracranial PACAP, thus leading to sustained allodynia [106].

Satellite Glial Cells

Satellite in CNS Disorders

In peripheral sensory and autonomic ganglia, including TG, satellite glial cells (SGCs) wrap around neuron bodies and interact with them through the synaptic cleft [107–109]. Surgery, inflammation, and other sensory nerve injuries stimulate NO production that diffuses from neurons to surrounding SGCs, increasing predisposition to calcium and eukaryotic protein kinase (EPK) signaling upregulation, which results in further inflammatory state of CNS, neural excitation, and pain sensitization [18].

The pain circuit runs mostly by neuron–glia interaction. ATP secreted from neural soma activates P2X7Rs on SGCs. Activated SGC expresses P2Y1, P2Y2, P2Y4, P2Y6, P2Y12, and P2Y13 receptors to provide an inflammatory environment. The extracellular ATP in TG activates SGC via P2Y1, P2Y2, and P2Y4 receptors to potentiate calcium signaling propagation. This process is mainly accompanied by IL-1 β secretion and inflammatory status [110]. CGRP released from neurons binds to the CRL/RAMP1 receptor on neural soma and P2Y receptors on SGCs. NMDA receptor presented on both SGCs and neurons is responsible for pain events due to glutamatergic currents. Under normal conditions, GABA is secreted from neurons and stored by SGC for following neuroglial activation [111]. In inflammatory conditions, ATP activates SGCs, and TNF- α is released, which as a result, potentiates P2X3 receptors. ATP signaling contributes to neural sensitization by neuron–glial interactions through P2X3 receptors on trigeminal nerve endings. In addition to ATP, CGRP, nerve growth factors, cytokines, and prostaglandins could directly trigger pain receptors or indirectly induce pain via activating paracrine signaling. Additionally, activation of calmodulin-dependent serine protein kinase (CASK)/P2X3 complex affects neuronal plasticity [112, 113].

In the trigeminal ganglia, activation of P2 receptors, along with CGRP-induced inflammatory conditions, initiates migraine pain [113]. Inflammation in TG neurons and SGC is associated with chronic migraine. Edvinsson et al. reported increased CGRP and synaptosomal-associated protein, 25 kDa (SNAP-25) expression in neurons, and increased levels of iNOS in SGC [114]. Lukács et al. showed that locally induced inflammation of dura matter leads to long-term neuron–glia interaction. Inflammation stimulates the trigeminovascular system through the higher expression of the extracellular signal-regulated kinase (pERK)1/2 pathway in SGC; therefore, it results in enhanced release of IL-1 β and CGRP in neurons of TG. This inflammatory

condition causes vasoconstriction of the middle meningeal artery [115].

Satellite Glial Cells' Role in Migraine Attacks

There is a direct relationship between TG and CNS glial cells and allodynia. Temporomandibular joint inflammation increased circulatory neuronal GFAP⁺ (glial fibrillary acidic protein) SGC and activated macrophages. In the trigeminal nucleus, triggered microglia significantly upregulated ionized calcium-binding adaptor molecule 1 (Iba1). No role for microglial P2Y12 receptors or astrogliosis is identified. [116]. HK-1 is released from sensory neurons and SGC interactions in inflammatory conditions. Aczél et al. found that trigeminal hyperalgesia in migraine is caused by the new tachykinin family member—hemokinin-1 (HK-1) [117]. According to some studies, astrocytic and microglial P2X4 receptors are associated with SGC P2X7 activation for chronic pain induction and maintenance [118, 119]. These findings suggest a prominent role for SGCs in neuron–glia interaction at periphery sites in migraine promotion, as shown in Fig. 2.

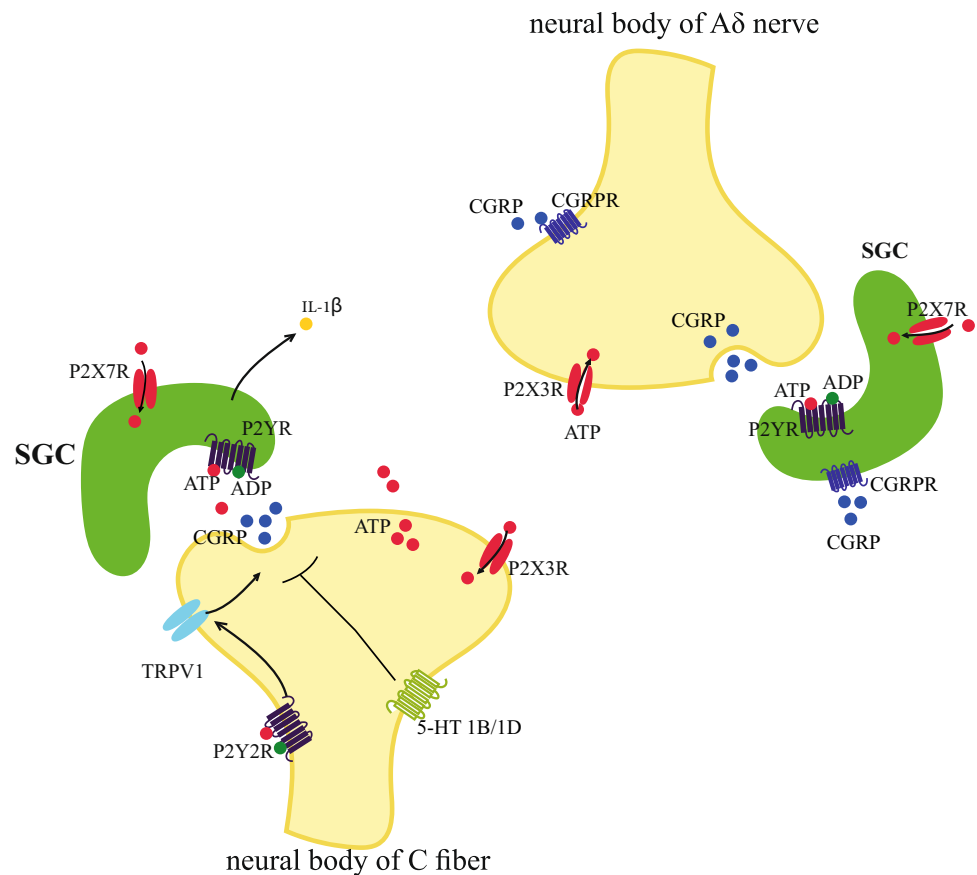
Glial Cells and Neuroinflammation in Migraine Headache

Innate Immune System

Glial Cell Interaction in Inflammation

The innate immune system is the body's first-line defense against invading pathogens. Pattern recognition receptors (PRRs) exert essential roles in the innate immune system against the pathogenic environment, including PIC expression and interferon-stimulated gene activation. Cytokine and chemokine receptors, mannose receptors, and constant region fragments of the immunoglobulin drive intracellular inflammatory signaling by activating Janus kinase (JAK)-STAT pathway, stimulating cytokines, and producing NF- κ B in order to mediate the innate immune system reactions [120–122]. In migraine, noxious stimuli provoke inflammatory reactions in the trigeminovascular system and trigeminal ganglion. Inflammatory states and types of involved cells predict protective or pathogenic characteristics of neuroinflammation [123]. Cytokines, NO, and prostaglandins in subarachnoid space activate trigeminal perivascular afferents, thus inducing headaches [34]. The expression of TNF- α and IL-1 β was increased in rat migraine models, implying an inflammatory state in the trigeminal nucleus pars caudalis. TLR4 antagonists inhibited the progression of symptoms. In addition, microgliosis and astrogliosis increased in the inflammatory soup-induced models of migraine [124, 125].

Fig. 2 The role of SGC in neuron-glia interaction at periphery sites in migraine. Extracellular ATP in TG activates SGC mainly via P2Y1, P2Y2, and P2Y4 receptors, principally accompanied by IL-1 β secretion and inflammatory status. ATP secreted from neural soma activates P2X7Rs on SGC. Neural released CGRP, as another aspect of the interaction, binds to the CRL/RAMP1 receptor on neural soma and P2Y receptors on SGC TRPV1 receptor on C fibers stimulation in the trigeminal ganglion to release CGRP. Activated 5-HT1B/1D receptors inhibit CGRP release. ATP, adenosine 5'-triphosphate; CGRPR, calcitonin gene-related peptide receptor; 5HT, 5-hydroxytryptamine; TRPV1, transient receptor potential cation channel subfamily V member 1; IL, interleukin; P2XR, purinergic receptor; P2YR, purinergic receptor



Rueda-Carrasco et al. explored the microglia-astrocyte interaction in chronic neuroinflammation. They found that astrocytes secrete frizzled-related protein 1 (SFRP1) to keep microglia active. This interaction upregulates hypoxia-induced factors and NF- κ B pathway molecules, albeit NF- κ B pathway molecules are much less expressed compared to hypoxia-induced factors; however, NF- κ B production in astrocytes leads to NO synthase and cyclooxygenase-2 activation. [126].

Pannexin 1 Channel and Inflammatory Cascade

In CSD induction, pannexin 1 channels temporarily open and can activate inflammasome to start the innate inflammatory procedure [126]. In that process, HMGB1 release and IL-1 β production stimulate astrocytes' NF- κ B transcription and secretion of NO and cytokines from microglia and astrocyte pedicles. After multiple CSD, for example, in FMH mutations, hyperactivated microglia produce more ROS, IL-1 β , and TNF- α to keep the long-lasting sterile inflammatory reactions in the meninges [34, 36, 127]. Moreover, the opening of the pannexin 1 channel and K⁺ outflow from P2X7R resulted in the formation of NLRP3 inflammasome. NLRP3 inflammasome, along

with activation of caspase-1, stimulates IL-1 β and IL-18 formation and further trigeminovascular activation. In the other side of the story, CSD releases the ATP via pannexin 1. In meninges, ATP binds to high-affinity P2X3 receptors. CGRP release can control the sensitization of the P2X3 receptor. ATP induces the cortical astrocytes and microglia to release TNF- α . TNF- α stimulates ATP production by activating P2X3 receptors to enhance sensory signaling. Microglia elevate extracellular potassium concentration, which is essential for the induction of CSD [73, 128–131]. The anti-inflammatory regulatory system produces acetylcholine in the vagus nerve, which binds to mitochondrial α 7 nicotinic acetylcholine receptor α 7 nAChR to decrease mitochondrial-induced oxidative stress and suppress NLRP3 inflammasome [123]. The α 7 nAChR is a ligand-gated ion channel in a cholinergic anti-inflammatory pathway. Activated α 7 nAChR polarizes microglia to M2 phenotype [132]. It also deactivates microglia and astrocytes in chronic migraine via phosphorylated c-Jun N-terminal kinase (p-JNK)–mitogen-activated protein kinase (MAPK) signaling and inhibits the expression of TNF- α , IL-1 β , and CGRP [132]. These findings provide insight into the role of all glial cells and the inflammatory pathways in innate immune response in migraine disease.

Adaptive Immune System

T Cells

Adaptive immunity is the second-line immune system with delayed and antigen-specific responses. The components include B cells and T cells [133, 134]. Immune system dysfunction or autoimmunity can decrease regulatory T cells during migraine headaches [135]. The lower CD4⁺ T cells in migraine episodes are a biomarker to determine more severe attacks [136]. PACAP and vasoactive intestinal peptide (VIP) support helper T cell 2 (Th2) and regulatory T cell production and stabilize Th1 and Th17 to regulate T cell activity [137]. In some cases, mast cells and lymphocytes express VIP and PACAP in lymphoid structures innervated by autonomic neurons. They inhibit TNF- α and IL-6 and produce anti-inflammatory molecules, such as IL-10 and IL-1Ra, to suppress the inflammatory macrophages [138].

Mast Cells

Mast cells have a prominent role in migraine adaptive and innate neuroinflammatory responses [139]. Gonadal steroids, corticotropin-releasing hormone, nerve growth factors, and neuropeptides mediate the mast cell localization patterns in the brain (dorsal thalamus, postrema medullary) [139]. Moreover, interactions between glial and mast cells, mediated by PICs, exert essential roles in inducing neurogenic inflammation and neuroinflammation. Astrocytes' IL-37, Tregs' IL-10, and dendritic cells' TGF- β could suppress mast cells, hence preventing migraine pain. However, the role of mast cells in the migraine mechanism has not been completely determined and is still controversial, especially in humans [18, 139–141]. Dural mast cells have a role in the persistency of migraines' hyperalgesia by secreting 5-HT, prostaglandin I₂ (PGI₂), and histamine [142]. Another study shows that degranulation of dural mast cells increases the duration of nociceptor and spinal trigeminal nucleus activation [143].

Oligodendrocytes

Pusic et al. demonstrated the oligodendrocytes and myelin roles in CSD pathogenesis. CSD triggers T lymphocyte accumulation and IFN- γ /TNF- α production, creating an oxidative environment suitable for activating neutral sphingomyelinase and disrupting the myelin sheath, enhancing CSD susceptibility [144]. Oligodendrocytes react to neural signaling and activate astrocytes and microglia [145]. Genetic factors related to oligodendrocytes and astrocytes differ in migraines with aura and without aura [146]. Oligodendrocytes also react to neural signaling and activate astrocytes and microglia. [145]. In chronic migraine, the

trigeminal spinal nucleus is hyperactive with a higher myelin density [147]. The hyperdensity of white matter is connected to migraine in older ages due to earlier in-life alternations [148]. White matter lesions in brain MRI of migraine patients are due to repetitive neural hyperexcitability with subsequent activity of myelin modulation or dendritic mass [149]. Taken together, glial cells' interaction with the adaptive immune system can modify inflammatory status, which is assumed to be beneficial as a therapeutic target. Moreover, mast cells play a significant role in migraine pathophysiology directly or via their interaction with glial cells [18, 150].

The Role of the Glial Cells in the Modulating Neurotransmitters

GABA

Gamma-aminobutyric acid (GABA), besides the inhibitory role in CNS, regulates the pain threshold in TNC. Inhibitory interneurons of the superficial spinal dorsal horn release GABA to suppress nociception [151]. In particular, GABA can decrease the attacks and decrease levels after a severe attack [152]. GABAergic medications are helpful in migraine without aura treatment, and antilglutamatergic agents are beneficial for those with aura [151].

Recent studies delineated the role of GABA in excitatory-inhibitory imbalances and central hypersensitization of CNS disorders [153]. Aguila et al. found an association between increased GABA levels with higher pain scores and central allodynia in migraine [154]. GABA has a vasodilation effect in CSD, and the concentration is an accurate tool to diagnose migraine [155, 156]. A systematic review revealed the unique pattern of GABA in pain syndromes—higher concentrations in migraineurs and no change in the musculoskeletal pain and chronic pain syndrome were observed compared with controls. In contrast, glutamate significantly increased in migraine and chronic pain syndromes [157]. However, a study observed that cortical GABA level from mildly affected migraine with aura patients was similar to the control group [158].

Different GABA receptor subtypes are responsible for the other nociceptive processes in the trigeminovascular system. PICs, including TNF- α , secreted from microglia, can decrease the expression of GABAB receptors, expressed on SGC in TNC, and augment the expression of AMPA receptors in neurons, hence inducing neural hyperexcitability [159, 160]. In resting status, GABA inhibits transient receptor potential cation channel subfamily V member 1 (TRPV1) and the following nociception. GABAB receptor subtypes and TRPV1 complex exist on intact neurons with analgesic features. Also, GABAB can suppress neural hyperexcitation resulting from the ATP-mediated P2X3 receptors. Moreover,

in typical situations, SGC can store neuron-produced GABA and release it when glial cells and neurons are activated. The exact role of GABA in cortical pain perception should be further explored [111].

Glutamate

The thalamocortical relay is where the glutamate activates NMDA receptors for long-lasting responses and non-NMDA receptors for short excitations in CNS. Glutamatergic inputs from dura-sensitive trigeminothalamic circuits drive Vesicular-glutamate transporter 2, mainly to excite neurons in the trigeminovascular system [161]. Studies show that glutamate levels are significantly enhanced in platelets, plasma, and CSF in migraine with aura patients [162].

NMDA receptor subtypes (NR1, NR2A-D, and NR3AB) are expressed in different cell types with specific functions. Astrocytes express NR2B subunit for extrasynaptic activities [163]. These cells release glutamate, which causes depolarization, has a role in K^+ concentration regulation, and facilitates Ca^{2+} waves [11]. Microglia secretes IL-1 β to induce the release of TNF- α , IL-1 β , and IL-6 from astrocytes to inhibit Na^+ -dependent EAAT2 and reduce astrocytes' glutamate uptake, hence causing hyperalgesia [164]. Astrocyte elevated gene-1 (AEG-1), an oncogene highly expressed in cancer with physiologic roles in controlling cellular processes in migraine and inflammation, can downregulate EAAT2, thus increasing glutamate in the synaptic cleft and lead to CSD and allodynia. The anti-AEG-1 antibody can suppress the activity of this oncogene and treat migraine [165, 166].

Glutamate activates NMDA receptors in the neural body of TG and meningeal nerve endings to trigger migraine pain. CGRP increases neurons with NMDA receptors, but activated NMDA receptors and glutamate usually do not increase extracellular CGRP [167]. Polymorphism of SRR, encoding rate-limiting enzyme for D-serine synthesis, decreases D-serine availability, leading to lower migraine risks [168].

Excessive homocysteine levels via metabolic enzyme polymorphism have a role in migraine with aura. NMDA and mGluR5 receptors in neurons activate this process. The mGluR5 receptors in neurons lead to an elevated concentration of cellular calcium, which is neurotoxic for both neurons and SGCs in TG [169]. Glutamate receptor genes *GRIA1* and *GRIA3* are indirectly connected to migraine in genome-wide association studies [170].

Serotonin

Serotonin, 5-hydroxytryptamine (5-HT), modifies potassium, calcium channels, TRPV1, and intracellular calcium signaling and regulates sensory neural activity [171].

Meningeal mast cells secrete 5-HT, which, along with vasodilation and inflammation (triggered via ATP and CGRP), stimulates long-term nociception in peripheral nerve endings via 5-HT3 receptors [172].

Higher 5-HT concentrations also act through 5-HT2A receptors during the attacks, followed by lower 5-HT levels between episodes, which make the patient susceptible to stimuli. Following stimulation, serotonin released from the periaqueductal gray area inhibits the pain circuit and analgesic effects [173]. Indeed, serotonin inhibits and facilitates pain depending on the region and subtypes of activated receptors. The counterbalance circuit suppresses central inhibitory interneurons in the brainstem and upper cervical cord with the 5-HT3 receptors [172]. Evidence from animal experiments suggests that estrogen modulates serotonin's role in the pain mechanism [171]. The noninvasive vagus nerve stimulation (nVNS) activates descending inhibitory projections through 5-HT3 and 5-HT7 receptors and releases glycine and GABA to suppress trigeminal nociceptor functions [174]. There is a debate over the effectiveness of 5-HT3 receptor antagonists in migraine treatment due to the dual role of 5-HT3 receptors in migraine pathophysiology [175].

5-HT1B is in meningeal endothelial vessels and TG nerves, and 5-HT1D exists on TG nerve endings projected to meningeal vessels. Activated 5-HT1B/1D receptors may lead to vasoconstriction, neurogenic nociception, and central neurotransmitter suppression. Migraine treatments, including rizatriptan and sumatriptan, stimulate 5-HT1B/1D for vasoconstriction and central nociception [176, 177]. Debates about the role of serotonin in migraine pathophysiology and its related therapeutic agents indicate further study to decipher unknown aspects of its mechanisms in migraine.

CGRP and Procalcitonin

Hyperalgesia of trigeminovascular sensory nerves and the release of neurotransmitters/neuromodulators, including PACAP, CGRP, and VIP, are involved in migraine generation [105]. Pulsating pain and neural inflammatory cascade result from a positive feedback loop aiming to hypersensitize nociceptors. Stress activates the primary nuclei of trigeminal sensory neurons, producing CGRP, substance P, neurokinins A and B, and hemokinin. These products degranulate mast cells to release neuroinflammatory mediators (bradykinin, histamine, prostaglandins, TNF- α , vascular endothelial growth factor, and serotonin) to impact sensory neurons for further CGRP release. CGRP and substance P release from perivascular trigeminal nerves vasodilates meningeal vessels and induces extravasation of plasma proteins via endothelial neurokinin 1 receptors, respectively [139, 178–181].

CSD alters the brain blood flow of the visual cortex and generates aura. The primary hyperemia and mast cell degranulation activate CGRP and inflammatory signaling

following meningeal plasma extravasation. The process is due to increased c-Fos expression in TNC and long-lasting peripheral nociception in neurons of the trigeminovascular system [180, 182–184]. CGRP regulates IL-1 β and NO release from trigeminal glial cells. A study on peripheral blood mononuclear cells of menstrual migraine patients isolated with melatonin for 12 h showed that melatonin protects against the proinflammatory trigeminal microenvironment and reduces iNOS and CGRP gene expression [185].

CGRP and its receptor components are expressed in the nerve fiber layers of the retina and have a role in photophobia. Overexpression of receptor activity-modifying protein 1, a CGRP receptor component, increases light sensitivity in rats. Moreover, CGRP, by inducing vascular dilation, triggers photophobia-like behavior in mice. Intraocular inhibition of the trigeminal root ganglion prevented reaction to bright light in rats [186, 187]. CGRP via gap junctions and paracrine signaling in neuron-glia interaction change the glial function to hypersensitize the trigeminal ganglion [188]. SGC has CGRP receptors to increase PICs following further synthesis of CGRP in neurons, which means the role of SGC in neural sensitization and sustained inflammatory condition in a feedback loop.

Other neuropeptides are also involved in meningeal nociception. Acetylcholine, VIP, and PACAP are released from parasympathetic nerve endings. Acetylcholine degranulates dural mast cells, inducing an inflammatory state. VIP and PACAP rise during migraine attacks to facilitate autonomic system activity and are deemed pro-nociceptive molecules [189, 190]. Adenosine and its purinergic signaling have a dual function in nociception and vasodilation in TG via different receptors (A2A is a vasodilator and TG activator, while the A1 subtype is a TG suppressor) [191]. Guo et al. reported elevated CGRP, neuropeptide Y, PACAP, VIP, and nociception after repeated TG stimulation in migraine models [192]. A schematic view of neurotransmission in migraine is depicted in Fig. 3.

Brain Vasculature

BBB separates the brain microenvironment from the periphery and serves as an interface to support CNS hemostasis. BBB destruction is a sequel to many disorders. The neurovascular unit is a component of BBB, consisting of endothelial cells wrapped by pericytes and astrocytes, along with neurons, microglia, and peripheral immune cells. Pathologies in this unit participate in migraine disorder [193]. In neurovascular theory, inflammatory vascular status vasodilates intracranial meninges and activate the meningeal afferent in migraine disease. As previously discussed, CSD, through unbalanced synaptic neurotransmission, stimulates meningeal sensory, and in subsequent processes, mast cells degranulate for inflammation

and further changes in BBB [194]. This sterile inflammation activates nociceptors, mainly peripheral C-fibers, to release substance P, CGRP, and prostanooids from trigeminal terminals. Together with plasma protein extravasation, vascular leakage, edema, and mast cell degranulation, all these phenomena are called “neurogenic inflammation” [195, 196].

Moreover, inflammation activates the trigeminovascular system to potentiate pannexin 1 hemichannels and activate caspase-1 in migraine attacks. CSD cannot cause migraine without trigeminovascular pain predisposition [34, 197–199]. Chen et al. showed that in hyperalgesia, the higher permeability of BBB and thus increased IL-17A penetration to the medulla oblongata could activate microglia and NF- κ B-mediated inflammation [200]. Prolonged BBB disruption results in increased S100B (an astrocytic damage marker) and decreased neuron-specific enolase (neuronal death marker) during and after migraine attacks [201]. Artemin, a vasculature-derived growth factor, modulates sympathetic function via glial cell line–derived neurotrophic factor (GDNF) family receptor α 3 (GFR α 3) in inflammatory allodynia. Artemin stimulates TRPV1 channels to release CGRP, contributing to vasodilation and mast cell degranulation following migraine-related inflammatory conditions [202].

Vascular status is also a trigger of aura in migraine. Some Mendelian disorders of small vessels and infarct-like conditions, including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS), confirmed the link. Stroke is also more frequent in migraine with aura patients than in other migraineurs [34, 197–199].

Meningeal lymphatic vessels participate in CNS detoxification and may have a role in migraine [38]. CSD closes perivascular spaces by affecting astrocyte pedicles and disrupts the lymphatic flow in migraine, which defines the part of the glymphatic system in migraine [203]. Contrastingly, in another study, a lack of a glymphatic system resulted in decreased IL12-p70 and CGRP. Although increased mast cell-activating cytokine (MCP-1), which is correlated with migraine headaches, was observed, changes in cytokine or ATP-mediated sensitization or activation of trigeminal nociceptive receptors were not significant [204]. In a pilot study from Lee et al., glymphatic dysfunction was insignificant in migraine patients compared to controls [205]. Overall, inflammatory downstream vasculature disruptions are essential to migraine symptoms exhibition.

Future Neuroprotective and Anti-inflammatory Targets

Early diagnosis and treatment will result in superior outcomes for migraine. Treatment relies on relieving acute symptoms and preventing further recurrence of the attacks.

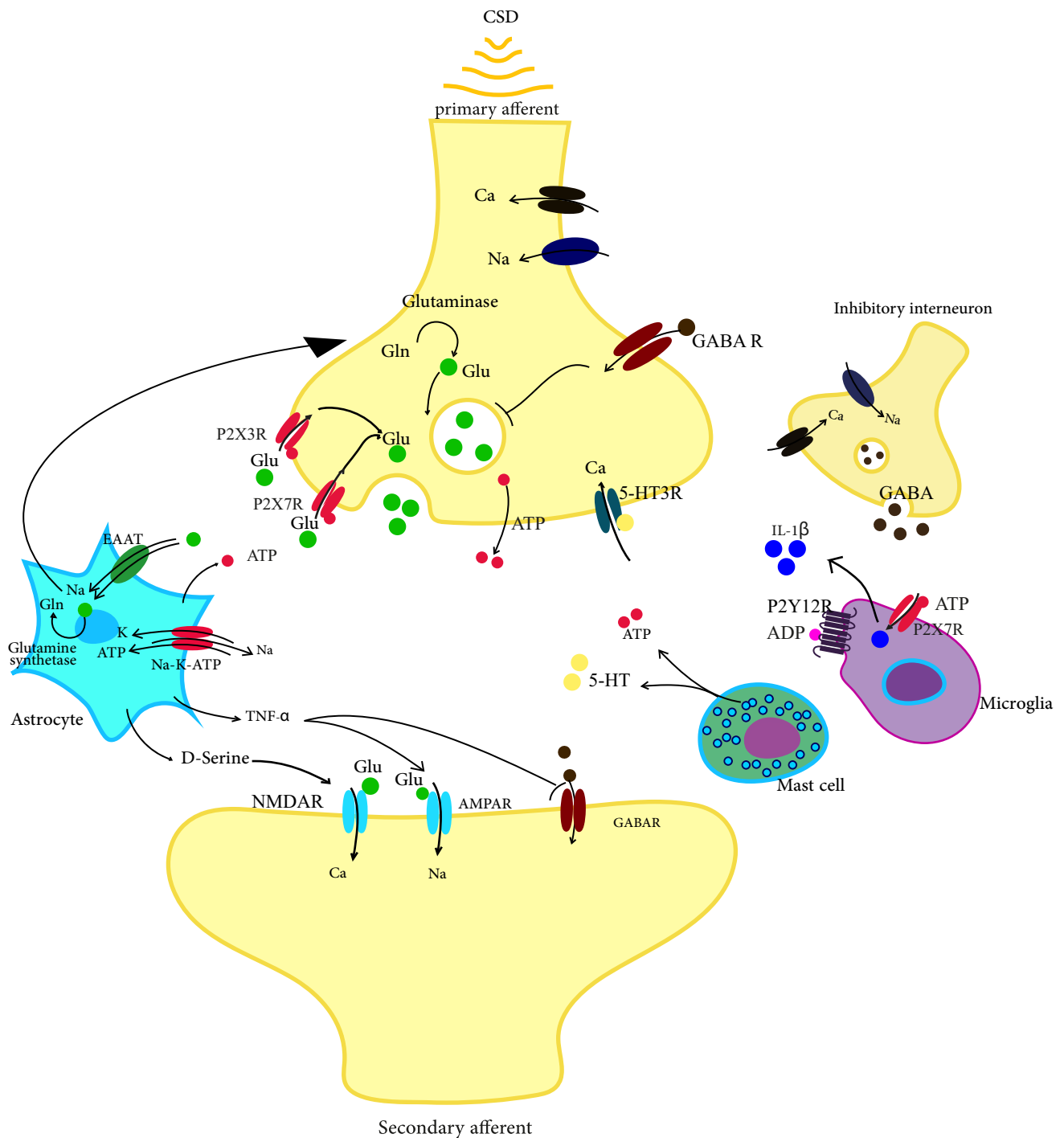


Fig. 3 Schematic diagram of synaptic neurotransmission in migraine. CSD result in more glutamatergic and presynaptic production. Astrocytes release $\text{TNF-}\alpha$ and ATP. ATP excites presynaptic glutamatergic activity via P2X3 and P2X7 receptors, and $\text{TNF-}\alpha$ increases postsynaptic AMPA receptors and decreases GABA_A receptors. Astrocytes' D-serine binds with glutamate to NMDA receptors, causing hyperexcitation in secondary afferents. On the other hand, all defects in the glutamatergic system, from a mutation in calcium channels to loss of function in Na-K-ATP channels and even lower inhibitory part from GABAergic neurons and EAAT mutations, lead to increased

glutamate in the synaptic cleft and more neural excitation. Mast cells release serotonin and ATP for pronociceptive via 5-HT₃ and P2X₃ receptors, respectively. Activated microglia upregulate P2Y₁₂ receptors and produce inflammation ($\text{IL-1}\beta$) via P2X₇ receptors activation. GABA_R, gamma-aminobutyric acid receptor; EAAT, excitatory amino acid transporters; ATP, adenosine 5'-triphosphate; NMDAR, N-methyl-D-aspartate receptor; 5HT, 5-hydroxytryptamine; $\text{TNF-}\alpha$, tumor necrosis factor- α ; IL, interleukin; P2XR, purinergic receptor; P2YR, purinergic receptor

Acute treatment aims at suppressing pain by inhibiting vasodilation and inflammatory processes [206]. Triptans are selective serotonin agonists that act as vasoconstrictors of meningeal vessels via 5-HT_{1B} and inhibit proinflammatory products of the trigeminal ganglion via 5-HT_{1D}. SGC activation provides a proinflammatory environment that changes the neural excitement threshold, lessening the effectiveness of triptans [207]. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are drugs used to treat mild to moderate migraine attacks [208, 209]. Ergotamine can act via serotonin, dopamine, and norepinephrine receptors [210, 211]. Glial cell inhibitors such as naloxone, naltrexone, minocycline, and IL-10 could be used in migraine treatment. Naloxone and naltrexone antagonize microglial TLR4 to alleviate pain symptoms [32, 212].

Cromolyn and antihistamines were mostly ineffective prophylaxis in migraines because of the diversity of mast cell mediators and reactions [213, 214]. As an antihistamine, ketotifen decreases mast cell granulation and can reduce nociception and inflammation in widespread chronic pain. Its effectiveness for migraine treatment should be explored further [215]. Herbal derivate explored for migraine treatment. A previous systematic review showed that butterburs' root extracts are effective for migraine prophylaxis. Curcumin, along with omega 3, has greater efficacy for the prevention and treatment of migraine than the control group. Feverfew efficacy is controversial and less supported. It usually acts by inhibiting serotonin release and blocking TRPA1 involved in CGRP release [216, 217]. Capsaicin enhances communication between neurons and SGCs through TRPV1 receptors and C fibers stimulation in the trigeminal ganglion. Capsaicin also elevates intracellular Ca²⁺ in neurons and increases S100B in neurons and SGCs, inducing inflammation in nociceptive neurons [218, 219].

Clinical trials are currently investigating divergent antibodies' effectiveness in treating migraine. More novel treatments, including fremanezumab and galcanezumab, are FDA-approved monoclonal antibodies that make a complex with CGRP and prevent it from activating the targets. Erenumab is another FDA-approved monoclonal antibody that blocks CGRP receptor activation by triggering the extracellular domain. These drugs possibly act on peripheral A δ neurons and prevent the prolonged trigeminovascular stimulation and subsequently inhibit the release of neuropeptides in the trigeminal ganglion, such as CGRP and inflammatory substances, to stop migraine chronification [220, 221]. Erenumab is primarily effective in antagonizing peripheral CGRP receptors, with a significant reduction in mean monthly migraine days and a better patient-reported outcome in 3 months [222–225]. Galcanezumab decreases monthly migraine headache days and improves the migraine-related quality of life and

global patient impression of severity ratings with erythema and pain at the injection site as the most common adverse effect [226–229]. Fremanezumab reduces migraine-specific acute headache medication use and migraine headache days, with injection site reaction as the most common adverse event [230–233]. Eptinezumab, another CGRP inhibitor, shortens the median time to headache, and improves patients' quality of life with a lower burden and adverse effects in 2 years with frequent nasopharyngitis, upper respiratory tract infection, and migraine as adverse events [234–236]. Ubrogepant and rimegepant are among the FDA-approved oral drugs that are small molecules that block CGRP receptors with established vasodilatory impacts, confirmed safety profile, and high treatment efficacy for acute migraine treatment [237, 238].

Other pharmacologic and non-pharmacologic treatments related to migraine microenvironmental alteration are also investigated. It is hypothesized that kynurenic acid, an NMDA antagonist, protects against migraine attacks. Knyihár-Csillik et al. demonstrated that trigeminal ganglion stimulation could cause increased environmental kynurenine aminotransferase from neural, Schwann cells, and macrophage sources to vasodilate via activated NMDA receptors [239]. Tonabersat, a benzopyrene compound that reduces the expression of this protein, was evaluated in phase 2 trials for migraine with aura prevention. Tonabersat blocks TNF- α , which leads to a reduced connexin26 signaling, which participates in SCG interaction with trigeminal ganglion with subsequently inhibited p38 and neural hypersensitization. Hawkins et al. proved that non-invasive vagus nerve stimulation could inhibit trigeminal ganglion nociception in episodic migraine. Also, it could repress the expression of substances that can potentially sensitize trigeminal neurons, including IL-1 β in microglia, PERK level in trigeminal ganglion primary afferent neurons, and GFAP in astrocytes [240]. Other potential glial cell-related targets have been summarized in Table 1.

VanderPluym et al. conducted a systematic review to evaluate the harms and effects of migraine treatments in adults. Results proved evidence for NSAIDs, triptans, acetaminophen, dihydroergotamine, CGRP antagonists, lasmiditan, and nonpharmacologic therapies, such as non-invasive vagal nerve stimulation. Moreover, although opioids demonstrated a positive effect in the acute reduction of pain, there was low robustness of evidence [279].

In recent years, nutritional prophylaxis has been explored. The dietary pattern can activate the microglia inflammatory process induced in migraine by vagus afferent neurons from the intestine. Low-fat and low-sugar diets prevent microglial activity by suppressing oxidative conditions, stimulating TLR activity, and decreasing vagal afferent gut-brain interaction and peripheral inflammatory signaling. A high-protein diet excites NMDA receptors

Table 1 Potential pharmacologic glial-related targets for migraine treatment

Glial cell	Pharmacologic compound	Mechanism of action	Reference
Astrocyte	<i>Jatropha curcas</i> L., a Brazilian medicinal plant	Suppression of paclitaxel-induced neuropathic pain via inhibition of primary sensory cortex astrocytes	[241]
	Goshajinkigan, a traditional Japanese herbal medicine	Suppression of paclitaxel-induced neuropathic pain via inhibition of primary sensory cortex astrocytes	[242]
	Rosmarinic acid, a natural polyphenolic substance	Preventive against ROS and NO production in combination with suppression of astrocyte-mediated hyperactivity	[243]
	Cinobufacini, toad skin extract, and a Chinese anticancer drug	Inhibition of paclitaxel-induced pain via TRPV1 downregulation, astrocyte deactivation, and reduced spinal TNF- α and IL-1 β levels	[244]
	Isothiocyanates	The attenuator of astrocytes' oxidative activity and inhibitor of matrix metalloproteinase in various neurologic disorders	[245]
	Curcumin	Suppression of astrocyte overactivation in Alzheimer's disease, ischemia stroke, spinal cord injury, multiple sclerosis, and Parkinson's disease	[246]
	Mirtazapine, a serotonergic antidepressant	Antioxidants upregulation (metallothionein) in striatal astrocytes by HT1A receptors in Parkinson's disease	[247]
	Decursin, the extract of <i>Angelica Gigas</i> Nakai root	Mitigation of astrocytes' pedicle damage and BBB disruption in cerebral ischemia	[248]
	Ursolic acid, a natural triterpenoid	Upregulation of CNTF in astrocytes and improved oligodendrocytes' myelination in multiple sclerosis	[249]
	Baicalin	Anti-ROS creation and regulator of astrocytes glutamine synthetase homeostasis in acute ischemic stroke	[250]
	Maresin 1, a pro-resolving lipid moderator	Analgesic activity via Inhibited NF- κ B signaling, decreased IL-1 β and TNF- α expression, activated astrocyte and microglial, and increased CGRP release in dorsal root ganglion	[251]
	6-Gingerol, <i>Zingiber officinale</i> extraction	Dose-dependent suppression of TNF- α , IL-6, and cellular ROS, NO, and iNOS in cognitive dysfunction	[252]
	Estrogen and selective estrogen receptor modulators	Increased astrocytes' glutamate transporters via EAAT1 and EAAT2 activity modulation in cellular PI3K-Akt, TGF- α , ERK, and NF- κ B signaling	[253]
	Melatonin	Astrocyte and microglial cell deactivation with anti-inflammatory activity and autophagy regulation	[254]
	Cannabis sativa compounds	Antioxidation and neuroprotection via an increase in cortical 5-HT and neurotransmission	[255]
	Rotigotine, an anti-Parkinson drug	Upregulation of antioxidants (metallothionein) via astrocytes' HT1A receptors	[256]
	Fluoxetine, an anti-depressant	Increased astrocytes' BDNF via P2Y11, adenosine A2b receptors, and ATP-induced transmission	[257]
	Epigallocatechin-3-gallate, a natural ingredient	Attenuation of postoperative pain via diminished astrocytes and microglial NF- κ B, iNOS, COX-2, and PGE2 overexpression	[258]
	IL-33	Increase in the survival rate of astrocytes and their neurotrophic factors in a hypoxic glucose-starving environment	[259]
	Fasudil, a Rho kinase inhibitor	Direct and astrocytes/pericytes-mediated protection of BBB integrity in acute ischemic stroke	[260]
	<i>Ailanthus altissima</i> , an East Asian medicine	Reduction in astrocytes' iNOS, COX-2, NF- κ B, ERK, and JNK expression of the neurodegenerative process	[261]
	Pectolarigenin, a flavonoid compound	Astrocytes' inhibition of IL-1 β , IL-6, fibrillary acidic protein overexpression, NF- κ B, and ERK1/2 phosphorylation	[262]
	D-Serine	Intracerebral infusion mitigated nociceptive behaviors in rats	[263]

Table 1 (continued)

Glial cell	Pharmacologic compound	Mechanism of action	Reference
Microglia	Gypenoside	Inhibition of microglial activation with phenotype switching to M2 with mitigated BBB extravasation in high-altitude cerebral edema	[264]
	α 1-antitrypsin	Reduction in microglial-induced inflammation via NLRP3 inflammasome suppression and neuroprotection by reduction of glutamatergic neural toxicity in Alzheimer's disease	[265]
	Fluoroquinolone antibiotic	Anti-inflammatory function through suppression of microglial TLR4/NF- κ B signaling	[266]
	Fibroblast growth factor 21 (FGF21)	Attenuation of NF- κ B and PPAR- γ signaling with anti-M1 polarization property in stroke models	[267]
	Vinpocetine, vinca alkaloid vincamine synthetic compound	Reduction in iNOS and COX-2, TNF- α , IL-6, and IL-1 β via stimulated AMPK phosphorylation	[268]
	Mefenamic acid, a COX inhibitor	Microglia inactivation by suppressed ERK1/2, P38 MAPK, and iNOS expression and lower phagocytic activity in depression	[268]
	Urinary kallidinogenase	Anti-inflammatory function, antioxidation, and neuroprotection, reduction of TLR4, and diminished NF- κ B signaling	[269]
	Oxyresveratrol, a phytochemical compound	Microglial IL-1 β attenuation through suppressed PI3K/AKT and ERK1/2 MAPK signaling	[270]
	Isoquinolines	Neuroprotection against microglial activation in Alzheimer's disease and anti-inflammation	[271]
	<i>Rheum tanguticum</i> , a Tibetan medicine	A rise in IL-10, secreted from microglia to reduce inflammatory substances and oxidative markers	[272]
	6-Gingerol	Suppression of microglial IL-6, IL-1 β , and NO production via inhibition of Akt-mTOR-STAT3 signaling	[273]
	7-O-esters of taxifolin	Microglial inflammatory modulation without antioxidative effects	[274]
	Epigallocatechin-3-gallate, an antioxidant from green tea	Mitigation of microglial inflammatory compound (NO and TNF- α)	[275]
	Caffeine	Adenosine receptor inhibition	[276]
	Minocycline antibiotic	Anti-inflammation	[277]
	Nicotinic α 7 nAChR agonists	Cholinergic anti-inflammation and inhibition in NF- κ B signaling	[278]

Abbreviations: ROS, reactive oxygen species; NO, nitric oxide; TRPV1, transient receptor potential cation channel subfamily V member 1; TNF- α , tumor necrosis factor- α ; IL-1 β , interleukin-1 β ; HT1A, 5-hydroxytryptamine 1A receptor; BBB, blood-brain barrier; CNTF, ciliary neurotrophic factor; NF- κ B, nuclear factor- κ B; CGRP, calcitonin gene-related peptide; iNOS, inducible nitric oxide synthase; EAAT1, excitatory amino acid transporter 1; PI3K, phosphatidylinositol-3-kinase; TGF- α , transforming growth factor- α ; ERK, extracellular signal-regulated kinase; 5-HT, 5-hydroxytryptamine; BDNF, brain-derived neurotrophic factor; ATP, adenosine triphosphate; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2; JNK, c-Jun N-terminal kinase; NLRP3, NLR family pyrin domain containing 3; TLR4, toll-like receptor 4; PPAR- γ , peroxisome proliferator-activated receptors- γ ; AMPK, amp-activated protein kinase; mTOR, mammalian target of rapamycin; STAT, signal transducer and activator of transcription; mRNA, messaging ribonucleic acid; FGF21, fibroblast growth factor; α 7 nAChR, α 7 nicotinic acetylcholine receptor

leading to central sensitization through polyamines products (from clonal fermentation) [280]. Evidence shows that alkaloid and opioid-like food derivatives, including gluten and citrus, may cross the BBB and initiate the sensitization process in migraine [281, 282].

Future studies should focus on diminishing the long-term side effects and improving cost-effectiveness of monoclonal antibodies for migraine treatment. Additionally, efforts should be made to enhance the tolerance of oral drugs. Moreover, the neuroinflammation-based targets could be further studied as potential therapeutic

approaches for migraine [2, 283]. The focus of research should be on examining the correlation between genetic markers and clinical symptoms in TNG, with the goal of identifying the initial trigger of an attack. Other promising targets for therapy-oriented studies include malfunctioning TRPV family members and K channels. A deeper understanding of the role of endothelial and glial cells in the progression of migraines is needed [284–286].

Conclusion

It has shown that oxidative stress sensitizes involved neurons through CGRP-dependent pathways in inflammatory conditions; on the other hand, the inflammatory status stimulates the oxidative state and exaggerates allodynia. Newly designed anti-CGRP drugs prevent this vicious cycle and suppress the development of migraine attacks. Astrocytes have a significant role initiation of CSD. Meanwhile, different channel mutations in astrocytes and the GABA-glutamatergic circuit lead to disrupted concentration of glutamine levels in synaptic gaps, as seen in FHM. Serotonin has a modulatory function in the migraine circuit through particular receptor subtypes. Inflammatory molecules and all other micro-environmental substances can cause vascular integrity disruption and long-lasting vasodilation, which is the final step in the most prominent explained theory about the pathophysiology of migraine disorder. More research is required to present the undetermined roles of immune cells and particles as an ordinary aspect of the microenvironment. Its impression on downstream neural activation leads to vascular changes. These findings could be used for more efficient multi-target drugs in migraine treatment.

Author Contribution HA conceptualized the title, prepared the first draft, and designed the figures and tables. ASK conceptualized the title, prepared the first draft, edited the first draft, and prepared final draft. GMT conceptualized the title, critically revised the manuscript, and finalized the draft. AT conceptualized the title, supervised the project, critically revised the manuscript, and finalized the draft. All the authors have read the final manuscript and approved it.

Data Availability Not applicable.

Declarations

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

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References

- Goadsby PJ (2012) Pathophysiology of migraine. *Ann Indian Acad Neurol* 15(Suppl 1):S15–S22
- Puledda F, Messina R, Goadsby PJ (2017) An update on migraine: current understanding and future directions. *J Neurol* 264(9):2031–2039
- Djalali M, Djalali M, Abdolahi M, Mohammadi H, Heidari H, Hosseini S et al (2020) The effect of nano-curcumin supplementation on pentraxin 3 gene expression and serum level in migraine patients. *Rep Biochem Mol Biol* 9(1):1–7
- Razeghi Jahromi S, Ghorbani Z, Martelletti P, Lampl C, Togha M (2019) On behalf of the School of Advanced Studies of the European Headache F. Association of diet and headache. *J Headache Pain* 20(1):106
- Yamanaka G, Suzuki S, Morishita N, Takeshita M, Kanou K, Takamatsu T et al (2021) Experimental and clinical evidence of the effectiveness of riboflavin on migraines. *Nutrients* 13(8):2612
- Gross EC, Klement RJ, Schoenen J, D'Agostino DP, Fischer D (2019) Potential protective mechanisms of ketone bodies in migraine prevention. *Nutrients* 11(4)
- Pescador Ruschel MA DJO. Migraine headache (2022) In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Jan-[Updated 2022 Jul 6]
- Hanslik KL, Marino KM, Ulland TK (2021) Modulation of glial function in health, aging, and neurodegenerative disease. *Front Cell Neurosci* 15:718324
- Malchow RP, Tchernookova BK, Choi J-iV, Smith PJS, Kramer RH, Kreitzer MA (2021) Review and hypothesis: a potential common link between glial cells, calcium changes, modulation of synaptic transmission, spreading depression, migraine, and epilepsy—H+. *Front Cell Neurosci* 15
- Lebedeva A, Plata A, Nosova O, Tyurikova O, Semyanov A (2018) Activity-dependent changes in transporter and potassium currents in hippocampal astrocytes. *Brain Res Bull* 136:37–43
- Ricci G, Volpi L, Pasquali L, Petrozzi L, Siciliano G (2009) Astrocyte-neuron interactions in neurological disorders. *J Biol Phys* 35(4):317–336
- De Fusco M, Marconi R, Silvestri L, Atorino L, Rampoldi L, Morgante L et al (2003) Haploinsufficiency of ATP1A2 encoding the Na⁺/K⁺ pump alpha2 subunit associated with familial hemiplegic migraine type 2. *Nat Genet* 33(2):192–196
- Edvinsson L (2001) Calcitonin gene-related peptide (CGRP) and the pathophysiology of headache: therapeutic implications. *CNS Drugs* 15(10):745–753
- Meng ID, Cao L (2007) From migraine to chronic daily headache: the biological basis of headache transformation. *Headache* 47(8):1251–1258
- Weir GA, Cader MZ (2011) New directions in migraine. *BMC Med* 9:116
- Fried NT, Maxwell CR, Elliott MB, Oshinsky ML (2018) Region-specific disruption of the blood-brain barrier following repeated inflammatory dural stimulation in a rat model of chronic trigeminal allodynia. *Cephalalgia* 38(4):674–689
- Abbott NJ, Rönnbäck L, Hansson E (2006) Astrocyte-endothelial interactions at the blood-brain barrier. *Nat Rev Neurosci* 7(1):41–53
- Edvinsson L, Haanes KA, Warfvinge K (2019) Does inflammation have a role in migraine? *Nat Rev Neurol* 15(8):483–490
- Afroz S, Arakaki R, Iwasa T, Oshima M, Hosoki M, Inoue M et al (2019) CGRP induces differential regulation of cytokines from satellite glial cells in trigeminal ganglia and orofacial nociception. *Int J Mol Sci* 20(3):711

20. Messlinger K, Russo AF (2019) Current understanding of trigeminal ganglion structure and function in headache. *Cephalalgia* 39(13):1661–1674
21. Teepker M, Munk K, Mylius V, Haag A, Möller JC, Oertel WH et al (2009) Serum concentrations of s100b and NSE in migraine. *Headache* 49(2):245–252
22. Covelli V, Maffione AB, Munno I, Jirillo E (1990) Alterations of nonspecific immunity in patients with common migraine. *J Clin Lab Anal* 4(1):9–15
23. Gazerani P, Pourpak Z, Ahmadiani A, Hemmati A, Kazemnejad A (2003) A correlation between migraine, histamine and immunoglobulin e. *Scand J Immunol* 57(3):286–290
24. Covelli V, Munno I, Pellegrino NM, Altamura M, Decandia P, Marcuccio C et al (1991) Are TNF-alpha and IL-1 beta relevant in the pathogenesis of migraine without aura? *Acta Neurol (Napoli)* 13(2):205–211
25. Iyengar S, Johnson KW, Ossipov MH, Aurora SK (2019) CGRP and the trigeminal system in migraine. *Headache* 59(5):659–681
26. Raddant AC, Russo AF (2014) Reactive oxygen species induce procalcitonin expression in trigeminal ganglia glia. *Headache* 54(3):472–484
27. Liu H, Xin T, He W, Li F, Su ZQ (2014) Myelinated Ah-type trigeminal ganglion neurons in female rats: neuroexcitability, chemosensitivity to histamine, and potential clinical impact. *Neurosci Lett* 567:74–79
28. Hirata E, Ishibashi K, Kohsaka S, Shinjo K, Kojima S, Kondo Y et al (2020) The brain microenvironment induces DNMT1 suppression and indolence of metastatic cancer cells. *iScience* 23(9):101480
29. Nosedà R, Jakubowski M, Kainz V, Borsook D, Burstein R (2011) Cortical projections of functionally identified thalamic trigeminovascular neurons: implications for migraine headache and its associated symptoms. *J Neurosci* 31(40):14204–14217
30. Olesen J, Burstein R, Ashina M, Tfelt-Hansen P (2009) Origin of pain in migraine: evidence for peripheral sensitisation. *Lancet Neurol* 8(7):679–690
31. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S (2017) Pathophysiology of migraine: a disorder of sensory processing. *Physiol Rev* 97(2):553–622
32. Hutchinson MR, Bland ST, Johnson KW, Rice KC, Maier SF, Watkins LR (2007) Opioid-induced glial activation: mechanisms of activation and implications for opioid analgesia, dependence, and reward. *SciWorldJ* 7:98–111
33. Peters O, Schipke CG, Hashimoto Y, Kettenmann H (2003) Different mechanisms promote astrocyte Ca²⁺ waves and spreading depression in the mouse neocortex. *J Neurosci* 23(30):9888–9896
34. Karatas H, Erdener SE, Gursoy-Ozdemir Y, Lule S, Eren-Koçak E, Sen ZD et al (2013) Spreading depression triggers headache by activating neuronal Pannx1 channels. *Science (New York, NY)* 339(6123):1092–1095
35. Costa C, Tozzi A, Rainero I, Cupini LM, Calabresi P, Ayata C et al (2013) Cortical spreading depression as a target for anti-migraine agents. *J Headache Pain* 14(1):62
36. Erdener SE, Kaya Z, Dalkara T (2021) Parenchymal neuroinflammatory signaling and dural neurogenic inflammation in migraine. *J Headache Pain* 22(1):138
37. Brennan KC, Bates EA, Shapiro RE, Zyuzin J, Hallows WC, Huang Y et al (2013) Casein kinase iδ mutations in familial migraine and advanced sleep phase. *Sci Transl Med* 5(183):183ra56 (1–11)
38. Louveau A, Plog BA, Antila S, Alitalo K, Nedergaard M, Kipnis J (2017) Understanding the functions and relationships of the glymphatic system and meningeal lymphatics. *J Clin Invest* 127(9):3210–3219
39. Freitag FG (2013) Why Do migraines often decrease as we age? *CURR PAIN HEADACHE REP* 17(10)
40. Charles AC, Baca SM (2013) Cortical spreading depression and migraine. *Nat Rev Neurol* 9(11):637–644
41. Hadjikhani N, Sanchez Del Rio M, Wu O, Schwartz D, Bakker D, Fischl B et al (2001) Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci U S A* 98(8):4687–4692
42. Rogawski MA (2008) Common pathophysiologic mechanisms in migraine and epilepsy. *Arch Neurol* 65(6):709–714
43. Lucas C (2021) Migraine with aura. *Revue neurologique* 177(7):779–784
44. Albrecht DS, Mainero C, Ichijo E, Ward N, Granziera C, Zürcher NR et al (2019) Imaging of neuroinflammation in migraine with aura: A [(11)C]PBR28 PET/MRI study. *Neurology* 92(17):e2038–e2050
45. Wiggers A, Ashina H, Hadjikhani N, Sagare A, Zlokovic BV, Lauritzen M et al (2022) Brain barriers and their potential role in migraine pathophysiology. *J Headache Pain* 23(1):16
46. Yamanaka G, Suzuki S, Morishita N, Takeshita M, Kanou K, Takamatsu T et al (2021) Role of neuroinflammation and blood-brain barrier permeability on migraine. *Int J Mol Sci* 22(16)
47. Kowalska M, Prendecki M, Piekut T, Kozubski W, Dorszewska J (2021) Migraine: calcium channels and glia. *Int J Mol Sci* 22(5)
48. da Costa SC, Passos IC, Réus GZ, Carvalho AF, Soares JC, Quevedo J (2016) The comorbidity of bipolar disorder and migraine: the role of inflammation and oxidative and nitrosative stress. *Curr Mol Med* 16(2):179–186
49. Neri M, Frustaci A, Milic M, Valdiglesias V, Fini M, Bonassi S et al (2015) A meta-analysis of biomarkers related to oxidative stress and nitric oxide pathway in migraine. *Cephalalgia* 35(10):931–937
50. Shatillo A, Koroleva K, Giniatullina R, Naumenko N, Slastnikova AA, Aliev RR et al (2013) Cortical spreading depression induces oxidative stress in the trigeminal nociceptive system. *Neuroscience* 253:341–349
51. Mickel AD, Shepherd AJ, Mohapatra DP (2016) Nociceptive TRP channels: sensory detectors and transducers in multiple pain pathologies. *Pharmaceuticals (Basel, Switzerland)* 9(4)
52. Borkum JM (2016) Migraine triggers and oxidative stress: a narrative review and synthesis. *Headache* 56(1):12–35
53. Akopian AN (2011) Regulation of nociceptive transmission at the periphery via TRPA1-TRPV1 interactions. *Curr Pharm Biotechnol* 12(1):89–94
54. Burow P, Meyer A, Naegel S, Watzke S, Zierz S, Kraya T (2021) Headache and migraine in mitochondrial disease and its impact on life-results from a cross-sectional, questionnaire-based study. *Acta Neurol Belg* 121(5):1151–1156
55. Vollono C, Primiano G, Della Marca G, Losurdo A, Servidei S (2017) Migraine in mitochondrial disorders: prevalence and characteristics. *Cephalalgia : an international journal of headache* 38(6):1093–1106
56. Tiehuis LH, Koene S, Saris CGJ, Janssen MCH (2020) Mitochondrial migraine; a prevalence, impact and treatment efficacy cohort study. *Mitochondrion* 53:128–132
57. Gross EC, Putananickal N, Orsini AL, Vogt DR, Sandor PS, Schoenen J et al (2021) Mitochondrial function and oxidative stress markers in higher-frequency episodic migraine. *Sci Rep* 11(1):4543
58. Fila M, Chojnacki C, Chojnacki J, Blasiak J (2021) Nutrients to improve mitochondrial function to reduce brain energy deficit and oxidative stress in migraine. *Nutrients* 13(12)

59. Geyik S, Altunışık E, Neyal AM, Taysi S (2016) Oxidative stress and DNA damage in patients with migraine. *J Headache Pain* 17:10
60. Tuncel D, Tolun FI, Gokce M, Imrek S, Ekerbiçer H (2008) Oxidative stress in migraine with and without aura. *Biol Trace Elem Res* 126(1–3):92–97
61. Grech O, Sassani M, Terwindt G, Lavery GG, Mollan SP, Sinclair AJ (2022) Alterations in metabolic flux in migraine and the translational relevance. *J Headache Pain* 23(1):127
62. Togha M, Razeghi Jahromi S, Ghorbani Z, Ghaemi A, Rafiee P (2019) An investigation of oxidant/antioxidant balance in patients with migraine: a case-control study. *BMC Neurol* 19(1):323
63. Zangar RC, Bollinger N, Weber TJ, Tan RM, Markillie LM, Karin NJ (2011) Reactive oxygen species alter autocrine and paracrine signaling. *Free Radical Biol Med* 51(11):2041–2047
64. Olesen J (2010) Nitric oxide-related drug targets in headache. *Neurotherapeutics: the journal of the American Society for Experimental NeuroTherapeutics* 7(2):183–190
65. Aral LA, Ergun MA, Bolay H (2021) Cellular iron storage and trafficking are affected by GTN stimulation in primary glial and meningeal cell culture. *Turk J Biol* 45(1):46–55
66. Dini E, Mazzucchi S, De Luca C, Cafalli M, Chico L, Lo Gerfo A, et al (2019) Plasma levels of oxidative stress markers, before and after BoNT/a treatment, in chronic migraine. *Toxins* 11(10)
67. Tripathi GM, Kalita J, Misra UK (2018) A study of oxidative stress in migraine with special reference to prophylactic therapy. *Int J Neurosci* 128(4):318–324
68. Gómez-Nicola D, Franssen NL, Suzzi S, Perry VH (2013) Regulation of microglial proliferation during chronic neurodegeneration. *J Neurosci* 33(6):2481–2493
69. Hammond TR, Robinton D, Stevens B (2018) Microglia and the brain: complementary partners in development and disease. *Annu Rev Cell Dev Biol* 34:523–544
70. Colonna M, Butovsky O (2017) Microglia function in the central nervous system during health and neurodegeneration. *Annu Rev Immunol* 35:441–468
71. Su M, Ran Y, He Z, Zhang M, Hu G, Tang W et al (2018) Inhibition of toll-like receptor 4 alleviates hyperalgesia induced by acute dural inflammation in experimental migraine. *Mol Pain* 14:1744806918754612
72. Nimmerjahn A, Kirchhoff F, Helmchen F (2005) Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science (New York, NY)* 308(5726):1314–1318
73. Franceschini A, Hullugundi SK, van den Maagdenberg A, Nistri A, Fabbretti E (2013) Effects of LPS on P2X3 receptors of trigeminal sensory neurons and macrophages from mice expressing the R192Q Ca α 1a gene mutation of familial hemiplegic migraine-1. *Purinergic Signalling* 9(1):7–13
74. Shim HJ, Park S, Lee JW, Park HJ, Baek SH, Kim EK et al (2016) Extracts from *Dendropanax morbifera* leaves have modulatory effects on neuroinflammation in microglia. *Am J Chin Med* 44(1):119–132
75. Tang Y, Le W (2016) Differential roles of M1 and M2 microglia in neurodegenerative diseases. *Mol Neurobiol* 53(2):1181–1194
76. Mosher KI, Wyss-Coray T (2014) Microglial dysfunction in brain aging and Alzheimer's disease. *Biochem Pharmacol* 88(4):594–604
77. Pusic KM, Pusic AD, Kemme J, Kraig RP (2014) Spreading depression requires microglia and is decreased by their M2a polarization from environmental enrichment. *Glia* 62(7):1176–1194
78. Pusic KM, Won L, Kraig RP, Pusic AD (2019) IFN gamma-stimulated dendritic cell exosomes for treatment of migraine modeled using spreading depression. *FRONT NEUROSCI* 13
79. Gaojian T, Dingfei Q, Linwei L, Xiaowei W, Zheng Z, Wei L et al (2020) Parthenolide promotes the repair of spinal cord injury by modulating M1/M2 polarization via the NF- κ B and STAT 1/3 signaling pathway. *Cell Death Discov* 6(1):97
80. Wen QW, Wang YF, Pan Q, Tian RM, Zhang DK, Qin GC, et al (2021) MicroRNA-155–5p promotes neuroinflammation and central sensitization via inhibiting SIRT1 in a nitroglycerin-induced chronic migraine mouse model. *J NEUROINFLAMMATION* 18(1)
81. Jiang L, Zhang Y, Jing F, Long T, Qin G, Zhang D et al (2021) P2X7R-mediated autophagic impairment contributes to central sensitization in a chronic migraine model with recurrent nitroglycerin stimulation in mice. *J Neuroinflammation* 18(1):5
82. Chen S-P, Qin T, Seidel JL, Zheng Y, Eikermann M, Ferrari MD et al (2017) Inhibition of the P2X7–PANX1 complex suppresses spreading depolarization and neuroinflammation. *Brain* 140(6):1643–1656
83. Jiang L, Zhang YX, Jing F, Long T, Qin GC, Zhang DK, et al (2021) P2X7R-mediated autophagic impairment contributes to central sensitization in a chronic migraine model with recurrent nitroglycerin stimulation in mice. *J NEUROINFLAMMATION* 18(1)
84. Sorge RE, Mapplebeck JC, Rosen S, Beggs S, Taves S, Alexander JK et al (2015) Different immune cells mediate mechanical pain hypersensitivity in male and female mice. *Nat Neurosci* 18(8):1081–1083
85. Karkhaneh A, Ansari M, Emamgholipour S, Rafiee MH (2015) The effect of 17 β -estradiol on gene expression of calcitonin gene-related peptide and some pro-inflammatory mediators in peripheral blood mononuclear cells from patients with pure menstrual migraine. *Iran J Basic Med Sci* 18(9):894–901
86. Rothstein JD, Patel S, Regan MR, Haenggeli C, Huang YH, Bergles DE et al (2005) Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. *Nature* 433(7021):73–77
87. Rossi D, Volterra A (2009) Astrocytic dysfunction: insights on the role in neurodegeneration. *Brain Res Bull* 80(4–5):224–232
88. Peteri U-K, Niukkanen M, Castrén ML (2019) Astrocytes in neuropathologies affecting the frontal cortex. *Front Cell Neurosci* 13:44
89. Khakh BS, Beaumont V, Cachepe R, Munoz-Sanjuan I, Goldman SA, Grantyn R (2017) Unravelling and exploiting astrocyte dysfunction in Huntington's disease. *Trends Neurosci* 40(7):422–437
90. Jiang R, Diaz-Castro B, Looger LL, Khakh BS (2016) Dysfunctional calcium and glutamate signaling in striatal astrocytes from Huntington's disease model mice. *J Neurosci* 36(12):3453–3470
91. Steinhäuser C, Seifert G, Bedner P (2012) Astrocyte dysfunction in temporal lobe epilepsy: K $^{+}$ channels and gap junction coupling. *Glia* 60(8):1192–1202
92. Steinhäuser C, Grunnet M, Carmignoto G (2016) Crucial role of astrocytes in temporal lobe epilepsy. *Neuroscience* 323:157–169
93. Zou J, Wang Y-X, Dou F-F, Lü H-Z, Ma Z-W, Lu P-H et al (2010) Glutamine synthetase down-regulation reduces astrocyte protection against glutamate excitotoxicity to neurons. *Neurochem Int* 56(4):577–584
94. Zamanian JL, Xu L, Foo LC, Nouri N, Zhou L, Giffard RG et al (2012) Genomic analysis of reactive astrogliosis. *J Neurosci* 32(18):6391–6410
95. Medvedeva YV, Lin B, Shuttleworth CW, Weiss JH (2009) Intracellular Zn $^{2+}$ accumulation contributes to synaptic failure, mitochondrial depolarization, and cell death in an acute slice oxygen-glucose deprivation model of ischemia. *J Neurosci* 29(4):1105–1114

96. Monje ML, Toda H, Palmer TD (2003) Inflammatory blockade restores adult hippocampal neurogenesis. *Science* (New York, NY) 302(5651):1760–1765
97. Ghaemi A, Alizadeh L, Babaei S, Jafarian M, Ghadiri MK, Meuth SG et al (2018) Astrocyte-mediated inflammation in cortical spreading depression. *Cephalalgia* 38(4):626–638
98. Zhao J, Blaeser AS, Levy D (2021) Astrocytes mediate migraine-related intracranial meningeal mechanical hypersensitivity. *Pain* 162(9):2386–2396
99. Leite JA, Isaksen TJ, Heuck A, Scavone C, Lykke-Hartmann K (2020) The $\alpha(2)$ Na(+)/K(+)-ATPase isoform mediates LPS-induced neuroinflammation. *Sci Rep* 10(1):14180
100. Ellman DG, Isaksen TJ, Lund MC, Dursun S, Wrenfeldt M, Jørgensen LH et al (2017) The loss-of-function disease-mutation G301R in the Na(+)/K(+)-ATPase $\alpha(2)$ isoform decreases lesion volume and improves functional outcome after acute spinal cord injury in mice. *BMC Neurosci* 18(1):66
101. Zhou X, Liang J, Wang J, Fei Z, Qin G, Zhang D et al (2020) Up-regulation of astrocyte excitatory amino acid transporter 2 alleviates central sensitization in a rat model of chronic migraine. *J Neurochem* 155(4):370–389
102. Tang J, Bair M, Descalzi G (2021) Reactive astrocytes: critical players in the development of chronic pain. *Front Psychiatry* 12
103. Kilic K, Karatas H, Dönmez-Demir B, Eren-Kocak E, Gursoy-Ozdemir Y, Can A et al (2018) Inadequate brain glycogen or sleep increases spreading depression susceptibility. *Ann Neurol* 83(1):61–73
104. Li J, Ye X, Zhou Y, Peng S, Zheng P, Zhang X, et al (2022) Energy metabolic disorder of astrocytes may be an inducer of migraine attack. *Brain Sci* 12(7)
105. Waschek JA, Baca SM, Akerman S (2018) PACAP and migraine headache: immunomodulation of neural circuits in autonomic ganglia and brain parenchyma. *J Headache Pain* 19(1):1–13
106. Yokai M, Kurihara T, Miyata A (2016) Spinal astrocytic activation contributes to both induction and maintenance of pituitary adenylate cyclase-activating polypeptide type 1 receptor-induced long-lasting mechanical allodynia in mice. *Mol Pain* 12:1744806916646383
107. Jasmin L, Vit JP, Bhargava A, Ohara PT (2010) Can satellite glial cells be therapeutic targets for pain control? *Neuron Glia Biol* 6(1):63–71
108. Huang LY, Gu Y, Chen Y (2013) Communication between neuronal somata and satellite glial cells in sensory ganglia. *Glia* 61(10):1571–1581
109. Pannese E (2018) Biology and pathology of perineuronal satellite cells in sensory ganglia. *Biology and Pathology of Perineuronal Satellite Cells in Sensory Ganglia*: Springer 1–63
110. Cieślak M, Czarnecka J, Roszek K, Komoszyński M (2015) The role of purinergic signaling in the etiology of migraine and novel antimigraine treatment. *Purinergic Signal* 11(3):307–316
111. Matsuka Y, Afroz S, Dalanon JC, Iwasa T, Waskitho A, Oshima M (2020) The role of chemical transmitters in neuron-glia interaction and pain in sensory ganglion. *Neurosci Biobehav Rev* 108:393–399
112. Fabbretti E (2013) ATP P2X3 receptors and neuronal sensitization. *Front Cell Neurosci* 7
113. Yegutkin GG, Guerrero-Toro C, Kilinc E, Koroleva K, Ishchenko Y, Abushik P et al (2016) Nucleotide homeostasis and purinergic nociceptive signaling in rat meninges in migraine-like conditions. *Purinergic Signalling* 12(3):561–574
114. Edvinsson J, Warfvinge K, Edvinsson L (2015) Modulation of inflammatory mediators in the trigeminal ganglion by botulinum neurotoxin type A: an organ culture study. *J Headache Pain* 16(1)
115. Lukács M, Haanes KA, Majláth Z, Tajti J, Vécsei L, Warfvinge K, et al (2015) Dural administration of inflammatory soup or complete Freund's adjuvant induces activation and inflammatory response in the rat trigeminal ganglion. *J Headache Pain* 16(1)
116. Villa G, Ceruti S, Zanardelli M, Magni G, Jasmin L, Ohara PT, et al (2010) Temporomandibular joint inflammation activates glial and immune cells in both the trigeminal ganglia and in the spinal trigeminal nucleus. *MOL PAIN* 6
117. Aczel T, Kecskes A, Kun J, Szenthe K, Banati F, Szathmary S, et al (2020) Hemokinin-1 gene expression is upregulated in trigeminal ganglia in an inflammatory orofacial pain model: potential role in peripheral sensitization. *Int J Mol Sci* 21(8)
118. Chen Y, Zhang X, Wang C, Li G, Gu Y, Huang LY (2008) Activation of P2X7 receptors in glial satellite cells reduces pain through downregulation of P2X3 receptors in nociceptive neurons. *Proc Natl Acad Sci U S A* 105(43):16773–16778
119. Bernier LP, Ase AR, Séguéla P (2018) P2X receptor channels in chronic pain pathways. *Br J Pharmacol* 175(12):2219–2230
120. Bahat A, MacVicar T, Langer T (2021) Metabolism and innate immunity meet at the mitochondria. *Front Cell Dev Biol* 9
121. Brubaker SW, Bonham KS, Zanon I, Kagan JC (2015) Innate immune pattern recognition: a cell biological perspective. *Annu Rev Immunol* 33:257–290
122. Bhat R, Steinman L (2009) Innate and adaptive autoimmunity directed to the central nervous system. *Neuron* 64(1):123–132
123. Kursun O, Yemisci M, van den Maagdenberg AMJM, Karatas H (2021) Migraine and neuroinflammation: the inflammasome perspective. *J Headache Pain* 22(1):55
124. Wieseler J, Ellis A, McFadden A, Stone K, Brown K, Cady S et al (2017) Supradural inflammatory soup in awake and freely moving rats induces facial allodynia that is blocked by putative immune modulators. *Brain Res* 1664:87–94
125. Wang Y, Shan Z, Zhang L, Fan S, Zhou Y, Hu L et al (2022) P2X7R/NLRP3 signaling pathway-mediated pyroptosis and neuroinflammation contributed to cognitive impairment in a mouse model of migraine. *J Headache Pain* 23(1):75
126. Rueda-Carrasco J, Martin-Bermejo MJ, Pereyra G, Mateo MI, Borroto A, Brosseron F et al (2021) SFRP1 modulates astrocyte-microglia crosstalk in acute and chronic neuroinflammation. *EMBO Rep* 22(11):e51696
127. Eren-Koçak E, Dalkara T (2021) Ion channel dysfunction and neuroinflammation in migraine and depression. *Front Pharmacol* 12:777607
128. Shibata M, Suzuki N (2017) Exploring the role of microglia in cortical spreading depression in neurological disease. *J Cereb Blood Flow Metab* : official journal of the International Society of Cerebral Blood Flow and Metabolism 37(4):1182–1191
129. Cha YH, Millett D, Kane M, Jen J, Baloh R (2007) Adult-onset hemiplegic migraine with cortical enhancement and oedema. *Cephalalgia* 27(10):1166–1170
130. Goloncsér F, Baranyi M, Iring A, Hricisak L, Otrókcsi L, Benyo Z et al (2021) Involvement of P2Y₁₂ receptors in a nitroglycerin-induced model of migraine in male mice. *Br J Pharmacol* 178(23):4626–4645
131. Franceschini A, Nair A, Bele T, van den Maagdenberg A, Nistri A, Fabbretti E (2012) Functional crosstalk in culture between macrophages and trigeminal sensory neurons of a mouse genetic model of migraine. *BMC NEUROSCI* 13
132. Liu Q, Liu C, Jiang L, Li M, Long T, He W et al (2018) $\alpha 7$ Nicotinic acetylcholine receptor-mediated anti-inflammatory effect in a chronic migraine rat model via the attenuation of glial cell activation. *J Pain Res* 11:1129–1140
133. Bonilla FA, Oettgen HC (2010) Adaptive immunity. *J Allergy Clin Immunol* 125(2 Suppl 2):S33–40
134. Marshall JS, Warrington R, Watson W, Kim HL (2018) An introduction to immunology and immunopathology. *Allergy Asthma Clin Immunol* 14(2):49

135. Faraji F, Shojapour M, Farahani I, Ganji A, Mosayebi G (2021) Reduced regulatory T lymphocytes in migraine patients. *Neurol Res* 43(8):677–682
136. Pavelek Z, Souček O, Krejsek J, Sobíšek L, Klímová B, Masopust J et al (2020) The role of the immune system and the biomarker CD3 + CD4 + CD45RA-CD62L- in the pathophysiology of migraine. *Sci Rep* 10(1):12277
137. Delgado M, Pozo D, Ganea D (2004) The significance of vasoactive intestinal peptide in immunomodulation. *Pharmacol Rev* 56(2):249–290
138. Delgado M, Munoz-Elias EJ, Gomariz RP, Ganea D (1999) Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide enhance IL-10 production by murine macrophages: in vitro and in vivo studies. *J Immunol (Baltimore, Md : 1950)* 162(3):1707–16
139. Conti P, D'Ovidio C, Conti C, Gallenga CE, Lauritano D, Caraffa A et al (2019) Progression in migraine: role of mast cells and pro-inflammatory and anti-inflammatory cytokines. *Eur J Pharmacol* 844:87–94
140. Yuan H, Silberstein SD (2018) Histamine and migraine. *Headache: The Journal of Head and Face*. *Pain* 58(1):184–93
141. Skaper SD, Facci L, Giusti P (2014) Mast cells, glia and neuroinflammation: partners in crime? *Immunology* 141(3):314–327
142. Zhang XC, Strassman AM, Burstein R, Levy D (2007) Sensitization and activation of intracranial meningeal nociceptors by mast cell mediators. *J Pharmacol Exp Ther* 322(2):806–812
143. Levy D, Burstein R, Kainz V, Jakubowski M, Strassman AM (2007) Mast cell degranulation activates a pain pathway underlying migraine headache. *Pain* 130(1–2):166–176
144. Pusic AD, Mitchell HM, Kunkler PE, Klauer N, Kraig RP (2015) Spreading depression transiently disrupts myelin via interferon-gamma signaling. *Exp Neurol* 264:43–54
145. Magni G, Boccazzi M, Bodini A, Abbracchio MP, van den Maagdenberg AM, Ceruti S (2019) Basal astrocyte and microglia activation in the central nervous system of familial hemiplegic migraine type I mice. *Cephalalgia : an international journal of headache* 39(14):1809–1817
146. Eising E, de Leeuw C, Min JL, Anttila V, Verheijen MH, Terwindt GM et al (2016) Involvement of astrocyte and oligodendrocyte gene sets in migraine. *Cephalalgia : an international journal of headache* 36(7):640–647
147. Henssen D, Kluin SJP, Kleerebezem J, Cappellen Van, van Walsum AM, Mulleners WM, Vissers K (2022) White matter changes in the trigeminal spinal tract in chronic migraineurs: an ex vivo study combining ultra-high-field diffusion tensor imaging and polarized light imaging microscopy. *Pain* 163(4):779–85
148. Hamedani AG, Rose KM, Peterlin BL, Mosley TH, Coker LH, Jack CR et al (2013) Migraine and white matter hyperintensities: the ARIC MRI study. *Neurology* 81(15):1308–1313
149. Messina R, Rocca MA, Colombo B, Pagani E, Falini A, Comi G et al (2015) White matter microstructure abnormalities in pediatric migraine patients. *Cephalalgia : an international journal of headache* 35(14):1278–1286
150. Borsook D, Erpelding N, Lebel A, Linnman C, Veggeberg R, Grant PE et al (2014) Sex and the migraine brain. *Neurobiol Dis* 68:200–214
151. D'Andrea G, Granella F, Cataldini M, Verdelli F, Balbi T (2001) GABA and glutamate in migraine. *J Headache Pain* 2(1):s57–s60
152. Bigal ME, Hetherington H, Pan J, Tsang A, Grosberg B, Avdievich N et al (2008) Occipital levels of GABA are related to severe headaches in migraine. *Neurology* 70(22):2078–2080
153. Wu J, Gao M, Shen J-X, Qiu S-F, Kerrigan JF (2015) Mechanisms of intrinsic epileptogenesis in human gelastic seizures with hypothalamic hamartoma. *CNS Neurosci Ther* 21(2):104–111
154. Aguila MR, Rebbeck T, Leaver AM, Lagopoulos J, Brennan PC, Hübscher M et al (2016) The association between clinical characteristics of migraine and brain GABA levels: an exploratory study. *J Pain* 17(10):1058–1067
155. Aguila ME, Lagopoulos J, Leaver AM, Rebbeck T, Hübscher M, Brennan PC et al (2015) Elevated levels of GABA+ in migraine detected using (1) H-MRS. *NMR Biomed* 28(7):890–897
156. Brennan KC, Charles A (2010) An update on the blood vessel in migraine. *Curr Opin Neurol* 23(3):266–274
157. Peek AL, Rebbeck T, Puts NA, Watson J, Aguila MR, Leaver AM (2020) Brain GABA and glutamate levels across pain conditions: a systematic literature review and meta-analysis of 1H-MRS studies using the MRS-Q quality assessment tool. *Neuroimage* 210:116532
158. Stærnøse TG, Knudsen MK, Kasch H, Blicher JU (2019) Cortical GABA in migraine with aura -an ultrashort echo magnetic resonance spectroscopy study. *J Headache Pain* 20(1):110
159. Sokolov A, Lyubashina O, Amelin A, Pantelev S (2014) The role of gamma-aminobutyric acid in migraine pathogenesis. *Neurochem J* 8:89–102
160. Grinberg YY, Milton JG, Kraig RP (2011) Spreading depression sends microglia on Lévy flights. *PLoS One* 6(4):e19294
161. Nosedà R, Borsook D, Burstein R (2017) Neuropeptides and neurotransmitters that modulate thalamo-cortical pathways relevant to migraine headache. *Headache* 57(Suppl 2):97–111
162. D'Andrea G, Leon A (2010) Pathogenesis of migraine: from neurotransmitters to neuromodulators and beyond. *Neurol Sci : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 31(Suppl 1):S1–7
163. Shatillo A, Salo RA, Giniatullin R, Gröhn OH (2015) Involvement of NMDA receptor subtypes in cortical spreading depression in rats assessed by fMRI. *Neuropharmacology* 93:164–170
164. Boakye PA, Tang S-J, Smith PA (2021) Mediators of neuropathic pain; focus on spinal microglia, CSF-1, BDNF, CCL21, TNF- α , Wnt ligands, and interleukin 1 β . *Front Pain Res* 41.
165. Ni N, Wang Q, Lin X, Hong Y, Feng Y, Shen L (2019) Studies on the mechanism of glutamate metabolism in NTG-induced migraine rats treated with DCXF. *Evid Based Complement Alternat Med* 2019:1324797
166. Yoo BK, Emdad L, Lee SG, Su ZZ, Santhekadur P, Chen D et al (2011) Astrocyte elevated gene-1 (AEG-1): a multifunctional regulator of normal and abnormal physiology. *Pharmacol Ther* 130(1):1–8
167. Guerrero-Toro C, Koroleva K, Ermakova E, Gafurov O, Abushik P, Tavi P et al (2022) Testing the role of glutamate NMDA receptors in peripheral trigeminal nociception implicated in migraine pain. *Int J Mol Sci* 23(3):1529
168. Van der Auwera S, Teumer A, Hertel J, Homuth G, Völker U, Lucht MJ et al (2016) The inverse link between genetic risk for schizophrenia and migraine through NMDA (N-methyl-D-aspartate) receptor activation via D-serine. *Eur Neuropsychopharmacol* 26(9):1507–1515
169. Abushik PA, Niittykoski M, Giniatullina R, Shakirzyanova A, Bart G, Fayuk D et al (2014) The role of NMDA and mGluR5 receptors in calcium mobilization and neurotoxicity of homocysteine in trigeminal and cortical neurons and glial cells. *J Neurochem* 129(2):264–274
170. Gasparini CF, Smith RA, Griffiths LR (2016) Genetic insights into migraine and glutamate: a protagonist driving the headache. *J Neurol Sci* 367:258–268
171. Paredes S, Cantillo S, Candido KD, Knezevic NN (2019) An association of serotonin with pain disorders and its modulation by estrogens. *Int J Mol Sci* 20(22)
172. Kilinc E, Guerrero-Toro C, Zakharov A, Vitale C, Gubert-Olive M, Koroleva K et al (2017) Serotonergic mechanisms of

- trigeminal meningeal nociception: implications for migraine pain. *Neuropharmacology* 116:160–173
173. Deen M, Christensen CE, Hougaard A, Hansen HD, Knudsen GM, Ashina M (2017) Serotonergic mechanisms in the migraine brain - a systematic review. *Cephalalgia* 37(3):251–264
 174. Cornelison LE, Woodman SE, Durham PL (2020) Inhibition of trigeminal nociception by non-invasive vagus nerve stimulation: investigating the role of GABAergic and serotonergic pathways in a model of episodic migraine. *Front Neurol* 11
 175. Giniatullin R (2022) 5-hydroxytryptamine in migraine: the puzzling role of ionotropic 5-HT(3) receptor in the context of established therapeutic effect of metabotropic 5-HT(1) subtypes. *Br J Pharmacol* 179(3):400–415
 176. Cortes-Altamirano JL, Olmos-Hernandez A, Jaime HB, Carrillo-Mora P, Bandala C, Reyes-Long S et al (2018) Review: 5-HT₁, 5-HT₂, 5-HT₃ and 5-HT₇ receptors and their role in the modulation of pain response in the central nervous system. *Curr Neuropharmacol* 16(2):210–221
 177. Tepper SJ, Rapoport AM, Sheftell FD (2002) Mechanisms of action of the 5-HT_{1B/1D} receptor agonists. *Arch Neurol* 59(7):1084–1088
 178. Frederiksen SD, Haanes KA, Warfvinge K, Edvinsson L (2019) Perivascular neurotransmitters: regulation of cerebral blood flow and role in primary headaches. *J Cereb Blood Flow Metab*: official journal of the International Society of Cerebral Blood Flow and Metabolism 39(4):610–632
 179. Bowen EJ, Schmidt TW, Firm CS, Russo AF, Durham PL (2006) Tumor necrosis factor- α stimulation of calcitonin gene-related peptide expression and secretion from rat trigeminal ganglion neurons. *J Neurochem* 96(1):65–77
 180. Ottosson A, Edvinsson L (1997) Release of histamine from dural mast cells by substance P and calcitonin gene-related peptide. *Cephalalgia* 17(3):166–174
 181. Theoharides TC, Donelan J, Kandere-Grzybowska K, Konstantinidou A (2005) The role of mast cells in migraine pathophysiology. *Brain Res Brain Res Rev* 49(1):65–76
 182. Olesen J, Larsen B, Lauritzen M (1981) Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. *Ann Neurol* 9(4):344–352
 183. Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA (2002) Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nat Med* 8(2):136–142
 184. Zhang X, Levy D, Nosedá R, Kainz V, Jakubowski M, Burstein R (2010) Activation of meningeal nociceptors by cortical spreading depression: implications for migraine with aura. *J Neurosci* 30(26):8807–8814
 185. Ansari M, Karkhaneh A, Kheirollahi A, Emamgholipour S, Rafiee MH (2017) The effect of melatonin on gene expression of calcitonin gene-related peptide and some proinflammatory mediators in patients with pure menstrual migraine. *Acta Neurol Belg* 117(3):677–685
 186. Okamoto K, Tashiro A, Chang Z, Bereiter DA (2010) Bright light activates a trigeminal nociceptive pathway. *Pain* 149(2):235–242
 187. Blixt FW, Radziwon-Balicka A, Edvinsson L, Warfvinge K (2017) Distribution of CGRP and its receptor components CLR and RAMP1 in the rat retina. *Exp Eye Res* 161:124–131
 188. Thalakoti S, Patil VV, Damodaram S, Vause CV, Langford LE, Freeman SE et al (2007) Neuron-glia signaling in trigeminal ganglion: implications for migraine pathology. *Headache* 47(7):1008–23 (discussion 24–5)
 189. Mikhailov N, V. Mamontov O, A. Kamshilin A, Giniatullin R. Parasympathetic Cholinergic and Neuropeptide Mechanisms of Migraine. *Anesth Pain Med.* 2017 7(1):e42210. <https://doi.org/10.5812/aapm.42210>
 190. Shelukhina I, Mikhailov N, Abushik P, Nurullin L, Nikolsky EE, Giniatullin R (2017) Cholinergic nociceptive mechanisms in rat meninges and trigeminal ganglia: potential implications for migraine pain. *Front Neurol* 8:163
 191. Thuraiaiyah J, Kokoti L, Al-Karagholi MA-M, Ashina M (2022) Involvement of adenosine signaling pathway in migraine pathophysiology: a systematic review of preclinical studies. *J Headache Pain* 23(1):43
 192. Guo Y, Cheng Y, An J, Qi Y, Luo G (2021) Neuropeptide changes in an improved migraine model with repeat stimulations. *Transl Neurosci* 12(1):523–532
 193. Theodorakis PE, Müller EA, Craster RV, Matar OK (2017) Physical insights into the blood–brain barrier translocation mechanisms. *Phys Biol* 14(4):041001
 194. Hendriksen E, van Bergeijk D, Oosting RS, Redegeld FA (2017) Mast cells in neuroinflammation and brain disorders. *Neurosci Biobehav Rev* 79:119–133
 195. Ramachandran R (2018) Neurogenic inflammation and its role in migraine. *Semin Immunopathol* 40(3):301–314
 196. Matsuda M, Huh Y, Ji RR (2019) Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. *J Anesth* 33(1):131–139
 197. Dreier JP, Reiffurth C (2015) The stroke-migraine depolarization continuum. *Neuron* 86(4):902–922
 198. Bartsch T, Schönfeld R, Müller FJ, Alfke K, Leplow B, Aldenhoff J et al (2010) Focal lesions of human hippocampal CA1 neurons in transient global amnesia impair place memory. *Science (New York, NY)* 328(5984):1412–1415
 199. Dichgans M, Mayer M, Uttner I, Brüning R, Müller-Höcker J, Rungger G et al (1998) The phenotypic spectrum of CADASIL: Clinical findings in 102 cases. *Ann Neurol* 44(5):731–739
 200. Chen H, Tang X, Li J, Hu B, Yang W, Zhan M et al (2022) IL-17 crosses the blood-brain barrier to trigger neuroinflammation: a novel mechanism in nitroglycerin-induced chronic migraine. *J Headache Pain* 23(1):1
 201. Celikbilek A, Sabah S, Tanik N, Ak H, Atalay T, Yilmaz N (2014) Is serum S100B protein an useful biomarker in migraine? *Neurol Sci*: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 35(8):1197–1201
 202. McIlvried LA, Albers K, Gold MS (2010) Distribution of artemin and GFR α 3 labeled nerve fibers in the dura mater of rat: artemin and GFR α 3 in the dura. *Headache* 50(3):442–450
 203. Yi T, Gao P, Zhu T, Yin H, Jin S (2022) Glymphatic system dysfunction: a novel mediator of sleep disorders and headaches. *Front Neurol* 13
 204. Mikhailov N, Virenque A, Koroleva K, Eme-Scolan E, Teleman M, Abdollahzadeh A et al (2022) The role of the meningeal lymphatic system in local meningeal inflammation and trigeminal nociception. *Sci Rep* 12(1):8804
 205. Lee DA, Lee H-J, Park KM (2022) Normal glymphatic system function in patients with migraine: a pilot study. *Headache: The Journal of Head and Face Pain* 62(6):718–725
 206. Sarrouilhe D, Dejean C, Mesnil M (2014) Involvement of gap junction channels in the pathophysiology of migraine with aura. *FRONT PHYSIOL* 5
 207. de Corato A, Capuano A, Currò D, Tringali G, Navarra P, Dello Russo C (2011) Trigeminal satellite cells modulate neuronal responses to triptans: relevance for migraine therapy. *Neuron Glia Biol* 7(2–4):109–116
 208. D’Andrea G, Colavito D, Dalle Carbonare M, Leon A (2011) Migraine with aura: conventional and non-conventional treatments. *Neurol Sci*: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 32(Suppl 1):S121–S129

209. Goadsby PJ, Lipton RB, Ferrari MD (2002) Migraine—current understanding and treatment. *N Engl J Med* 346(4):257–270
210. Bhalla P, Sharma HS, Wurch T, Pauwels PJ, Saxena PR (2002) Molecular cloning and expression of the porcine trigeminal ganglion cDNA encoding a 5-HT(1F) receptor. *Eur J Pharmacol* 436(1–2):23–33
211. Tfelt-Hansen P, Saxena PR, Dahlfö C, Pascual J, Láinez M, Henry P et al (2000) Ergotamine in the acute treatment of migraine: a review and European consensus. *Brain* 123(1):9–18
212. Milligan ED, Soderquist RG, Malone SM, Mahoney JH, Hughes TS, Langer SJ et al (2006) Intrathecal polymer-based interleukin-10 gene delivery for neuropathic pain. *Neuron Glia Biol* 2(4):293–308
213. Rossi P, Fiermonte G, Pierelli F (2003) Cinnarizine in migraine prophylaxis: efficacy, tolerability and predictive factors for therapeutic responsiveness An open-label pilot trial. *Funct Neurol* 18(3):155–159
214. Koyuncu Irmak D, Kilinc E, Tore F (2019) Shared fate of meningeal mast cells and sensory neurons in migraine. *Front Cell Neurosci* 13:136
215. Meloto CB, Ingelmo P, Perez EV, Pitt R, González Cárdenas VH, Mohamed N et al (2021) Mast cell stabilizer ketotifen fumarate reverses inflammatory but not neuropathic-induced mechanical pain in mice. *Pain reports* 6(2):e902
216. Lopresti AL, Smith SJ, Drummond PD (2020) Herbal treatments for migraine: a systematic review of randomised-controlled studies. *Phytotherapy research* : PTR 34(10):2493–2517
217. Yarnell E (2017) Herbal medicine and migraine. *Altern Complementary Ther* 23(5):192–201
218. Nor MNM, Rupenthal ID, Green CR, Acosta ML (2020) Connexin hemichannel block using orally delivered tonabersat improves outcomes in animal models of retinal disease. *Neurotherapeutics* : the journal of the American Society for Experimental NeuroTherapeutics 17(1):371–387
219. Durham PL, Garrett FG (2010) Emerging importance of neuron-satellite glia interactions within trigeminal ganglia in craniofacial pain. *Open Pain Journal* 3(1):3–13
220. Edvinsson L (2017) The trigeminovascular pathway: role of CGRP and CGRP receptors in migraine. *Headache* 57(Suppl 2):47–55
221. Melo-Carrillo A, Strassman AM, Nir RR, Schain AJ, Nosedá R, Stratton J et al (2017) Fremanezumab—a humanized monoclonal anti-CGRP antibody—inhibits thinly myelinated (A δ) but not unmyelinated (C) meningeal nociceptors. *J Neurosci* 37(44):10587–10596
222. Vu T, Ma P, Chen JS, de Hoon J, Van Hecken A, Yan L et al (2017) Pharmacokinetic-pharmacodynamic relationship of erenumab (AMG 334) and capsaicin-induced dermal blood flow in healthy and migraine subjects. *Pharm Res* 34(9):1784–1795
223. Takeshima T, Sakai F, Hirata K, Imai N, Matsumori Y, Yoshida R et al (2021) Erenumab treatment for migraine prevention in Japanese patients: efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled study. *Headache* 61(6):927–935
224. Lipton RB, Burstein R, Buse DC, Dodick DW, Koukakis R, Klatt J et al (2021) Efficacy of erenumab in chronic migraine patients with and without ictal allodynia. *Cephalalgia* : an international journal of headache 41(11–12):1152–1160
225. Wang S-J, Roxas AA Jr, Saravia B, Kim B-K, Chowdhury D, Riachi N et al (2021) Randomised, controlled trial of erenumab for the prevention of episodic migraine in patients from Asia, the Middle East, and Latin America: The EMPOWER study. *Cephalalgia* : an international journal of headache 41(13):1285–1297
226. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR (2018) Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. *JAMA Neurol* 75(9):1080–1088
227. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY (2018) Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia* : an international journal of headache 38(8):1442–1454
228. Reuter U, Lucas C, Dolezil D, Hand AL, Port MD, Nichols RM et al (2021) Galcanezumab in patients with multiple previous migraine preventive medication category failures: results from the open-label period of the CONQUER trial. *Adv Ther* 38(11):5465–5483
229. Hirata K, Takeshima T, Sakai F, Tatsuoka Y, Suzuki N, Igarashi H et al (2021) A long-term open-label safety study of galcanezumab in Japanese patients with migraine. *Expert Opin Drug Saf* 20(6):721–733
230. Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R et al (2019) Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet (London, England)* 394(10203):1030–1040
231. Brandes JL, Kudrow D, Yeung PP, Sakai F, Aycardi E, Blankenbiller T et al (2020) Effects of fremanezumab on the use of acute headache medication and associated symptoms of migraine in patients with episodic migraine. *Cephalalgia* : an international journal of headache 40(5):470–477
232. Goadsby PJ, Silberstein SD, Yeung PP, Cohen JM, Ning X, Yang R et al (2020) Long-term safety, tolerability, and efficacy of fremanezumab in migraine: a randomized study. *Neurology* 95(18):e2487–e2499
233. Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R et al (2015) Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. *Lancet Neurol* 14(11):1081–1090
234. Winner PK, McAllister P, Chakhava G, Ailani J, Ettrup A, Krog Josiassen M et al (2021) Effects of intravenous eptinezumab vs placebo on headache pain and most bothersome symptom when initiated during a migraine attack: a randomized clinical trial. *JAMA* 325(23):2348–2356
235. Lipton RB, Goadsby PJ, Smith J, Schaeffler BA, Biondi DM, Hirman J et al (2020) Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology* 94(13):e1365–e1377
236. Kudrow D, Cady RK, Allan B, Pederson SM, Hirman J, Mehta LR et al (2021) Long-term safety and tolerability of eptinezumab in patients with chronic migraine: a 2-year, open-label, phase 3 trial. *BMC Neurol* 21(1):126
237. Dodick DW, Lipton RB, Ailani J, Lu K, Finnegan M, Trugman JM et al (2019) Ubrogepant for the treatment of migraine. *N Engl J Med* 381(23):2230–2241
238. Lipton RB, Croop R, Stock EG, Stock DA, Morris BA, Frost M et al (2019) Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med* 381(2):142–149
239. Knyihár-Csillik E, Chadaide Z, Okuno E, Krisztin-Péva B, Toldi J, Varga C et al (2004) Kynurenine aminotransferase in the supratentorial dura mater of the rat: effect of stimulation of the trigeminal ganglion. *Exp Neurol* 186(2):242–247
240. Hawkins JL, Cornelison LE, Blankenship BA, Durham PL (2017) Vagus nerve stimulation inhibits trigeminal nociception in a rodent model of episodic migraine. *PAIN REP* 2(6)
241. Muniz Santana Bastos E, Bispo da Silva A, Cerqueira Coelho PL, Pereira Borges JM, Amaral da Silva VD, Moreau da Cunha VH et al (2021) Anti-inflammatory activity of *Jatropha curcas* L. in brain glial cells primary cultures. *J Ethnopharmacol* 264:113201

242. Takanashi K, Shibata K, Mizuno K, Komatsu R, Koizumi S (2021) Goshajinkigan attenuates paclitaxel-induced neuropathic pain via cortical astrocytes. *Pharmacol Res Perspect* 9(6):e00850
243. Fachel FNS, Dal Prá M, Azambuja JH, Endres M, Bassani VL, Koester LS et al (2020) Glioprotective effect of chitosan-coated rosmarinic acid nanoemulsions against lipopolysaccharide-induced inflammation and oxidative stress in Rat astrocyte primary cultures. *Cell Mol Neurobiol* 40(1):123–139
244. Ba X, Wang J, Zhou S, Luo X, Peng Y, Yang S et al (2018) Cinobufacini protects against paclitaxel-induced peripheral neuropathic pain and suppresses TRPV1 up-regulation and spinal astrocyte activation in rats. *Biomed pharmacother Biomed pharmacother* 108:76–84
245. Latronico T, Larocca M, Milella S, Fasano A, Rossano R, Liuzzi GM (2021) Neuroprotective potential of isothiocyanates in an in vitro model of neuroinflammation. *Inflammopharmacology* 29(2):561–571
246. Eghbaliferiz S, Farhadi F, Barreto GE, Majeed M, Sahebkar A (2020) Effects of curcumin on neurological diseases: focus on astrocytes. *Pharmacological reports* : PR 72(4):769–782
247. Kikuoka R, Miyazaki I, Kubota N, Maeda M, Kagawa D, Moriyama M et al (2020) Mirtazapine exerts astrocyte-mediated dopaminergic neuroprotection. *Sci Rep* 10(1):20698
248. Lee TK, Kang JJ, Sim H, Lee JC, Ahn JH, Kim DW, et al (2021) Therapeutic effects of decursin and Angelica gigas Nakai root extract in gerbil brain after transient ischemia via protecting BBB leakage and astrocyte endfeet damage. *Molecules (Basel, Switzerland)* 26(8)
249. Zhang Y, Li X, Ciric B, Curtis MT, Chen WJ, Rostami A et al (2020) A dual effect of ursolic acid to the treatment of multiple sclerosis through both immunomodulation and direct remyelination. *Proc Natl Acad Sci USA* 117(16):9082–9093
250. Song X, Gong Z, Liu K, Kou J, Liu B, Liu K (2020) Baicalin combats glutamate excitotoxicity via protecting glutamine synthetase from ROS-induced 20S proteasomal degradation. *Redox Biol* 34:101559
251. Fattori V, Pinho-Ribeiro FA, Staurengo-Ferrari L, Borghi SM, Rossaneis AC, Casagrande R et al (2019) The specialised pro-resolving lipid mediator maresin 1 reduces inflammatory pain with a long-lasting analgesic effect. *Br J Pharmacol* 176(11):1728–1744
252. Zhang F, Zhang JG, Yang W, Xu P, Xiao YL, Zhang HT (2018) 6-Gingerol attenuates LPS-induced neuroinflammation and cognitive impairment partially via suppressing astrocyte overactivation. *Biomed Pharmacother Biomed Pharmacother* 107:1523–9
253. Pajarillo E, Rizor A, Lee J, Aschner M, Lee E (2019) The role of astrocytic glutamate transporters GLT-1 and GLAST in neurological disorders: potential targets for neurotherapeutics. *Neuropharmacology* 161:107559
254. Ali T, Rahman SU, Hao Q, Li W, Liu Z, Ali Shah F et al (2020) Melatonin prevents neuroinflammation and relieves depression by attenuating autophagy impairment through FOXO3a regulation. *J Pineal Res* 69(2):e12667
255. di Giacomo V, Chiavaroli A, Recinella L, Orlando G, Cataldi A, Rapino M, et al (2020) Antioxidant and neuroprotective effects induced by cannabidiol and cannabigerol in Rat CTX-TNA2 astrocytes and isolated cortexes. *Int J Mol Sci* 21(10)
256. Isooka N, Miyazaki I, Kikuoka R, Wada K, Nakayama E, Shin K et al (2020) Dopaminergic neuroprotective effects of rotigotine via 5-HT1A receptors: possibly involvement of metallothionein expression in astrocytes. *Neurochem Int* 132:104608
257. Kinoshita M, Hirayama Y, Fujishita K, Shibata K, Shinozaki Y, Shigetomi E et al (2018) Anti-depressant fluoxetine reveals its therapeutic effect via astrocytes. *EBioMedicine* 32:72–83
258. Siracusa R, Monaco F, D'Amico R, Genovese T, Cordaro M, Interdonato L, et al (2021) Epigallocatechin-3-gallate modulates postoperative pain by regulating biochemical and molecular pathways. *Int J Mol Sci* 22(13)
259. Jiao M, Li X, Chen L, Wang X, Yuan B, Liu T et al (2020) Neuroprotective effect of astrocyte-derived IL-33 in neonatal hypoxic-ischemic brain injury. *J Neuroinflammation* 17(1):251
260. Sato K, Nakagawa S, Morofuji Y, Matsunaga Y, Fujimoto T, Watanabe D, et al (2022) Effects of fasudil on blood–brain barrier integrity. *Fluids Barriers of the CNS* 19(1)
261. Kim SR, Park Y, Li M, Kim YK, Lee S, Son SY, et al (2022) Anti-inflammatory effect of *Ailanthus altissima* (Mill.) Swingle leaves in lipopolysaccharide-stimulated astrocytes. *J Ethnopharmacol* 286
262. Heimfarth L, Nascimento LDS, Amazonas da Silva MDJ, Lucca Junior WD, Lima ES, Quintans-Junior LJ, et al (2021) Neuroprotective and anti-inflammatory effect of pectolarigenin, a flavonoid from Amazonian *Aegiphila integrifolia* (Jacq.), against lipopolysaccharide-induced inflammation in astrocytes via NF- κ B and MAPK pathways. *Food Chem Toxicol* 157
263. Wang X, Yu Z, He Z, Zhang Q, Yu S (2019) Intracerebroventricular infusion of D-serine decreases nociceptive behaviors induced by electrical stimulation of the dura mater of rat. *Neurol Res* 41(3):204–207
264. Geng Y, Yang J, Cheng X, Han Y, Yan F, Wang C, et al (2022) A bioactive gypenoside (GP-14) alleviates neuroinflammation and blood brain barrier (BBB) disruption by inhibiting the NF- κ B signaling pathway in a mouse high-altitude cerebral edema (HACE) model. *Int Immunopharmacol* 107
265. Ebrahimi T, Rust M, Kaiser SN, Slowik A, Beyer C, Koczulla AR et al (2018) α 1-antitrypsin mitigates NLRP3-inflammasome activation in amyloid β (1–42)-stimulated murine astrocytes. *J Neuroinflammation* 15(1):282
266. Zusso M, Lunardi V, Franceschini D, Pagetta A, Lo R, Stifani S et al (2019) Ciprofloxacin and levofloxacin attenuate microglia inflammatory response via TLR4/NF- κ B pathway. *J Neuroinflammation* 16(1):148
267. Wang D, Liu F, Zhu L, Lin P, Han F, Wang X et al (2020) FGF21 alleviates neuroinflammation following ischemic stroke by modulating the temporal and spatial dynamics of microglia/macrophages. *J Neuroinflammation* 17(1):257
268. Zhou Q, Guo D, Li X, Wang Y, Ye X, Xue S et al (2020) Anti-inflammatory effects of vinpocetine in LPS-stimulated microglia via activation of AMPK. *Anais da Academia Brasileira de Ciencias* 92(4):e20200241
269. Zhao Z, Xu Z, Liu T, Huang S, Huang H, Huang X (2019) Human urinary kallidinogenase reduces lipopolysaccharide-induced neuroinflammation and oxidative stress in BV-2 cells. *Pain Res Manage* 2019:6393150
270. Hankittichai P, Lou HJ, Wikan N, Smith DR, Potikanond S, Nimalmool W (2020) Oxyresveratrol inhibits IL-1 β -induced inflammation via suppressing AKT and ERK1/2 activation in human microglia, HMC3. *Int J Mol Sci* 21(17)
271. Wang YM, Ming WZ, Liang H, Wang YJ, Zhang YH, Meng DL (2020) Isoquinolines from national herb *Corydalis tomentella* and neuroprotective effect against lipopolysaccharide-induced BV2 microglia cells. *Bioorg Chem* 95:103489
272. Meng J, Ni J, Wu Z, Jiang M, Zhu A, Qing H et al (2018) The critical role of IL-10 in the antineuroinflammatory and antioxidative effects of rheum tanguticum on activated microglia. *Oxid Med Cell Longev* 2018:1083596
273. Liu Y, Deng S, Zhang Z, Gu Y, Xia S, Bao X et al (2020) 6-Gingerol attenuates microglia-mediated neuroinflammation and ischemic brain injuries through Akt-mTOR-STAT3 signaling pathway. *Eur J Pharmacol* 883:173294
274. Gunesch S, Hoffmann M, Kiermeier C, Fischer W, Pinto AFM, Maurice T et al (2020) 7-O-esters of taxifolin with pronounced

- and overadditive effects in neuroprotection, anti-neuroinflammation, and amelioration of short-term memory impairment in vivo. *Redox Biol* 29:101378
275. Cheng CY, Barro L, Tsai ST, Feng TW, Wu XY, Chao CW, et al (2021) Epigallocatechin-3-gallate-loaded liposomes favor anti-inflammation of microglia cells and promote neuroprotection. *Int J Mol Sci* 22(6)
 276. Lazarus M, Shen H-Y, Cherasse Y, Qu W-M, Huang Z-L, Bass CE et al (2011) Arousal effect of caffeine depends on adenosine A_{2A} receptors in the shell of the nucleus accumbens. *J Neurosci* 31(27):10067
 277. Garrido-Mesa N, Zarzuelo A, Gálvez J (2013) Minocycline: far beyond an antibiotic. *Br J Pharmacol* 169(2):337–352
 278. Chen Y, Lian P, Peng Z, Wazir J, Ma C, Wei L et al (2022) Alpha-7 nicotinic acetylcholine receptor agonist alleviates psoriasis-like inflammation through inhibition of the STAT3 and NF-κB signaling pathway. *Cell Death Discov* 8(1):141
 279. VanderPluym JH, Halker Singh RB, Urtecho M, Morrow AS, Nayfeh T, Torres Roldan VD et al (2021) Acute treatments for episodic migraine in adults: a systematic review and meta-analysis. *JAMA* 325(23):2357–2369
 280. Nijs J, Tumkaya Yilmaz S, Elma Ö, Tatta J, Mullie P, Vanderweeën L et al (2020) Nutritional intervention in chronic pain: an innovative way of targeting central nervous system sensitization? *Expert Opin Ther Targets* 24(8):793–803
 281. Teschemacher H (2003) Opioid receptor ligands derived from food proteins. *Curr Pharm Des* 9(16):1331–1344
 282. Hadjivassiliou M, Gibson A, Davies-Jones GA, Lobo AJ, Stephenson TJ, Milford-Ward A (1996) Does cryptic gluten sensitivity play a part in neurological illness? *Lancet* (London, England) 347(8998):369–371
 283. Johnson B, Freitag FG (2022) New approaches to shifting the migraine treatment paradigm. *Front Pain Res (Lausanne, Switzerland)* 3:873179
 284. Ashina M, Terwindt GM, Al-Karaghali MA, de Boer I, Lee MJ, Hay DL et al (2021) Migraine: disease characterisation, biomarkers, and precision medicine. *Lancet* (London, England) 397(10283):1496–1504
 285. Ashina M, Hansen JM, Do TP, Melo-Carrillo A, Burstein R, Moskowitz MA (2019) Migraine and the trigeminovascular system-40 years and counting. *Lancet Neurol* 18(8):795–804
 286. Su M, Yu S (2018) Chronic migraine: a process of dysmodulation and sensitization. *Mol Pain* 14:1744806918767697

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