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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

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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

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-Kb	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	α7 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
GFRα3	Growth family receptor α3
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-etiologic 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-1β (IL-1β) 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-glial 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 CKIδ 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-1β production in glia. IL-1β 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

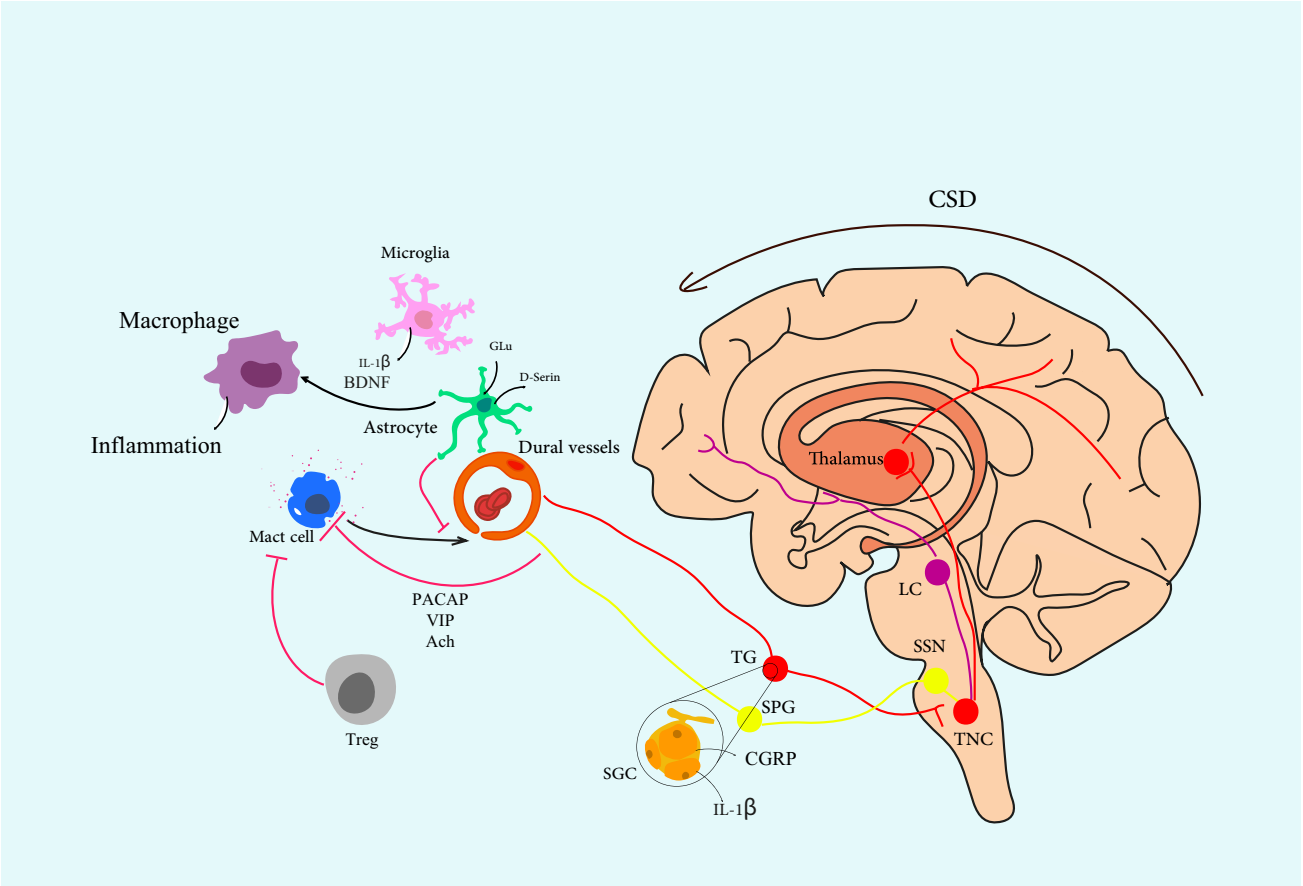

Fig. 1 Summary of glia involvement in migraine. The central and peripheral nervous systems interact with each other during migraine pathophysiology. In neurogenic inflammation, CSD stimulates peripheral nerves to release substance P and CGRP from TG, leading to further vascular leakage and mast cell degranulation. Neuroglial signaling at peripheral sites induces inflammation and nociception, which start an inflammation-allodynia positive loop in TG. Moreover, glial-glial 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-1β, interleukin-1β; 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].

Glial 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 (BNDF) 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-1β, 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-1β, 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-Kb) 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-1β, 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 17β-estradiol and patients with menstrual migraine. 17β-estradiol decreased CGRP, IL-1β, 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 Ca^{2+} 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-1β, 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^+, Ca^{2+}, 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 (GABAA) 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-1β [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-1α 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-1β 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-1β 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-κB 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-1β 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 astrocytosis increased in the inflammatory soup-induced models of migraine [124, 125].

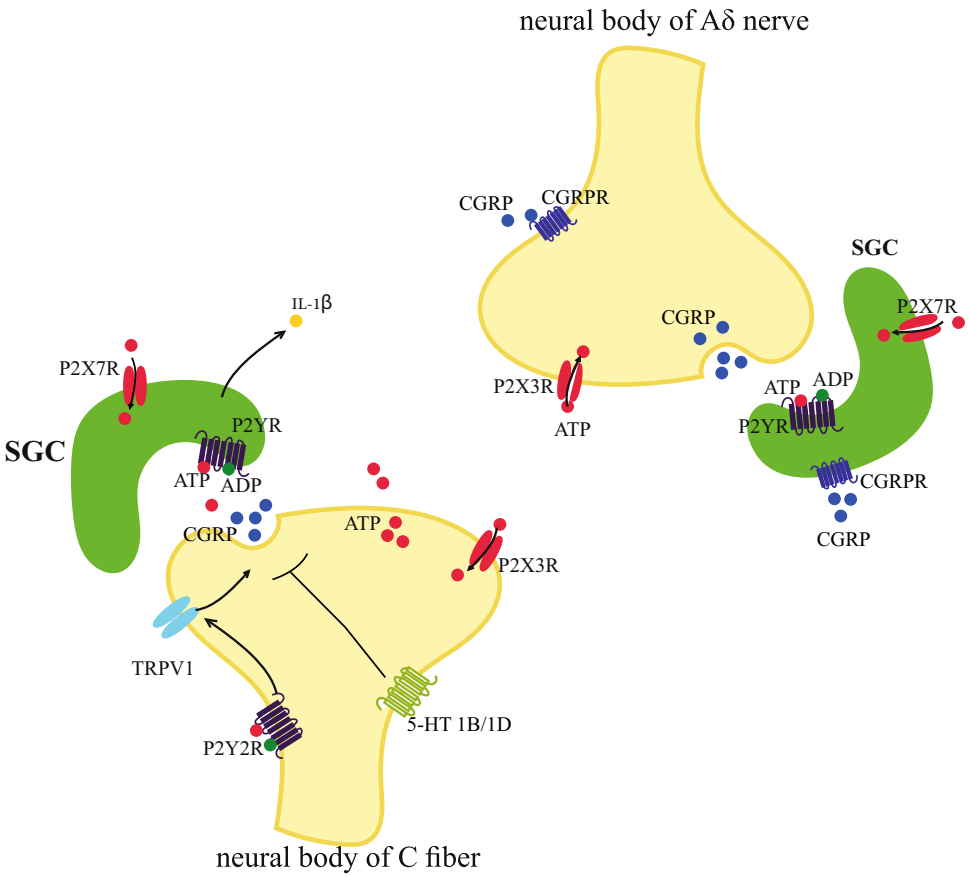

Fig. 2 The role of SGC in neuron-glia interaction at periphery sites in migraine. Extracellular ATP in TG activates SGC mainly via P2Y1, P2Y2, and P2Y4 receptors, principally accompanied by IL-1β secretion and inflammatory status. ATP secreted from neural soma activates P2X7Rs on SGC. Neural released 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-κB pathway molecules, albeit NF-κB pathway molecules are much less expressed compared to hypoxia-induced factors; however, NF-κB 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-1β production stimulate astrocytes' NF-κB 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-1β, 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-1β 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 α7 nicotinic acetylcholine receptor α7 nAChR to decrease mitochondrial-induced oxidative stress and suppress NLRP3 inflammasome [123]. The α7 nAChR is a ligand-gated ion channel in a cholinergic anti-inflammatory pathway. Activated α7 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-1β, 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 antiglutamatergic 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. Glutaminergic 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-1β to induce the release of TNF-α, IL-1β, 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-1β 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 prostanoids 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-κB-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 α3 (GFRα3) 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.

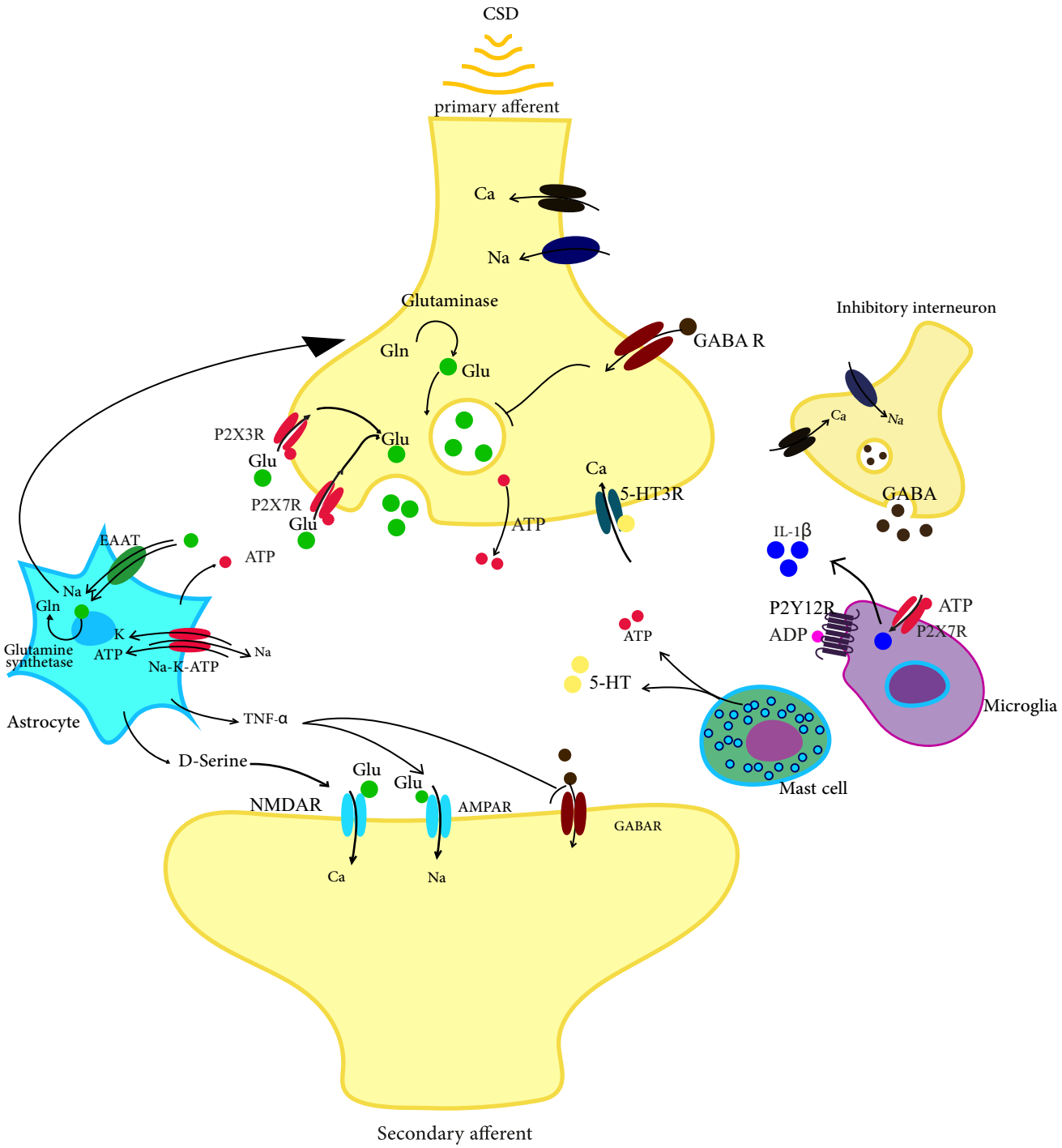

Fig. 3 Schematic diagram of synaptic neurotransmission in migraine. CSD result in more glutamatergic and presynaptic production. Astrocytes release TNF-α and ATP. ATP excites presynaptic glutamatergic activity via P2X3 and P2X7 receptors, and TNF-α increases postsynaptic AMPA receptors and decreases GABAA 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 (IL-1β) via P2X7 receptors activation. GABAR, gamma-aminobutyric acid receptor; EAAT, excitatory amino acid transporters; ATP, adenosine 5′-triphosphate; NMDAR, N-methyl-D-aspartate receptor; 5HT, 5-hydroxytryptamine; TNF-α, 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-HT1B and inhibit proinflammatory products of the trigeminal ganglion via 5-HT1D. 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 Ca^{2+} 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 Aδ 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 alternation 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 noninvasive 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-1β 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 noninvasive 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	*Jatropha curcas* 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-medicated 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-1β 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 Angelica Gigas 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-κB signaling, decreased IL-1β and TNF-α expression, activated astrocyte and microglial, and increased CGRP release in dorsal root ganglion	[251]
	6-Gingerol, *Zingiber officinale* 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-κB 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' BNDF 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-κB, 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]
	Ailanthus altissima, an East Asian medicine	Reduction in astrocytes' iNOS, COX-2, NF-κB, ERK, and JNK expression of the neurodegenerative process	[261]
	Pectolinarigenin, a flavonoid compound	Astrocytes' inhibition of IL-1β, IL-6, fibrillary acidic protein overexpression, NF-κB, 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]
	α1-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-κB signaling	[266]
	Fibroblast growth factor 21 (FGF21)	Attenuation of NF-κB 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-1β 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-κB signaling	[269]
	Oxyresveratrol, a phytochemical compound	Microglial IL-1β attenuation through suppressed PI3K/AKT and ERK1/2 MAPK signaling	[270]
	Isoquinolines	Neuroprotection against microglial activation in Alzheimer's disease and anti-inflammation	[271]
	Rheum tanguticum, 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-1β, 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 α7 nAChR agonists	Cholinergic anti-inflammation and inhibition in NF-κB 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-1β*, interleukin-1β; *HT1A*, 5-hydroxytryptamine 1A receptor; *BBB*, blood-brain barrier; *CNTF*, ciliary neurotrophic factor; *NF-κB*, nuclear factor-κB; *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; *α7 nAChR*, α7 nicotinic acetylcholine receptor

leading to central sensitization through polyamines products (from clonal fermentation) [280]. Evidence shows that alkaloid and opioid-like food derivates, 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.

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Declarations

Ethics Approval and Consent to Participate Not applicable.

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