Glial Fibrillary Acidic Protein: A Potential Therapeutic Target for Migraine

Lina Liao[1, 2, †], Siyue Luo[1, 3, †], Ziquan Zeng[1], Yi Luo[1, 4], Fangju Mao[1, 4, *]

[1]Department of Neurology, The First Affiliated Hospital of Yangtze University, Jingzhou 434000, China
[2]Department of Neurology, The People's Hospital of Chi Bi, Xianning 437300, China
[3]The Politics and Public Administration College of Shanxi University, Taiyuan 030032, China
[4]Department of Stroke Center, The First Affiliated Hospital of Yangtze University, Jingzhou 434000, China

Abstract: Glial fibrillary acidic protein (GFAP), a pivotal intermediate filament protein predominantly expressed in astrocytes, serves as a core structural and functional regulator in the central nervous system, and is deeply implicated in the pathological cascades underlying a wide spectrum of neurological disorders, ranging from neurodegenerative diseases to neuroinflammatory conditions and episodic neurological disorders. In this paper, we reviewed the current research progress on the biological function, expression regulation and involvement in the process of neuroinflammation of GFAP, and discussed the potential of GFAP as a new target for the treatment of migraine. We reviewed the epidemiological characteristics, complex pathophysiological mechanisms, and clinical burden of migraine, a highly prevalent neurovascular disorder, while underscoring the inherent limitations of current mainstream therapeutic approaches, including incomplete efficacy, frequent recurrence, and prominent adverse effects, which highlight the unmet clinical demand for novel, targeted, and mechanism-driven therapeutic strategies. Evidence from preclinical and clinical studies suggests that the regulation of GFAP may affect the key mechanisms of migraine, including glial cell activation, neuroinflammation and neuronal excitability. Although challenges associated with technical barriers in drug development remain, this review highlights the translational potential of targeting GFAP to improve patient outcomes. Future interdisciplinary research and collaborative efforts are crucial for the introduction of GFAP based therapy into clinical practice.

Keywords: GFAP; Glial Cells; Migraine; Neuroinflammation; Therapeutic Target

DOI: 10.57237/j.wjcm.2026.01.001

1 Introduction

GFAP is a type III intermediate filament protein, which is mainly expressed in astrocytes of central nervous system (CNS). It plays an important role in maintaining cell structural integrity, supporting synaptic plasticity and regulating the function of blood-brain barrier (BBB) [1, 2]. As a typical marker of astrocyte activation, GFAP is dynamically up-regulated in the process of neuroinflammatory stimulation, mechanical injury and neurodegeneration, making it a key factor to evaluate glial reactivity in various neuropathologies [2]. In traumatic brain injury (TBI), multiple sclerosis (MS), Alzheimer's disease (AD) and neuromyelitis optica spectrum disorder (NMOSD), the levels of GFAP in cerebrospinal fluid (CSF) and serum increased, reflecting the degree of astrocyte injury, and serving as a quantifiable biomarker of disease severity and progression [3-7]. Autoimmune GFAP astrocytopathy is a disease characterized by

*Corresponding author: Fangju Mao, 304776801@qq.com

†These authors contributed equally to this work.

Received: 6 January 2026; Accepted: 3 February 2026; Published Online: 6 February 2026 http://www.wjclinmed.com

inflammatory CNS disorder. The presence of GFAP autoantibodies in CSF is a pathological manifestation, often accompanied by typical MRI imaging findings, including periventricular linear enhancement and longitudinal extensive lesions in the spinal cord. It is emphasized that astrocytes are directly involved in immune-mediated nerve injury. [8]. The imbalance of GFAP expression is not only a bystander effect, but also actively involved in astrocyte morphological changes, impaired glutamate clearance, ion homeostasis disorders and abnormal neurovascular coupling processes, which are increasingly related to the pathogenesis of migraine. Cortical diffusion inhibition (CSD) is an electrophysiological phenomenon of migraine aura, which can cause deep depolarization of neurons and glial cells, trigger calcium wave and potassium outflow, activate astrocyte signal cascade, and may lead to sustained GFAP overexpression [9, 10]. In addition, the activated astrocytes release pro-inflammatory mediators, such as interleukin-1 β (IL-1 β), tumor necrosis factor-α (TNF-α) and nitric oxide (NO), which sensitize the trigeminal neurovascular afferent and promote the central sensitization, thus promoting the transformation from paroxysmal migraine to chronic migraine [11]. Preclinical evidences show that the high reactivity of astrocytes precedes and regulates the pain pathway of migraine [12, 13]. In view of the strategic position of astrocytes in integrating neurons, blood vessels and immune signals in the trigeminal nociceptive network, GFAP is not only a potential biomarker of glial activation in migraine, but also a promising molecular node for the treatment of migraine.

2 GFAP

2.1 Definition and Function of GFAP

GFAP is encoded by the GFAP gene located on chromosome 17q21. This structural protein plays a critical role in maintaining the morphological integrity and functional stability of astrocytes. The gene produces multiple isoforms through alternative splicing, including GFAP-α, β, δ, and ζ, which play different regulatory roles in cell dynamics. Among the most abundant isoforms, GFAP-α, the head domain is followed by a rod domain composed of four coiled-coil structures (1A, 1B, 2A, 2B), which are surrounded by three connecting regions (1, 1.2, and 2) (Figure 1). [14]. Although GFAP is mainly located in the cytoskeleton of astrocytes. Its expression has also been detected in non-CNS cell types (such as Schwann cells, intestinal glia, fibroblasts and chondrocytes), indicating a broader physiological correlation outside the CNS [2].

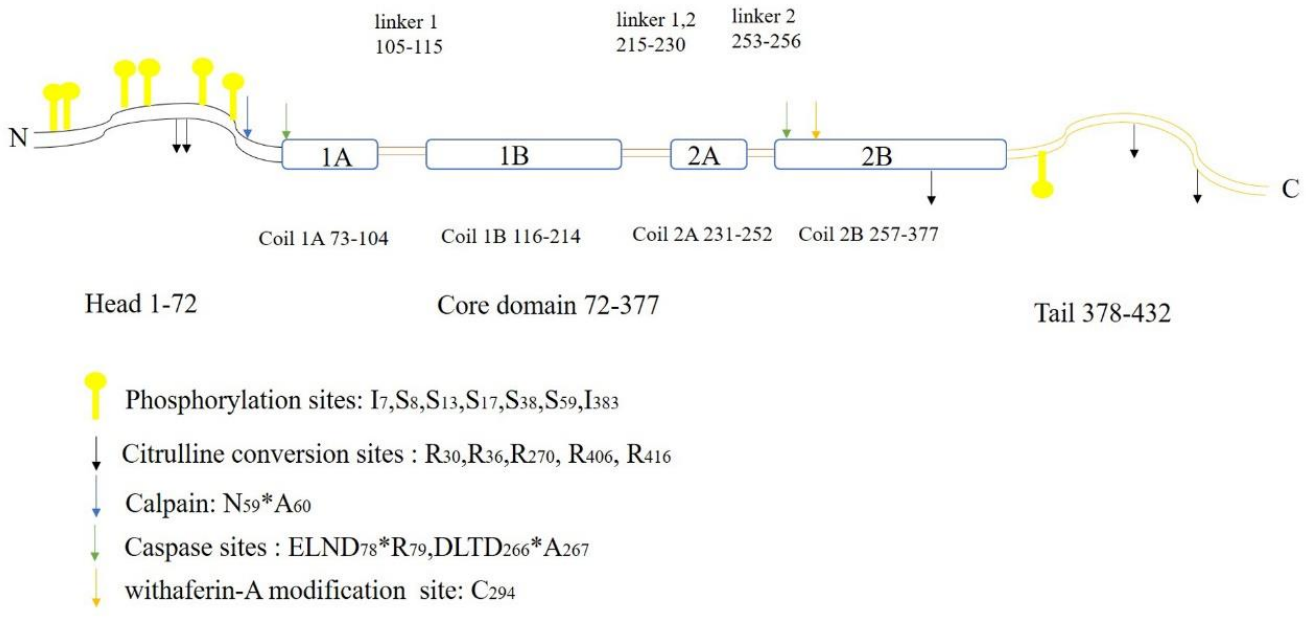

Figure 1 Linear structure, functional domains and key modifications of Glial fibrillary Acidic Protein (GFAP)

The primary biological function of GFAP is to form a robust intermediate filament network, which imparts mechanical strength to astrocytes, enabling them to withstand biomechanical stress and maintain the structural stability of the neural parenchyma. This cytoskeleton scaffold is crucial for the extension and anchoring of astrocytes to blood

vessels, thereby supporting the integrity of the BBB through direct interaction with endothelial cells and pericytes [1, 2]. In Alexander's disease caused by dominant negative mutation of GFAP gene, GFAP filament breakage leads to severe astrocytosis, which is characterized by Rosenthal fiber aggregation, progressive white matter degeneration and neurological deficits [15].

In addition to structural support, astrocytes expressing GFAP actively participate in synaptic regulation and neurotransmitter homeostasis. They regulate extracellular glutamate levels through excitatory amino acid transporter (EAAT), preventing excitotoxicity and maintaining neuronal excitability within optimal ranges [16, 17]. GFAP dynamics are closely related to synaptic plasticity. Reactive astrocyte proliferation, marked by up regulation of GFAP expression, regulates synaptic development and dendritic spine remodeling in response to injury or neuroinflammatory stimuli [18]. In addition, GFAP is a key biomarker under various neuropathological conditions. Elevated CSF and serum levels of GFAP are closely related to astrocyte activation in TBI, MS and neurodegenerative diseases such as AD [4, 7, 15, 19]. Our previous study reported GFAP antibody -positive in CSF was found in a patient with idiopathic intracranial hypertension [20]. Autoantibodies targeting GFAP define a unique clinical entity, autoimmune GFAP astrocytosis with meningoencephalitis as the manifestation and responsive to immunotherapy, emphasizing its important role in neuroimmune regulation [8, 21].

2.2 Expression and Regulation of GFAP

The expression of GFAP is dynamically regulated during development, with lower levels in neural progenitor cells and significantly upregulated simultaneously with astrocyte differentiation [14].

The transcriptional regulation of GFAP is controlled by complex interactions between signaling pathways and epigenetic modifications. The proximal promoter region of the GFAP gene contains key response elements for nuclear factor κB (NF-κB), activator protein 1 (AP-1), and signal transducer and transcriptional activator 3 (STAT3), allowing for responses to pro-inflammatory cytokines such as IL-6 and TNF-α. The activation of downstream JNK/c-Jun cascade induced by injury-induced calcium influx promotes AP-1 binding to the GFAP promoter, thereby driving reactive astrocyte proliferation. In epigenetics, histone acetylation and DNA demethylation of CpG islands within the promoter region promote chromatin accessibility and enhance transcriptional activity under pathological conditions. After transcription, alternative splicing produces multiple subtypes of GFAP—among which GFAP-α is the most abundant, and each subtype exhibits different assembly characteristics and cellular localization. MicroRNAs, including miR-125b and miR-146a, it can fine tune the expression of GFAP by targeting 3' untranslated region of GFAP, thus regulating the reactivity of astrocytes in neuroinflammation and neurodegenerative diseases [2, 14, 22]. The dysregulation of these control mechanisms is associated with diseases such as Alexander disease, autoimmune GFAP astrocytopathy, and glioma progression, highlighting the importance of precise GFAP homeostasis in health and disease [15].

2.3 Role of GFAP in Neurological Disorders

In pathological context, upregulation of GFAP is a hallmark of reactive astrocyte proliferation, which is a conservative response to nerve damage or disease progression. In AD, elevated GFAP expression is consistently observed in brain regions affected by amyloid-beta (Aβ) plaque deposition, particularly in the hippocampus and neocortex. This increase is associated with the severity of neuropathological changes and cognitive decline, indicating that GFAP may become an early biomarker for neurodegenerative processes [7, 23, 24]. The astrocytes surrounding the Aβ plaque exhibit enlarged morphology and enhanced GFAP immunoreactivity, indicating their active involvement in the formation of glial scars. These scars may initially limit the expansion of the plaque, but ultimately lead to synaptic dysfunction through chronic neuroinflammatory signaling [23-25]. In addition, new evidence links GFAP positive astrocyte activation to tau pathology, where these cells interact with microglia to regulate tau phosphorylation and proliferation, further suggesting their involvement in the cascade of neuronal degeneration [24, 26].

In MS, GFAP dynamically reflects the stages of disease destruction and repair. During acute inflammation, due to the responsiveness of astrocytes to cytokine influx and BBB disruption, strong overexpression of GFAP appears at the edge of the lesion [27]. These reactive astrocytes secrete pro-inflammatory mediators such as IL-6 and chemokines, amplifying leukocyte infiltration and exacerbating demyelination [28]. On the contrary, in the later stages of pathological evolution, astrocytes expressing GFAP con-

tribute to extracellular matrix remodeling and secrete neurotrophic factors such as brain-derived neurotrophic factor (BDNF), supporting myelin regeneration and axonal stability [29]. However, persistent gliosis can lead to the formation of dense glial scars, hindering nerve regeneration and functional recovery. It is worth noting that soluble GFAP levels in CSF and serum have been shown to be associated with clinical recurrence rates and disability scores in MS patients, which enhances their utility as alternative biomarkers of disease activity [29]. The dual nature of GFAP related astrocyte proliferation - protective and harmful - highlights the complexity of treating this pathway in different neurological disease.

3 Migraine

3.1 Epidemiology of Migraine

Migraine is one of the most common and debilitating neurological disorders worldwide, affecting approximately 14-15% of the population worldwide [30]. This situation imposes a huge burden on individuals and healthcare systems, with impacts not limited to occasional headaches, but also including severe disruptions to daily functioning and long-term quality of life. This disease exhibits significant gender differences, with women being affected almost three times more frequently than men, mainly due to hormonal fluctuations, particularly those involving estrogen during the menstrual cycle, pregnancy, and perimenopausal transition [31].

The age distribution of migraine shows that the incidence peak is between 25 and 55 years old, which is consistent with the peak of occupational and family responsibilities. 3-10% of the cases occurred in children or adolescence, sometimes manifested as atypical abdominal migraine or periodic vomiting syndrome, which delayed the correct diagnosis. Although the incidence of migraine may decline in later life, persistent or late-onset cases in the elderly present unique challenges due to complications and multi drug treatment, and need to be carefully differentiated from secondary headache [30].

Economically, migraine can cause staggering direct and indirect costs. Direct expenditures include outpatient visits, neuroimaging and drug treatment, while indirect costs are due to absenteeism and productivity decline, amounting to billions of dollars per year in the United States alone [31]. Although the function is damaged, the presentationism phenomenon that individuals are still working further magnifies the economic loss. In the social aspect, migraine can lead to the decline of quality of life, social isolation and interpersonal tension. According to the global disease burden study, migraine is the main cause of multi-year disability [30].

3.2 Pathophysiology of Migraine

Migraine is a multifaceted neurovascular disease, which is characterized by recurrent pulsatile headache, often accompanied by autonomic and neurological symptoms, such as nausea, photophobia, voice fear, and sometimes transient focal defects in the aura [32]. Potential pathophysiology involves dynamic interactions between neuronal circuits, vascular responses, and inflammatory mediators in the central and peripheral nervous systems (PNS) as shown in Figure 2. CSD starts in the occipital cortex and spreads across the cortex, triggering a series of ion translocation, glutamate release and extracellular potassium accumulation, and then activating trigeminal nerve vascular afferent [11]. This activation leads to the release of calcitonin gene-related peptide (CGRP), substance P and other vasoactive neuropeptides from meningeal sensory nerve terminals, which promotes neurogenic inflammation, dural vasodilation and trigeminal nociceptor sensitization. Central sensitization can amplify pain signals, leading to hyperalgesia and prolonged headache duration [11].

Brain stem plays an important regulatory role in the occurrence of migraine. Functional imaging studies showed that during the attack of migraine, the activities of rostral dorsal pontine, periaqueductal gray matter and locus coeruleus are enhanced [33, 34]. These regions are part of the endogenous pain control system, which may show dysfunctional regulation in migraine, leading to the reduction of trigeminal neurovascular activation threshold. Serotonergic pathway originating from brain stem also contributes to the pathogenesis of migraine; Fluctuation of 5-hydroxytryptamine (5-HT) level affects susceptibility to CSD and trigeminal nociception [11, 33, 34]. Reducing the utilization of 5-HT can enhance cortical excitability, promote the spread of CSD, and relieve the inhibition of trigeminal caudate nucleus neurons, so as to promote the transmission of pain [35]. In addition, hormonal effects, especially estrogen fluctuations, are associated with menstrual migraine, possibly by regulating synaptic plasticity, ion channel expression and CGRP transcription [35]. Genetic susceptibility further leads to susceptibility to migraine. Gene polymorphisms related to ion transport and synaptic function

increase neuronal excitability [10, 36]. Environmental triggers such as stress, sleep interruption, dietary composition and atmospheric changes focus on these inherent vulnerabilities, which trigger attacks through mechanisms such as mitochondrial dysfunction, oxidative stress and glial cell activation. In general, these processes reflect a chronic state of neural instability, which eventually leads to intermittent dysfunction of sensory processing networks [11, 32].

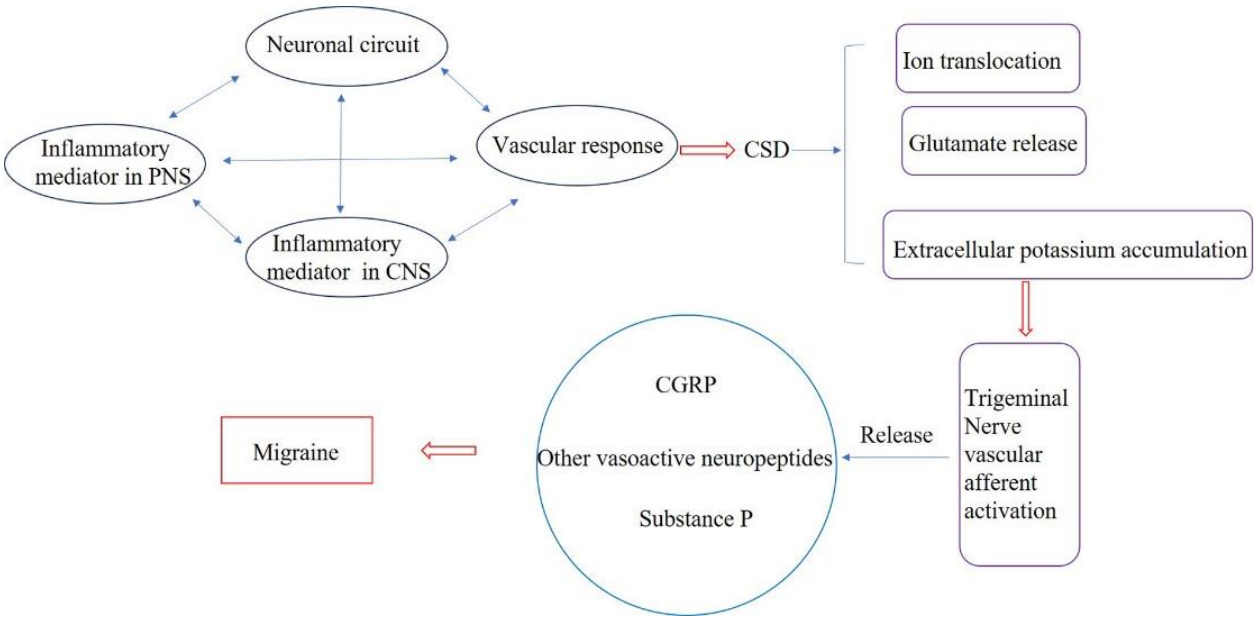

Figure 2 Potential Pathophysiology of Migraine

3.3 Current Treatment Strategies

The treatment of migraine currently relies on dual approaches including acute and preventive pharmacological strategies, each with different mechanisms and significant limitations. The purpose of acute treatment is to terminate the ongoing attack and restore function. As shown in Table 1, non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen are the first-line options because they can inhibit cyclooxygenase and reduce prostaglandin mediated pain signals [9]. However, in moderate to severe migraine attacks, the curative effect will be reduced. Long term use will make patients prone to gastrointestinal ulcer, renal insufficiency and drug overuse headache, which is a contradictory situation characterized by increased headache frequency [9]. Opioid and barbital compounds, although occasionally used, are discouraged due to the potential of high dependence, sedation, and chronic exacerbation of headache. Migraine specific drugs such as triptans play a role by selectively acting on 5-$HT_{1B/1D}$ receptors, inducing cerebral vasoconstriction and inhibiting the release of neuropeptides from trigeminal afferent nerves [9, 35]. Despite its clinical application, cardiovascular safety problems limit its application in patients with ischemic heart disease or cerebrovascular risk factors. Ergot derivatives have similar vasoactivity, but have a narrow therapeutic index and a high incidence of adverse events, including peripheral vasospasm and nausea [37]. The recently developed small molecule CGRP receptor antagonists, called gepants ((such as ubrogepant, rimegepant), provide a non-vasoconstrictive alternative to targeting the CGRP pathway. The CGRP pathway is a key mediator in the pathophysiology of migraine, but the risk of long-term hepatotoxicity and limited insurance coverage hinder its wide adoption [9, 38]. 5-HT_{1F} agonist lasmiditan can avoid vascular effects, but can induce inhibition of CNS, which limits its application in non-bedridden environment [39].

Table 1 Major agents for the treatment of acute migraine

Agent	Mechanism	Important contraindication
Ibuprofen	COX1/2 inhibitor	Gastrointestinal disorders
Naproxen	COX1/2 inhibitor	Gastrointestinal disorders
Ergotamine	Selective agonist of 5-HT_{1D} receptor	Coronary artery disease
Dihydroergotamine	Selective agonist of 5-HT_{1D} receptor	Coronary artery disease

Agent	Mechanism	Important contraindication
Rizatriptan	Non-selective agonist of 5-$HT_{1B/1D}$ receptor	Coronary artery disease
Almotriptan	Non-selective agonist of 5-$HT_{1B/1D}$ receptor	Coronary artery disease
Frovatriptan	Non-selective agonist of 5-$HT_{1B/1D}$ receptor	Coronary artery disease
Zolmitriptan	Non-selective agonist of 5-$HT_{1B/1D}$ receptor	Coronary artery disease
Naratriptan	Non-selective agonist of 5-$HT_{1B/1D}$ receptor	Coronary artery disease
Rimegepant	CGRP receptor antagonist	Hypersensitivity to the compound
Ubrogepant	CGRP receptor antagonist	Hypersensitivity to the compound
Lasmiditan	Selective agonist of 5-HT_{1F} receptors	Inhibition of central nervous system
Celecoxib	COX-2 inhibitor	Coronary artery disease

Preventive treatment is suitable for individuals who experience frequent or disabling attacks, including β-blockers, anticonvulsants, tricyclic antidepressants and monoclonal antibodies against CGRP or its receptors [9, 40]. As shown in Table 2, propranolol regulates norepinephrine tension and CSD sensitivity, but are poorly tolerated in patients with asthma or bradycardia [40]. Although topiramate is effective, it often causes cognitive retardation, paresthesia and metabolic acidosis. Sodium valproate has the risk of teratogenicity and hepatotoxicity [40]. Amitriptyline, although beneficial to the complications of tension type headache and insomnia, often leads to weight gain and anticholinergic side effects [40]. Onabotulinum toxin A reduces peripheral sensitization by inhibiting the release of vesicular neurotransmitters, which has been proved to be effective for chronic migraine, but requires repeated intramuscular injections [40]. The emergence of monoclonal antibodies targeting CGRP represent a milestone in migraine prevention, providing well tolerated mechanism. However, their high cost, burden of subcutaneous administration and uncertain long-term immunogenicity limit their availability [41]. In general, these therapies show different response rates, with up to 40% of patients classified as refractory, emphasizing the urgent need for new therapeutic targets based on glial and neuroinflammatory mechanisms [40].

Table 2 Major agents for migraine prophylaxis

Agent	Mechanism	Important contraindication
Propranolol	β-adrenoceptor antagonist	Bronchospastic lung disease and hypoglycaemia
Topiramate	Na^+ channel blocker, the excitatory glutamate pathway inhibitor, GABA activity stimulant and Ca^{2+} activity inhibitor	Metabolic acidosis, hyperammonaemia, oligohidrosis and hyperthermia
Valproic acid	GABA transaminase inhibitor	Hepatic dysfunction, hyperammonaemia and hyperthermia
Amitriptyline	Tricyclic antidepressant	Weight gain and anticholinergic side effect
Onabotulinum toxin A	CGRP release inhibitor, ACh release inhibitor	Hypersensitivity
Erenumab	CGRP receptor blocker	None

4 GFAP as a Therapeutic Target for Migraine

4.1 Evidence Supporting GFAP as a Target

Although direct studies linking GFAP with migraine are still limited, indirect evidence from neuroinflammation and glial cell activation models provides convincing reasons for its role in migraine related neurological dysfunction. In the context of migraine, new evidence shows that the activation of astrocytes reflects the change of GFAP expression in key pathophysiological processes. The pathogenesis of migraine involves a complex interaction between neuroexcitability, neuro-inflammation and glial regulation, in which CSD and trigeminal neurovascular system activation are the central mechanisms [2, 12, 17]. The upregulation of GFAP is observed in the preclinical model after CSD induction, especially in the trigeminal caudate nucleus and somatosensory cortex, indicating that reactive astrocyte proliferation is related to nociceptive sensitization and prolonged pain state in time [13, 42]. This morphological change is usually accompanied by functional changes, including excessive release of pro-inflammatory cytokines such IL-1β, TNF-α, and cyclooxygenase-2 (COX-2)-derived prostaglandins [36, 43]. In addition, elevated GFAP may reflect impaired glutamate homeostasis, leading to extracellular glutamate accumulation and subsequent N-methyl-D-aspartate receptor (NMDAR)-mediated neuronal excitability, a marker of migraine aura and central sensiti-

zation [12]. Previous studies have also shown that mitochondrial dysfunction in astrocytes may signal through cytoskeleton remodeling involving GFAP aggregation, which may damage the metabolic support to neurons, thereby reducing the threshold of CSD transmission [44]. Moreover, clinical studies on TBI and stroke have shown that serum GFAP levels are closely related to astrocyte injury and neuroinflammation [19]. It is suggested that it can be used as an alternative marker of CNS stress, which can also be observed during long-term or chronic migraine attacks. Clinical studies reported elevated levels of GFAP in serum or CSF during the acute phase of migraine, although the variability of different cohorts highlighted the need for standardized biomarker assessment [45, 46]. Although these findings do not establish a causal relationship, they positioned GFAP as a credible indicator of maladaptive glial response that may contribute to the transition from paroxysmal migraine to chronic migraine, providing a promising node for treatment intervention.

4.2 Mechanistic Insights into GFAP and Migraine

In the pathogenesis of migraine, the dysregulation of GFAP expression or post-translational modification may damage the structural stability of astrocytes, leading to abnormal function of astrocytes that contributes to neuronal hyperexcitability. Astrocytes participate in potassium buffering through Kir4.1 channel and glutamate clearance through EAATs, both of which depend on the complete GFAP cytoskeleton [12]. The destruction of this network will damage the spatial potassium buffer, leading to the accumulation of extracellular potassium ions, membrane depolarization and increased susceptibility to CSD [33]. At the same time, the reduction of glutamate uptake due to cytoskeletal instability may lead to synaptic glutamate overflow, promote NMDA receptor overactivation and excitotoxic signal cascade, thus reducing the threshold of trigeminal neurovascular activation.

Elevated GFAP levels also indicate reactive astrocyte proliferation, which is a marker of neuroinflammatory state observed in the chronic process of migraine [47]. Activated astrocytes show up regulation of GFAP expression and secretion of pro-inflammatory mediators, such as IL-6, TNF-α, and NO [2]. This neuroimmune crosstalk amplifies the peripheral and central sensitization, leading to hyperalgesia and prolonged headache. Moreover, GFAP positive astrocytes regulate purinergic and cytokine signaling pathways, affect the polarization of microglia to pro-inflammatory M1 phenotype, and further maintain the feedforward cycle of inflammation [17, 18]. The interaction between astrocyte GFAP dynamics and microglia reactivity may be the basis for the transition from paroxysmal migraine to chronic migraine.

At the neurovascular interface, GFAP supports the structural anchoring of astrocytic end-feet and cerebral vessels to ensure proper BBB integrity. The change of GFAP tissue structure can destroy aquaporin 4 polarization and tight junction protein expression in endothelial cells, and promote BBB leakage [1, 2, 17, 18]. This breakthrough allows the paracellular influx of plasma proteins and immune mediators into the perivascular space, triggering dural inflammation and activating trigeminal afferents. In addition, impaired gap junctional communication through connexin 43 in GFAP dysregulated astrocyte networks may hinder the transmission of intercellular calcium waves and disrupt the coordinated neuroregulatory response of brain regions involved in pain processing, including thalamus and cortex [48, 49]. The potential mechanism of GFAP and migraine is shown in Figure 3.

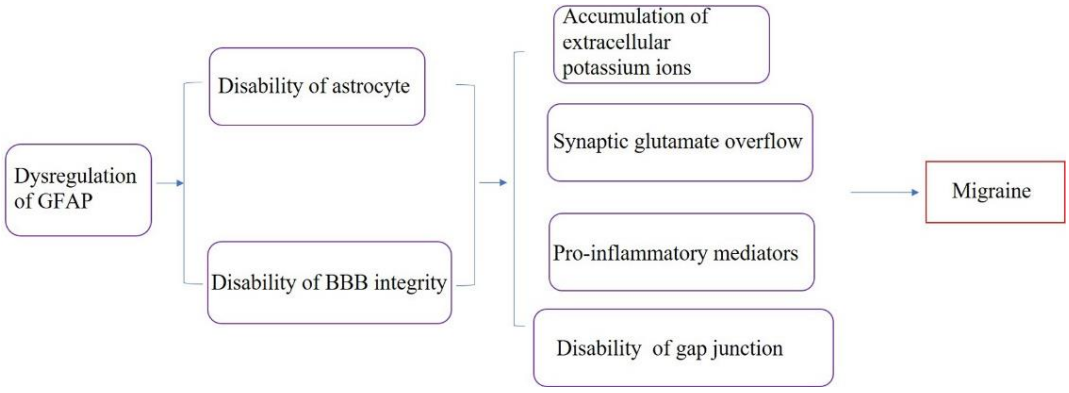

Figure 3 Potential mechanism of GFAP and migraine

4.3 Preclinical Studies on GFAP Inhibition

In the preclinical research model of migraine, the intervention of astrocyte reactive proliferation by regulating the expression or function of GFAP has shown potential therapeutic prospects. Animal experiments showed that in the nitroglycerin induced migraine model, astrocytes in the caudal trigeminal nucleus were significantly activated, while the expression of GFAP was up-regulated, and the release of pro-inflammatory cytokines such as IL-6, TNF-α and CCL2 were increased [13, 50]. Adeno associated virus mediated RNA interference driven by GFAP promoter could selectively down regulate the expression of GFAP in specific brain regions, which could effectively alleviate hyperalgesia and reduce the level of neuroinflammation [51]. It is worth noting that targeting GFAP does not directly affect neuronal excitability, but indirectly affects the sensitivity of the trigeminal neurovascular system by remodeling the glial microenvironment, stabilizing the integrity of BBB and regulating glutamate reuptake ability. Although no specific small molecule drugs targeting GFAP have been approved at present, in view of its upstream position in the neuroinflammatory cascade, the development of intervention strategies targeting GFAP polymer kinetics or its phosphorylation modification status may provide a new paradigm for non-neuronal targeted treatment of migraine. Future studies need to further verify its role in more complex neural circuits, and evaluate the potential effect of long-term inhibition of GFAP on the physiological function of astrocytes.

4.4 Potential Therapeutic Applications

The regulation of GFAP is a promising frontier in the development of new treatment strategies for migraine. Targeting GFAP provides a paradigm shift from traditional neuron centered therapies (such as triprotan and CGRP antagonists) to glial cell-oriented intervention strategies. By regulating the expression of GFAP or post-translational modification, it may reduce astrocyte driven inflammation, reduce the release of noxious mediators, and stabilize the peripheral astrocytes, which are crucial for cerebrovascular regulation. Preclinical models of CNS injury have demonstrated that inhibiting GFAP overexpression is associated with improving function and reducing inflammatory markers [5], suggesting that similar mechanism can be used for migraine. Small molecule inhibitors that selectively interfere with GFAP polymerization or its upstream regulators, such as Rho related kinase (rock) or signal transducer and activator of transcription 3 (STAT3), can precisely control the reactivity of astrocytes without damaging basic support functions. In addition, the progress of biotherapy, including monoclonal antibodies targeting abnormal GFAP fragments or autoantibodies associated with astrocytosis, can provide a template for the development of immunomodulatory methods for the subgroup of migraine patients with autoimmune characteristics.

The translational potential of GFAP targeted therapy has also been extended to precision medical applications, in which the level of GFAP in CSF or serum can be used as a biomarker to identify patients with significant glial cell involvement, so that patients can be stratified for targeted intervention. However, successful implementation requires overcoming challenges related to the long-term safety of target specificity, BBB penetration, and astrocyte regulation. Future studies must clarify the dynamic changes of GFAP during migraine attack and evaluate whether early intervention can prevent disease progression.

5 Limitations in Targeting GFAP

A pivotal area demanding further research is the development of selective GFAP-modulating agents with favorable pharmacokinetic profiles and BBB penetrance. High throughput screening platform combined with structure-based drug design can help identify small molecules or biological agents, which can normalize pathological GFAP aggregation without damaging the basic function of astrocytes. At the same time, the potential non targeted effects of synaptic plasticity, glutamate homeostasis and neurovascular coupling must be evaluated in safety assessment, because the abnormal inhibition of GFAP may destroy important neuroprotective mechanisms.

6 Conclusion

GFAP has become an important biomarker of astrocyte activation and reactivity in the context of migraine pathophysiology. More and more evidence shows that GFAP is dysregulated in the chronic neuroinflammatory cascade of migraine. Elevated GFAP levels were observed in both pre-

clinical models and clinical cohorts, suggesting that astrocyte overactivity is associated with the frequency and severity of migraine attacks. This upregulation is particularly significant during CSD. During CSD, astrocytes expressing GFAP contribute to the disturbance of potassium buffer, the destruction of glutamate homeostasis and the release of pro-inflammatory cytokines, thereby reducing the threshold of neuronal hyperactivity [18]. The dynamic expression of GFAP after trigeminal neurovascular system activation further supports its mediating role in the transition from paroxysmal migraine to chronic migraine, and positions it as a potential alternative marker of disease progression. Importantly, the experimental regulation of GFAP expression by genetic or pharmacological means has demonstrated the weakening of CSD transmission and the reduction of noxious signals in animal models [12, 13]. These findings suggest that targeting GFAP related astrocyte reactivity may disrupt the key pathway of migraine. These findings are consistent with the broader observation of nervous system diseases. In nervous system diseases, GFAP acts as a regulator of glial scar formation and synaptic remodeling, but in the case of migraine, its involvement seems more subtle, reflecting temporary functional plasticity rather than irreversible structural damage. Compared with other primary headache diseases, the specificity of elevated GFAP in migraine is still under study, although preliminary data show that serum and cerebrospinal fluid concentrations are related to attack duration and response to abortion treatment. However, the current treatment strategies are mainly focused on neuron targets such as CGRP or serotonin receptor [9], The current analysis emphasizes the necessity of expanding the target gene pool to include glial components, especially considering the limited efficacy of existing therapies in preventing central sensitization. Therefore, GFAP is not only a promising diagnostic biomarker, but also a feasible node to intervene in the pathogenesis of migraine in a complex network.

Availability of Data and Materials

No data are available.

Author Contributions

Lina liao and Siyue Luo: Writing – original draft. Ziquan Zeng: editing. Fangju Mao and Yi Luo: Writing, Review and Editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Because the study was a review article. it was allowed to be conducted by board without ethics approval or patients' consent.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Eliasson C, Sahlgren C, Berthold CH, Stakeberg J, Celis JE, Betsholtz C, et al. Intermediate filament protein partnership in astrocytes. J Biol Chem. 1999; 274: 23996-24006. https://doi.org/10.1074/jbc.274.34.23996

[2] Eng LF, Ghirnikar RS, Lee YL. Glial fibrillary acidic protein: GFAP-thirty-one years (1969-2000). Neurochem Res. 2000; 25: 1439-1451. https://doi.org/10.1023/a:1007677003387

[3] Petrou P, Kassis I, Levi Y, Yaghmour N, Epstein T, Ginzberg A, et al. Kinetics of serum NFL and GFAP and changes in cognitive functions, in MS patients treated with repeated administrations of autologous mesenchymal stem cells (MSC-NG01). J Neuroimmunol. 2025; 403: 578613. https://doi.org/10.1016/j.jneuroim.2025.578613

[4] Patel N, Agrawal N, Mishra R, Rekha MM, Nayak PP, Kaur M, et al. Emerging blood biomarkers in Alzheimer's disease: a proteomic perspective. Clin Chim Acta. 2025; 576: 120397. https://doi.org/10.1016/j.cca.2025.120397

[5] Bazarian JJ, Zetterberg H, Buki A, Dengler BA, Diaz-Arrastia R, Korley FK, et al. Blood-Based Biomarkers for Improved Characterization of Traumatic Brain Injury: Recommendations from the 2024 National Institute for Neurological Disorders and Stroke Traumatic Brain Injury Classification and Nomenclature Initiative Blood-Based Biomarkers Working Group. J Neurotrauma. 2025; 42: 1065-1085. https://doi.org/10.1089/neu.2024.0581

[6] Samadzadeh S, Sleator RD. The role of Neurofilament light (NfL) and glial fibrillary acidic protein (GFAP) in MS and AQP4-NMOSD: Advancing clinical applications. eNeurologicalSci. 2025; 38: 100550. https://doi.org/10.1016/j.ensci.2025.100550

[7] Kim KY, Shin KY, Chang KA. GFAP as a Potential Biomarker for Alzheimer's Disease: A Systematic Review and Meta-Analysis. Cells. 2023; 12: 1309. https://doi.org/10.3390/cells12091309

[8] Shan F, Long Y, Qiu W. Autoimmune Glial Fibrillary Acidic Protein Astrocytopathy: A Review of the Literature. Front Immunol. 2018; 9: 2802. https://doi.org/10.3389/fimmu.2018.02802

[9] Rushendran R, Vellapandian C. Advances in Migraine Treatment: A Comprehensive Clinical Review. Curr Protein Pept Sci. 2025; 26: 422-435. https://doi.org/10.2174/0113892037329429241123095325

[10] Gopalakrishnan R, Malan NS, Mandava N, Dunn EJ, Nero N, Burgess RC, et al. Magnetoencephalography studies in migraine and headache disorders: A systematic review. Headache. 2025; 65: 353-366. https://doi.org/10.1111/head.14867

[11] Charles A. The pathophysiology of migraine: implications for clinical management. Lancet Neurol. 2018; 17: 174-182. https://doi.org/10.1016/S1474-4422(17)30435-0

[12] Conti F, Pietrobon D. Astrocytic Glutamate Transporters and Migraine. Neurochem Res. 2023; 48: 1167-1179. https://doi.org/10.1007/s11064-022-03849-w

[13] Cropper HC, Conway CM, Wyche W, Pradhan AA. Glial activation in pain and emotional processing regions in the nitroglycerin mouse model of chronic migraine. Headache. 2024; 64: 973-982. https://doi.org/10.1111/head.14740

[14] Baba H, Nakahira K, Morita N, Tanaka F, Akita H, Ikenaka K. GFAP gene expression during development of astrocyte. Dev Neurosci. 1997; 19: 49-57. https://doi.org/10.1159/000111185

[15] Viedma-Poyatos Á, González-Jiménez P, Pajares MA, Pérez-Sala D. Alexander disease GFAP R239C mutant shows increased susceptibility to lipoxidation and elicits mitochondrial dysfunction and oxidative stress. Redox Biol. 2022; 55: 102415. https://doi.org/10.1016/j.redox.2022.102415

[16] Crivellaro G, Tottene A, Vitale M, Melone M, Casari G, Conti F, et al. Specific activation of GluN1-N2B NMDA receptors underlies facilitation of cortical spreading depression in a genetic mouse model of migraine with reduced astrocytic glutamate clearance. Neurobiol Dis. 2021; 156: 105419. https://doi.org/10.1016/j.nbd.2021.105419

[17] Finch CE. Neurons, glia, and plasticity in normal brain aging. Neurobiol Aging. 2003; 24 Suppl 1: S123-127. https://doi.org/10.1016/s0197-4580(03)00051-4

[18] Pekny M, Wilhelmsson U, Bogestål YR, Pekna M. The role of astrocytes and complement system in neural plasticity. Int Rev Neurobiol. 2007; 82: 95-111. https://doi.org/10.1016/S0074-7742(07)82005-8

[19] Ur Rehman A, Ahmed A, Ali T, Ali M, Jamil N, Malik FA, et al. Evaluating the S100β, GFAP, IL-6, and Oxidative Stress Markers in Traumatic Brain Injury. Cureus. 2025; 17: e90329. https://doi.org/10.7759/cureus.90329

[20] Luo Y, Tu Q. Cerebrospinal fluid glial fibrillary acidic protein-antibody in idiopathic intracranial hypertension: a case report. Acta Neurol Belg. 2023; 123: 1557-1559. https://doi.org/10.1007/s13760-022-02024-w

[21] Tomizawa Y, Okada H, Miyachi M, Hoshino Y, Cossu D, Kimura A, et al. Apathy in autoimmune GFAP Astrocytopathy: A case series and literature review. J Neuroimmunol. 2025; 408: 578733. https://doi.org/10.1016/j.jneuroim.2025.578733

[22] Brenner M. Structure and transcriptional regulation of the GFAP gene. Brain Pathol. 1994; 4: 245-257. https://doi.org/10.1111/j.1750-3639.1994.tb00840.x

[23] Doecke JD, Bellomo G, Vermunt L, Alcolea D, Halbgebauer S, In 't Veld S, et al. Diagnostic performance of plasma Aβ42/40 ratio, p-tau181, GFAP, and NfL along the continuum of Alzheimer's disease and non-AD dementias: An international multicenter study. Alzheimers Dement. 2025; 21: e14573. https://doi.org/10.1002/alz.14573

[24] Shir D, Graff-Radford J, Hofrenning EI, Lesnick TG, Przybelski SA, Lowe VJ, et al. Association of plasma glial fibrillary acidic protein (GFAP) with neuroimaging of Alzheimer's disease and vascular pathology. Alzheimers Dement (Amst). 2022; 14: e12291. https://doi.org/10.1002/dad2.12291

[25] Cousins KAQ, Irwin DJ, Chen-Plotkin A, Shaw LM, Arezoumandan S, Lee EB, et al. Plasma GFAP associates with secondary Alzheimer's pathology in Lewy body disease. Ann Clin Transl Neurol. 2023; 10: 802-813. https://doi.org/10.1002/acn3.51768

[26] Peretti DE, Boccalini C, Ribaldi F, Scheffler M, Marizzoni M, Ashton NJ, et al. Association of glial fibrillary acid protein, Alzheimer's disease pathology and cognitive decline. Brain. 2024; 147: 4094-4104. https://doi.org/10.1093/brain/awae211

[27] Abdelhak A, Huss A, Kassubek J, Tumani H, Otto M. Serum GFAP as a biomarker for disease severity in multiple sclerosis. Sci Rep. 2018; 8: 14798. https://doi.org/10.1038/s41598-018-33158-8

[28] Azzolini F, Gilio L, Pavone L, Iezzi E, Dolcetti E, Bruno A, et al. Neuroinflammation Is Associated with GFAP and sTREM2 Levels in Multiple Sclerosis. Biomolecules. 2022; 12: 222. https://doi.org/10.3390/biom12020222

[29] Maiworm M, Koerbel K, Anschütz V, Jakob J, Schaller-Paule MA, Schäfer JH, et al. BDNF levels in serum and CSF are associated with clinicoradiological characteristics of aggressive disease in MS patients. J Neurol. 2025; 272: 147. https://doi.org/10.1007/s00415-024-12875-3

[30] GBD 2021 Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024; 403: 2133-2161. https://doi.org/10.1016/S0140-6736(24)00757-8

[31] Burch R, Rizzoli P, Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. Headache. 2018; 58: 496-505. https://doi.org/10.1111/head.13281

[32] Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018; 38: 1-211. https://doi.org/10.1177/0333102417738202

[33] Schulte LH, Peng KP. Current understanding of premonitory networks in migraine: A window to attack generation. Cephalalgia. 2019; 39: 1720-1727. https://doi.org/10.1177/0333102419883375

[34] Ebersberger A. Pathophysiology of migraine: models to explain the generation of migraine headache. Anaesthesist. 2002; 51: 661-667. https://doi.org/10.1007/s00101-002-0342-5

[35] de Vries T, Villalón CM, MaassenVanDenBrink A. Pharmacological treatment of migraine: CGRP and 5-HT beyond the triptans. Pharmacol Ther. 2020; 211: 107528. https://doi.org/10.1016/j.pharmthera.2020.107528

[36] Subalakshmi S, Rushendran R, Vellapandian C. Revisiting Migraine Pathophysiology: from Neurons To Immune Cells Through Lens of Immune Regulatory Pathways. J Neuroimmune Pharmacol. 2025; 20: 30. https://doi.org/10.1007/s11481-025-10197-3

[37] Fahmy EM, Nada MA, El Hamid NAA, Sharaf SAE, Osama W, Elshebawy H. Migraine and ergot use increase plasma pentraxin 3 levels: an Egyptian study. Neurol Res. 2025; 47: 155-162. https://doi.org/10.1080/01616412.2025.2456708

[38] Chiang CC, Schwedt TJ. Calcitonin gene-related peptide (CGRP)-targeted therapies as preventive and acute treatments for migraine-The monoclonal antibodies and gepants. Prog Brain Res. 2020; 255: 143-170. https://doi.org/10.1016/bs.pbr.2020.06.019

[39] Shibata Y, Sato H, Sato A, Harada Y. Efficacy of Lasmiditan as a Secondary Treatment for Migraine Attacks after Unsuccessful Treatment with a Triptan. Neurol Int. 2024; 16: 643-652. https://doi.org/10.3390/neurolint16030048

[40] Burch R. Preventive Migraine Treatment. Continuum (Minneap Minn). 2021; 27: 613-632. https://doi.org/10.1212/CON.0000000000000957

[41] Rhyne C, Cohen JM, Seminerio MJ, Carr K, Krasenbaum LJ. Burden of migraine with acute medication overuse or psychiatric comorbidities and treatment with CGRP pathway-targeted monoclonal antibodies: A review. Medicine. 2023; 102: e33874. https://doi.org/10.1097/MD.0000000000033874

[42] Liu Y, Zhou MD, Zheng YQ, Sun MS, Wang ZW, Cai DJ, et al. Acupuncture relieves pain by inhibiting expression of Cx43 in astrocytes and release of interfe-ron-γ in neurons of trigeminal spinal nucleus in rats with migraine. Zhen Ci Yan Jiu. 2023; 48: 118-224. https://doi.org/10.13702/j.1000-0607.20220967

[43] Tang X, Chen H, Zhao M, Yang W, Shuang R, Xu S. α7nAChR-mediated astrocytic activation: A novel mechanism of Xiongzhi Dilong decoction in ameliorating chronic migraine. J Ethnopharmacol. 2024; 334: 118509. https://doi.org/10.1016/j.jep.2024.118509

[44] Daverey A, Agrawal SK. Curcumin alleviates oxidative stress and mitochondrial dysfunction in astrocytes. Neuroscience. 2016; 333: 92-103. https://doi.org/10.1016/j.neuroscience.2016.07.012

[45] Carta S, Chiodega V, Tiberi R, Pasquali A, Ferrari S, Bozzetti S, et al. GFAP as a marker of astrocytic damage correlated with medication overuse in migraine. Immunol Res. 2025; 73: 119. https://doi.org/10.1007/s12026-025-09674-x

[46] Gozalov E, Karlsson WK, Christensen RH, Al-Khazali HM, Hansen MB, Olsen DA, et al. Serum GFAP and NfL levels in migraine: A registry for migraine (REFORM) study. Cephalalgia. 2025; 45: 3331024251338178. https://doi.org/10.1177/03331024251338178

[47] Chiotis K, Johansson C, Rodriguez-Vieitez E, Ashton NJ, Blennow K, Zetterberg H, et al. Tracking reactive astrogliosis in autosomal dominant and sporadic Alzheimer's disease with multimodal PET and plasma GFAP. Mol Neurodegener. 2023; 18: 60. https://doi.org/10.1186/s13024-023-00647-y

[48] Fatemi SH, Folsom TD, Reutiman TJ, Pandian T, Braun NN, Haug K. Chronic psychotropic drug treatment causes differential expression of connexin 43 and GFAP in frontal cortex of rats. Schizophr Res. 2008; 104: 127-134. https://doi.org/10.1016/j.schres.2008.05.016

[49] Chekhonin VP, Baklaushev VP, Yusubalieva GM, Belorusova AE, Gulyaev MV, Tsitrin EB, et al. Targeted delivery of liposomal nanocontainers to the peritumoral zone of glioma by means of monoclonal antibodies against GFAP and the extracellular loop of Cx43. Nanomedicine. 2012; 8: 63-70. https://doi.org/10.1016/j.nano.2011.05.011

[50] Fried NT, Maxwell CR, Elliott MB, Oshinsky ML. Region-specific disruption of the blood-brain barrier following repeated inflammatory dural stimulation in a rat model of chronic trigeminal allodynia. Cephalalgia. 2018; 38: 674-689. https://doi.org/10.1177/0333102417703764

[51] Turcato F, Almeida C, Mota C, Kusuda R, Carvalho A, Nascimento GC, et al. Dynamic expression of glial fibrillary acidic protein and ionized calcium binding adaptor molecule 1 in the mouse spinal cord dorsal horn under pathological pain states. Neurol Res. 2019; 41: 633-643. https://doi.org/10.1080/01616412.2019.1603804