Molecular Biology Reports (2022) 49:1437–1452
https://doi.org/10.1007/s11033-021-06896-8

REVIEW

Pharmacological modulation of cytokines correlating neuroinflammatory cascades in epileptogenesis

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Received: 4 August 2021 / Accepted: 29 October 2021 / Published online: 9 November 2021

Abstract

Epileptic seizure-induced brain injuries include activation of neuroimmune response with activation of microglia, astrocytes cells releasing neurotoxic inflammatory mediators underlies the pathophysiology of epilepsy. A wide spectrum of neuroinflammatory pathways is involved in neurodegeneration along with elevated levels of inflammatory mediators indicating the neuroinflammation in the epileptic brain. Therefore, the neuroimmune response is commonly observed in the epileptic brain, indicating elevated cytokine levels, providing an understanding of the neuroinflammatory mechanism contributing to seizures recurrence. Clinical and experimental-based evidence suggested the elevated levels of cytokines responsible for neuronal excitation and blood–brain barrier (BBB) dysfunctioning causing the drug resistance in epilepsy. Therefore, the understanding of the pathogenesis of neuroinflammation in epilepsy, including migration of microglial cells releasing the inflammatory cytokines indicating the correlation of elevated levels of inflammatory mediators (interleukin-1beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) triggering the generation or recurrence of seizures. The current review summarized the knowledge regarding elevated inflammatory mediators as immunomodulatory response correlating multiple neuroinflammatory NF-kB, RIPK, MAPK, ERK, JNK, JAK-STAT signaling cascades in epileptogenesis. Further selective targeting of inflammatory mediators provides beneficial therapeutic strategies for epilepsy.

Keywords Epileptogenesis · Neuroinflammation · Cytokines · Neuroinflammatory cascades · Pharmacotherapy

Abbreviations

TNF α	Tumour necrosis factor alpha
ERK	Extracellular regulated kinase
JNK-c	Jun N-terminal kinase
AP-1	Activator protein-1
NF-κB	Nuclear factor kappa light chain enhancer of activated B cells
HMGB1	High mobility group box 1 protein
TRAF2	TNF Receptor Associated Factor 2
JAK-STAT	Janus kinases signal transducer and activator of transcription proteins
BBB	Blood–brain barrier
NMDA	*N*-Methyl-D-aspartic acid
BCL2	B-cell lymphoma 2
COX-2	Cyclooxygenase2
P-gp	P-glycoprotein
AEDs	Antiepileptic drugs
PGE2	Prostaglandin E2
GABA	Gamma-Aminobutyric acid
GPCR	G-protein-coupled receptors
OS	Oxidative stress
BDNF	Brain-derived neurotrophic factor
ROS	Reactive oxygen species
miRNA	MicroRNAs
IL-1	Interleukin-1
TBI	Traumatic brain injury

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Introduction

Neuroinflammation is a crucial marker of epilepsy and epileptogenesis, and it includes both non-neuronal and neuronal components (glial cells including microglia and astrocytes) [1, 2]. Prolonged epileptic seizures associated with brain injury are marked with inadequate neuronal impairment suggesting brain damage with loss of neurons focusing excitotoxicity [3, 4]. Seizures are the abnormal brain activities seen amongst various pathological conditions like traumatic brain injury; post-stroke patients are at high risk of

developing epileptic seizures with an increased incidence of neuroinflammation [5, 6]. Neuroinflammatory responses in certain conditions may contribute to neuronal hyperexcitability underlying generation of secondary seizures mediated neuronal loss like neurologic comorbidities in epilepsy [7, 8]. Additionally, a life-threatening status epileptics the prolonged excessive seizures resulting various mechanisms with increased evidence of pro-inflammatory mediators as biomarkers highlighting the activation of the neuroimmune system indicating brain damage focusing excitotoxicity [9–11] Alterations in multiple neuroinflammatory mechanisms are related to prolonged seizures induced oxidative stress or apoptosis-like events seen in epileptic patients diagnosed with morphological changes in brain-like neuronal sprouting and increasing gliosis as an indicator of brain tissue injury [3, 12]. The increased expression of cytokines acts as a biomarker in the epileptic brain represents neuroinflammation in the epileptic brain and activation of group II mGluRs like receptors (NMDA) on glial cells are responsible for carrying the toxicity by releasing of cytotoxic substances TNF-α, IL-1β, and nitric oxide towards neurons [13, 14]. Therefore, indicating the relation of elevated cytokines and excitotoxicity as an adaptive mechanism of neuroimmune processes in response to the prolonged rapid epileptic seizures. The persistent activation of neuroglial cells in response to the concurrent seizures further causes neuronal excitotoxicity leading to neuronal death [3, 15]. Therefore, the various neuroinflammatory cascades get initiated in response to the prolonged seizure-induced neuronal injury, and the increase of pro-inflammatory mediators levels represents oxidative stress in the brain [3]. This aberrant migration of astrocytes and microglial cells releases cytotoxic substances like cytokines (IL-1 beta, TNF-alpha, IL-6, etc.) like factors exacerbate the blood–brain barrier and initiates the generation of secondary seizures [16, 17]. Therefore, the dysregulation of glia immune-inflammatory activity is a common factor that predisposes or leads to the generation of seizures, and brain inflammation promotes neuronal hyperexcitability and seizures manifested by neuronal damage. Seizures induced physiological changes in the epileptic brain are characterized by activation of various neuroinflammatory cascades like NF-kB, RIPK, MAPK, ERK, JNK, JAK-STAT signaling. The aberration and alteration of such molecular cascades have been adversely associated with neuroimmune responses producing cytotoxin substances like cytokines, chemokines as biomarkers for the pathogenesis of epileptogenesis [18]. Likewise, the involvement of Interleukin-1 beta seems to activate the PI3K/mTOR/Akt signaling pathways responsible for alteration in a hippocampal brain region, causing cognitive dysfunction in temporal lobe epilepsy or status epilepticus [19]. PI3K/mTOR/Akt signaling further interacts with caspase-3, BCL2 associated X, BH3 proteins inducing aberrant apoptotic hippocampal neuronal death in epileptogenesis as observed in preclinical and clinical studies [20]. Other neuroinflammatory signaling cascades, including NF-kB, RIPK, MAPK, ERK, JNK, JAK-STAT, etc., also seem to be activated under the prolonged seizure-induced oxidative stress and elevated levels of pro-inflammatory mediators interleukin1-β (pro-IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNFα) representing neuronal damage in epilepsy [18, 21]**.** Thus, providing the correlation of neuroinflammation with hyperactivation of purinergic receptors, metabotropic receptors, inflammasome that are highly expressed on non-neuronal cells. The increased expression of such receptors modulates intracellular neuroinflammatory signaling cascades with impaired elevated levels of pro-inflammatory mediators that appear to be the decisive factor in the development and progression of hyperexcitation in epilepsy [18]. The current review summarized the correlation of inflammatory mediators initiating various downstream cascade-mediated neuroinflammation mechanisms manifested by elevated levels of IL-1β, IL-6, and tumor necrosis factor- α (TNF-α). Therefore, the drugs targeting various inflammatory mediators act as a therapeutic strategy in preventing the neuroinflammation mediated generation of seizures in epilepsy.

Cytokines mediated activation of various molecular pathways in epileptogenesis

Alteration of metabotropic receptors in epilepsy is linked with elevated levels of inflammatory mediators that seem to be enhanced in response to the seizure-induced excitotoxicity activating the neuroimmune system involving the activation of glial cells. The activation of microglial and astrocyte cells releases neurotoxic material (IL-1 beta, TNF-alpha, IL-6, HMGB1, etc.,) promoting the seizures mediated neuronal loss [22]. Metabotropic receptors are likely to be expressed in astrocytes and glial cells that get activated by the stimulus of elevated levels of inflammatory mediators responsible for producing excitotoxicity in the brain. Elevated levels of TNF- alpha released by the activated microglial cells during seizures stimulate the excitatory glutamate neurotransmitter release, thereby; increasing the hyperactivation metabotropic receptor (NMDA) mediated increased intracellular calcium concentration directing neuronal hyperexcitability [23]. Additionally, the release of inflammatory mediators (interleukin-1β (IL-1β) and high-mobility group protein-1 (HMGB1) from astrocytes and glial cell activation during rapid seizure-induced neuronal injury have an impact on the GABAergic inhibitory transmission by altering the production of GABA with a consequent increase of the NMDA transmission [23]. Whereas the cytokine HMGB1 is released by glial cells in response to the concurrent seizures induced neuronal oxidative stress further binding to TLR4

promoting the activity of postsynaptic NMDA receptor and increasing the calcium influx leading to potentiates NMDA-induced excitotoxicity [24, 25]. Increased NMDA transmission and decreased GABAergic transmission focuses the excitotoxicity by enhancing the influx of calcium ions influx mediated neuronal oxidative stress by disrupting mitochondrial functioning [26]. Therefore, the increased ROS and elevated levels of inflammatory mediators initiate the excitotoxicity in epilepsy.

Furthermore, activation of transcriptional factor NF-kB in microglial cells is the feature of elevated levels of pro-inflammatory mediators representing involvement of NF-kB in overproduction of neurotoxic substances exacerbating the development of seizures mediated neuronal cell death [27]. Elevated levels of inflammatory mediators are the biomarkers in the epileptic brain indicating the neuronal damage [28] with activation of NF-kB upregulating mediators (IL-1β, IL-6, TNF-α, and Transforming-Growth-Factor Beta (TGF-β),) and reactive oxygen and nitrogen species (ROS)) (Fig. 1) [26, 29]. Studies evidence the alterations in NF-kB activity promoting neuronal death by upregulating pro-inflammatory mediators suggesting the degeneration of hippocampal neurons recognized with cognitive dysfunction seen in temporal lobe epilepsy and status epilepticus [18]. Increased immunoreactive responses of invasive migration of glial cells to the emotive neuronal insult in epilepsy further represent the neuroinflammation marked with activated intracellular neuroinflammatory NF-kB signaling increasing expression of pro-inflammatory mediators [30]. Elevated levels of pro-inflammatory mediators like high-mobility group box-1 (HMGB1), interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, transforming growth factor (TGF-β), nitric oxide (NO) are the indicator of neuron injury carries the noxious stimuli of amplifying the inflammatory signaling. Likewise, the elevated levels of tumor necrosis factor (TNF)-α binds to TNFR1, initiating RIPK1 signaling, further initiating NF-kB and MAPK/ERK signaling mediated neuronal death under the chronic seizure-induced oxidative stress [18]. Thus, the highly inducible expression of NF-kB and MAPK/ERK is further responsible for facilitating the p38/ JNK cascades regulating activator protein 1 (AP-1) mediated apoptotic neuronal death seen under prolonged seizures induced excitotoxicity [18]. Similarly, the upregulation of IL-6 inflammatory mediator stimuli activates JAK-STAT signaling pathway mediated neuronal death in epilepsy and activation of downstream cascades (MAPK, ERK, JNK, and p38) along with PI3K (phosphatidylinositol-3-kinase). Further amplifies the downstream intracellular signaling by protein kinase B mediated neuronal apoptosis along with neuroinflammation generating oxidative stress (ROS) under chronic epileptic seizures [18, 26]. Therefore, targeting inflammatory mediators can prevent the alteration of metabotropic receptor-mediated excitotoxicity in the epileptic brain (Fig. 1).

Pharmacotherapy targeting inflammatory mediators linked neuroinflammatory signaling cascades involved in epilepsy (Table 1)

Anakinra

Anakinra, an interleukin -1 type 1 (IL-1R1), receptor antagonist seems effective as an anticonvulsant in reducing neuroinflammation in epilepsy. In the epileptic brain, the high expression of a pro-inflammatory mediator (IL-1 beta) might get implicated in response to the excessive continuous seizures mediated neuronal injury and contributing to neuronal degeneration in epilepsy [31]. Therefore, targeting Il-1 beta tends to be a successful therapy for neuroprotection in epilepsy along with further suppressing activation of intracellular NF-kB, MAPK pathway representing the structural changes in neuroimmune cells (microglial cells), the excessive migration as well activation of glial cells further contributes to epileptogenesis as a long-term effect of seizure-induced brain stress [32]. Along with the production and release of the inflammatory mediator, the elevated level of interleukin-1 beta is a rapid effect. Further, it activates PI3K linked to the hyperactivation of excitatory receptors (NMDA-R & AMPA-R), contributing to hyperexcitability resulting in neuronal death in epilepsy [32, 33]. Therefore, anti-inflammatory drugs like anakinra and VX-765, widely used in neuroinflammatory diseases, seem to be effective in epilepsy by inhibiting the IL-1R1 and suppressing the activation of such intracellular pathways, mediated neurodegeneration in epilepsy [34, 35]. In conclusion, anakinra (Kineret) and VX-765 protect excitotoxicity by overactivation of GluN2B-containing NMDA receptors and showed an antiepileptic effect [36].

COX inhibitors

Prostaglandin D2 (PGD2), PGE2, PGF2, and PGI2, as well as thromboxane A2 (TXA2), are synthesized by cyclooxygenase (COX) [37]. COX-2 is a significant pro-inflammatory mediator that is generally undetectable in tissues but is strongly activated by fever, inflammation, infection, and other conditions such as high neuronal activity and growth factors. The selective COX-2 inhibitors etoricoxib, celecoxib, and nonselective COX-2 inhibitors nimesulide, indomethacin, parecoxib (valdecoxib), aspirin, NS398, SC58236, and SC58125 have been shown antiepileptic and neuroprotective effects [38, 39]. Cyclooxygenase (COX) inhibitors are Adjuvant therapy with AED. COX-2 regulates the expression of P-gp, a multidrug transporter known to be

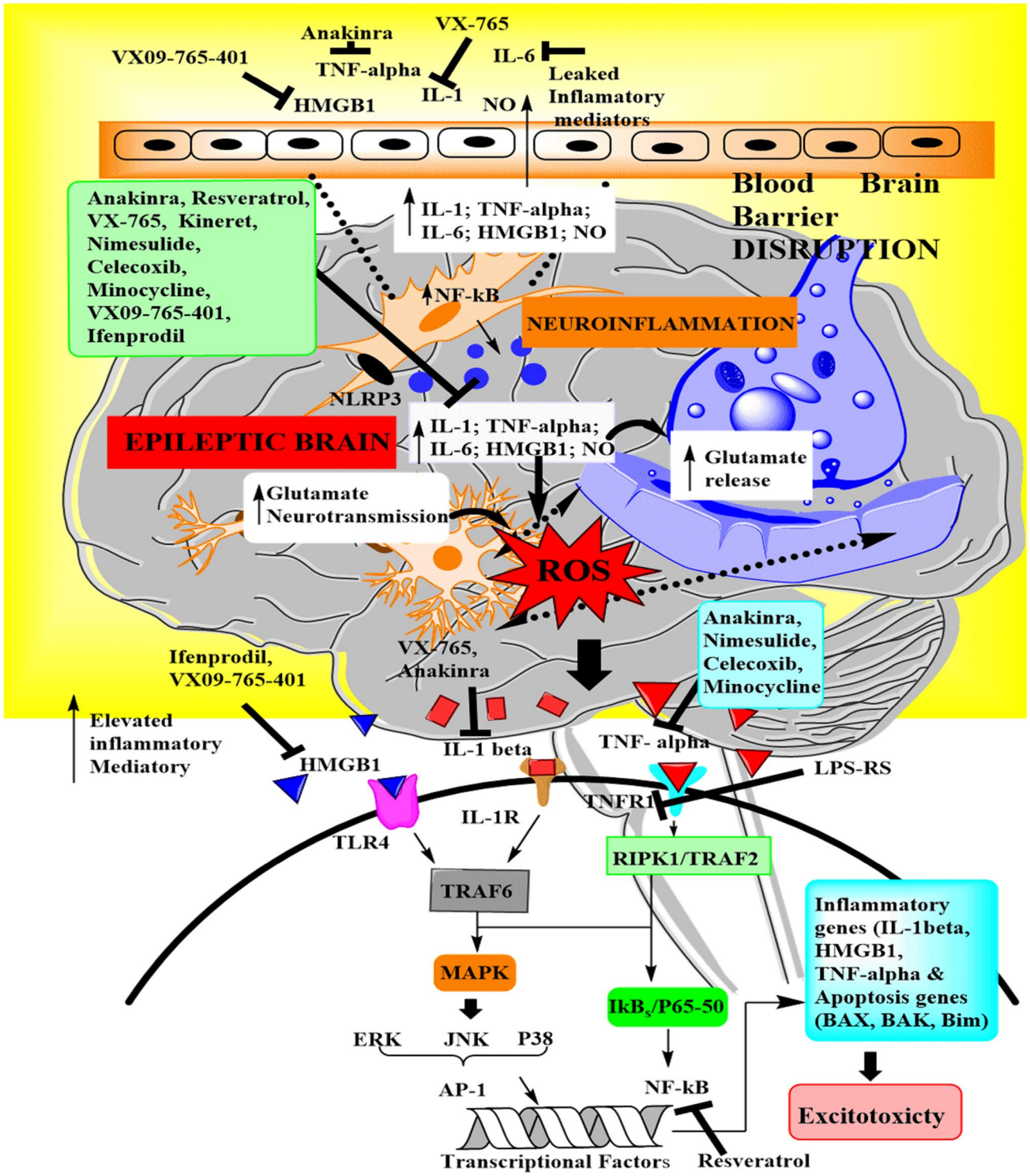

Fig. 1 Correlation of neuroimmune system and various cascades showing the neurodegeneration and excitotoxicity related to the brain damage and blood–brain barrier. Inhibitors of cytokines as a preventive approach in epilepsy

overexpressed in drug-resistant antiepileptic drugs [40]. The upregulation of COX-2 results in higher amounts of PGE2, which binds to the EP-1 receptor and activates transcription factor NF-kB increasing P-gp expression. Therefore, the increased expression of P-gp is a prominent cause of drug resistance in epilepsy. The increased levels of pro-inflammatory mediator COX-2 have a role in increasing the expression of P-gp in initiating drug resistance in epilepsy [42].

Table 1 Drugs targeting inflammatory mediators (cytokines) correlating neuroinflammatory cascades in epilepsy (Fig. 1)

S. no	Drugs	Neuroinflammatory targets of epilepsy	References
1	Anakinra	Interleukin 1β receptor antagonist	[31, 32, 34]
2	VX-765	Non-peptide inhibitor of IL-1β cleavage and release	[35]
3	Aspirin, Etoricoxib, Nimesulide, Parecoxib (valdecoxib), Indomethacin, Celecoxib, NS398, SC58125, SC58236	COX-2-nonselective and selective inhibitors	[38, 40]
4	Minocycline	Microglia and T cells inhibitor	[45, 46]
5	SC-51089, SC-51322	EP1 receptor antagonist	[56, 57]
6	SJN2511, SB431542	Selective TGF-β/ALK5 inhibitor	[64, 65]
7	Losartan	Angiotensin-II receptor antagonist	[63]
8	TG6-10-1, TG4-155	A selective antagonist of the ep2 receptor	[68, 69]
9	Resveratrol (3,5,4'-trihydroxystilbene)	NF-kB inhibitor	[70, 72]
10	LPS-Rs, Pseudo-peptide BOX A	TLR4 (Toll-like receptors-4) antagonist	[81, 82]

Therefore, the COX-2 inhibitors (celecoxib, NS398, and indomethacin heptyl ester) tend to possess therapeutic value in epilepsy by reducing drug resistance with the decrease in levels of P-gp, further suppressing the neuroinflammation by inhibiting the activation of NF-kB transcribing pro-inflammatory mediators in epilepsy [43, 44] (Table 2).

Minocycline

Minocycline is an anti-inflammatory drug that belongs to the second generation of tetracycline antibiotics. During the epilepsy attack, the inflammatory reaction also enhanced the chemokine, cytokine, and prostaglandins in the rodent's brain [45]. Therefore, anti-inflammatory drugs like minocycline could be a good alternative for reducing epileptic attacks. The Minocycline has both anti-inflammatory effects and antimicrobial properties, and it can also penetrate the BBB then affect the brain cells activity [46]. In the central nervous system, minocycline lowers both microglia activation and the release of inflammatory cytokines IL-1β, TNF-α, and IL-6, in the brain of mice. After the seizure, the IL-6 increased at the level of mRNA and protein and cause neuroinflammation [47]. The excessive released neuroinflammation cytokine can cause seizures by having cytotoxic effects on neurons. The minocycline is effective in decreasing the mRNA level of IL-1β and TLR2 and also the inflammatory gene such as MHCII (major histocompatibility complex class II), IL-6, IL-1β, and TLR2 had their mRNA expression reduced by minocycline [48]. That drug is effective and has shown a protective effect in neuroinflammation and reducing the seizure threshold by inhibiting the release of cytokine and inhibiting the effects on the surface of the cell [49].

SC-51089, SC-51322

SC-51089, SC-51322 is a selective prostaglandin-E2; EP1 receptor antagonist decreases cell death, brain edema and improves neurobehavioral/neuroprotective function after surgically induced brain injury [50]. The EP1 receptor is found in a variety of organs and tissues in rodents and guinea pigs, including the kidney, lung, and stomach, as well as multiple CNS sites. EP1 expression is restricted to a few organs and tissues in higher species such as humans, including the colon, mast cells, myometrium, pulmonary veins, and skin [52]. The EP1 receptor is linked to the G protein complex, which includes the Gq/11 and G/ dimer proteins then after PGE2 binding, Gaq is released from the complex, activating phospholipase C (PLC), which hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) to inositol triphosphate (IP3) and diacyl glycerol (DAG) [53]. IP3 regulates Ca^{2+} -sensitive signalling pathways by increasing cytosolic Ca^{2+} levels by interacting to IP3 receptors in the endoplasmic reticulum (ER) that function as calcium channels; whereas DAG acts as a second messenger by activating certain isoforms of protein kinase C (PKC) [54]. The EP1 receptor showed a neurotoxicity The EP1 receptor has long been implicated in neurotoxicity occurring from NMDA receptor overactivity and Ca^{2+} dysregulation from NMDA receptor overactivity and Ca^{2+} dysregulation after epileptic seizure. In Wistar rats, centrally administered EP1 receptor antagonist SC-19220 decreased acute seizures induced by pentylenetetrazol (PTZ) [52, 55].

SJN2511 or SB431542 and losartan

TGF-β signaling was also linked to quick changes in extracellular potassium and glutamate, as well as a decreased activation threshold for neurons. SJN2511, an effective and specific TGF-β/ALK5 inhibitor, can prevent albumin-induced synaptogenesis and seizures. [38]. The ALK5 antagonists SJN2511 or SB431542 inhibit albumin-induced TGF-β, IL-6 secretion, and SMAD2/3 phosphorylation. [56]. Losartan, an angiotensin-II receptor antagonist, has been shown to efficiently block albumin-induced TGF-activation in the

Table 2 Preclinical and Clinical Profiling of drugs in epilepsy with toxicological data at different doses

S. no	Drugs	Anti-inflammatory mechanism and target	Preclinical outcome	Clinical outcome	Side effects and complications	References
1	Anakinra	Anakinra is a human recombinant interleukin-1 receptor antagonist that effectively treats febrile infection-related epilepsy syndrome (FIRES) and autoinflammatory and autoimmune diseases	Drug-resistant seizures and chronic inflammatory epilepsy are effectively decreased, and the activity of both IL-1 and IL-1 is further blocked	Effective in febrile infection-related epilepsy syndrome (FIRES), decreased grand mal seizures, autoinflammatory or autoimmune conditions	Its safety profile was confirmed after long-term administration at doses ranging from 1 to 10 mg/kg/day (maximum 200 mg/day). Our patient experienced adverse effects, including infections, transaminitis, and neutropenia	[99, 100]
2	VX-765	The VX-765 is a caspase-1 inhibitor targeting the IL-1R1/TLR4 signaling pathway via IL-1β and HMGB1 biosynthesis, and release is reduced	VX765 can counteract neurological damage after TBI by reducing pyroptosis and HMGB1/TLR4/NF-κB pathway activities	In the CNS, treatment with VX-765 (50 mg/kg) decreases chronic stress-induced depressive symptoms in mice with reduced serum and hippocampal IL-1β levels. VX-765 decreases seizure-induced IL-1β production in the hippocampus, delays SE onset, and reduces seizure duration. The results from this Phase-II trial (NCT01048255) indicate a beneficial effect from a four-week treatment with VX-765	At 50 to 200 mg/kg VX-765, the number of seizures and their total length were reduced. At dosages of 100 and 200 mg/kg, the start of the first seizure was significantly delayed, and some Adverse events also occurred, such as headache, dizziness, fatigue, and gastrointestinal disorders	[12, 38, 101]

Table 2 (continued)

S. no	Drugs	Anti-inflammatory mechanism and target	Preclinical outcome	Clinical outcome	Side effects and complications	References
3	Aspirin, Etoricoxib, Nimesulide, Parecoxib (valdecoxib), Indomethacin, Celecoxib, NS398, SC58125, SC58236	Thus the mechanisms underlying the effects of COX-2 inhibition reduce the prostaglandin levels or the modulation of cannabinoid receptor type 1 (CB1) receptors, being COX-2 at the interface between the eicosanoid and the endocannabinoid systems	Neuronal death and microglial activation during the latent period of seizures decrease spontaneous recurrent seizures. The Decrease in seizures-induced up-regulation of endothelial P-glycoprotein ↓ Oxidative stress-induced at the brain level	The selective Cox inhibitors reduce neuronal damage, recurrent seizures, and behavior abnormalities and prevent neuronal death and microglial activation in the hippocampus. Side effects-10% Increased nosebleeds and bruising 5% severe side effects like significant bleeding, an allergic rash, hematemesis, subdural hematoma. The clinical trial of inflammatory drugs (diclofenac, paracetamol 15 mg/kg, and ibuprofen 10 mg/kg at four times of day) are conducted in phase-4 (NCT00568217) for evaluating the effect on Febrile Seizure	Celecoxib (20 mg/kg i.p.) Shown to reduce the severity of PTZ-induced seizure, an 81% decrease in the duration of generalized convulsions During or after a 15-day treatment, daily administration with nimesulide (2.5 or 5 mg/kg) reduced PTZ-induced kindling Aspirin (20 mg/kg i.p.) 20 days of status epilepticus ↓ spontaneous recurrent seizures ↓ hippocampal neuronal loss, mossy fiber sprouting, and aberrant neurogenesis. Treatment with COXIBs or non-selective NSAIDs had severe side effects, such as increasing seizures, more significant neuronal death, and a higher mortality rate	[42, 100]
4	Minocycline (25 mg/kg)	In a patient with astrocytoma and drug-resistant epilepsy, minocycline is an antibiotic with a broad spectrum of animal models, including suppression of microglial activation, pro-inflammatory cytokine production, and caspase-1 expression inhibitor resulted in a significant decrease in seizure frequency	Minocycline pretreatment was effective in reducing mRNA levels of IL-1b and TLR2. Also, minocycline decreased mRNA expression of inflammatory genes, including IL-6, IL-1b, MHCII, and TLR2, reducing the production of cytokines or blocking the effects on the cell surface	Minocycline having both antimicrobial properties and anti-inflammatory effects; it can cross BBB and alter brain cells activities. Its anti-inflammatory effect might be effective on epileptic seizures, amygdala kindling-induced seizures, and also in traumatic brain damages	minocycline shown protection from clonic seizure in all doses tested (75 mg/kg, 100 mg/kg, and 150 mg/kg). minocycline (170 mg/kg) displayed toxic effects, ranging from motor impairment to respiratory failure and death	[12, 102, 103]

Table 2 (continued)

S. no	Drugs	Anti-inflammatory mechanism and target	Preclinical outcome	Clinical outcome	Side effects and complications	References
5	SC-51089, SC-51322	Blocking the EP1 receptor by the antagonist, SC-51089 and SC-51322, in the pilocarpine-induced SE rat model prevented seizure-induced P-gp upregulation. The direct inhibition of P-gp may improve seizure control; however, its pan inhibition may lead to harmful effects	EP1 receptor inhibition with SC51089 or SC51322 reduced the hippocampal damage produced by oxygen–glucose deprivation and showed neuroprotection afforded by EP1 receptor inhibition involves the PI3K/AKT survival pathway	Inhibition or genetic inactivation of EP1 receptors counteracts the Ca^{2+} dysregulation induced by NMDA receptor overactivation and induces neuroprotection	SC-51089 dose is 3–30 mg/kg, shown an antiepileptic effect, and the highest dose is 30 mg/kg. When given 60 min before stimulation, it significantly reduced seizure severity and After-discharge duration. Tolerability issues were observed, including gastrointestinal and renal consequences and an elevated risk of cardiovascular and cerebrovascular events at a higher dose of EP1 receptor antagonist	[42, 104, 105]
6	SJN2511, SB431542	Pretreatment with SB431542 or the ALK5/TGF- specific blocker SJN2511 reduces albumin-induced TGF-1 upregulation in astrocytes, preventing synaptogenesis and epilepsy	SJN2511, SB431542 shown the TGF-β pathway inhibition prevents the activation of astrocytes during epileptogenesis, leading to a reduction in spontaneous seizure activity and brain inflammation. In people with brain injuries, the TGF-B pathway could be a therapeutic target for preventing seizure development	SJN2511, SB431542 respectively, prevented the microvascular changes and the pathologic consequences of BBB dysfunction, such as excitatory synaptogenesis, in epilepsy models. These treatments also reduced the incidence of epilepsy and the number of spontaneous seizures in the animals and reduced the neuroinflammatory response	—-	[2, 106]
7	Losartan	Losartan, previously known as a peripheral TGF-signaling blocker, successfully prevents epilepsy by blocking albumin-induced brain TGF-signaling	Losartan reduced albumin-induced increase in p-Smad2/3 levels as well as astrocytic activation. As TGF-β1 was also shown to induce the activation of vascular endothelial growth factor (VEGF) signaling, losartan may also prevent angiogenesis and BBB dysfunction, both known to contribute to the epileptogenic process	Losartan prevents TGF-β signaling in the brain and the differential effects of losartan on specific cell populations within the neurovascular unit. losartan may also prevent angiogenesis and BBB dysfunction, both known to contribute to decreasing seizure severity or enhancing antiepileptic efficacy in two rodent models of epilepsy	Losartan was injected (IP, 50-100 mg/kg) to investigate the efficacy of systemic losartan treatment in preventing epilepsy. Losartan shows mild side effects like hypertension in the long term	[12, 56]

Table 2 (continued)

S. no	Drugs	Anti-inflammatory mechanism and target	Preclinical outcome	Clinical outcome	Side effects and complications	References
8	TG6-10-1 (5 mg/kg, i.p.), TG4-155 (5 mg/kg, i.p.)	ACCORDING TO PHARMACODYNAMIC INVESTIGATIONS, both TG4–155 and TG6–10-1 block the EP2 receptor by competing with PGE2 for receptor binding	The massive elevation of many primary pro-inflammatory mediators such as cytokines interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor (TNF-) generated by activated microglia was reduced by pharmacological blockade of EP2 receptor	The seizure-triggered BBB disruption was primarily prevented by post-SE treatment with EP2 antagonist TG6–10-1 in pilocarpine-treated SE mice, kainic acid-treated mice, and DFP-treated rats, assessed by measuring the albumin levels in the brain parenchyma	Following pilocarpine-induced SE, systemic injection of TG6-10-1 (5 mg/kg, i.p.), TG4-155 (5 mg/kg, i.p.) enhanced short-term (1-week) survival from 60 to 90%, and long-term (2-month) survival from 48% to 83 percent in mice. Long-term high dose usage of selective EP2 receptor inhibitors has been shown to have adverse cardiovascular and cerebrovascular consequences	[64, 68, 107]
9	Resveratrol (3,5,4′-trihydroxystilbene)	The ability of resveratrol to pass the blood–brain barrier and have neuroprotective effects is due to its ability to influence redox pathways and the Sirtuin (SIRT) system, which modifies gene transcription and controls inflammation and apoptosis in the brain	Phosphorylation of MAPKs and activation of AMPK by resveratrol in neurons likely helps maintain cognitive functions and provides neuroprotection, including the temporal lobe epilepsy	Resveratrol treatment reduced ethanol-induced neuronal cell death, sodium nitroprusside induced hippocampal cell death, and intracellular ROS accumulation, and resveratrol pretreatment provided neuroprotection via its antioxidant actions	Resveratrol administration (i.p. 20 and 120 mg/kg) delayed the onset of epileptiform EEG abnormalities. Furthermore, therapy reduced brain MDA, a hallmark of OS; however, glutathione levels were not significantly different. Resveratrol, which is present in the skin of red grapes, can mediate a wide range of biological processes while having no negative side effects	[108, 109]
10	LPS-Rs, Pseudo-peptide BOX A	Initial and persistent seizures are reduced when the pseudo-peptide BOX A or LPS-RS—a deactivated LPS from the photosynthetic bacterium Rhodobacter sphaeroides—blocks HMGB1/TLR4 signaling	–	–	–	[38]

brain and prevent spontaneous seizures [56]. In epilepsy, the specific inflammatory pathway involvement determined the epileptogenic role of transforming growth factor-beta-β (TGF-β) signaling in BBB dysfunction. The BBB disruption has been associated with serum components like albumin and IgGs in a wide variety of cell types [57]. Neurons, astrocytes, and microglia all take up albumin, although to a lesser extent. In contrast, IgG uptake has been found in neurons. TGF-βRs (transforming growth factor-β receptors) promote albumin endocytosis in endothelial cells, resulting in phosphorylation of Smad2, the proximate effector of the canonical TGF-β signaling pathway, and translocation of the activated Smad2/Smad4 complex to the nucleus, thereby modifying astrocytic function. [58]. TGF-β signaling was also linked to quick changes in extracellular potassium and glutamate, as well as a decreased activation threshold for neurons [59, 60]. Specifically, astrocytes were shown to regulate synaptogenesis through the molecule antagonist for angiotensin II receptor type 1 (AT_1) that has been reported to block the peripheral TGF-β signaling, can effectively suppress albumin-induced TGF-β activation in the brain and prevent the subsequent spontaneous seizures. These results reinforce the notion that targeting TGF-β signaling is a feasible strategy for disease modification and prevention of epilepsy [63].

TG4-155 and TG6-10-1

The selective antagonist of the EP2 receptor (TG4-155 and TG6-10-1) is a subtype of prostaglandin E2. The COX pathway mediates many physiological and pathological activities by its prostanoid products [64, 65]. In response to seizure, the arachidonic acid is released and converts into PGH2 in presence of COX, the COX-1 (constitutive) and COX-2 (inducible) are the two types of COX then after the PGH_2 is quickly converted to five different types of prostanoids such as PGD_2, $PGF_{2\alpha}$, PGE_2, thromboxane TXA_2, and prostacyclin PGI_2 by prostanoid synthases that are tissue-specific [66, 67]. PGE_2 stimulates the action of the GPCR receptor and four E-type prostanoid receptors EP1, EP2, EP3, and EP4. PGE2 and its receptors play a major role in inflammatory prostaglandin signaling activation causing neuroinflammation in epilepsy. Therefore, the TG4-155 and TG6-10-1 antagonist of EP2 receptor possess a neuroprotective effect in epilepsy [68].

Resveratrol (3,5,4′-trihydroxystilbene)

The Antioxidant compounds have been considered a successful therapeutic approach in various neurological diseases [69]. The antioxidant compound resveratrol has shown an antiepileptic effect by decreasing oxidative stress and regulating Sirtuin (SIRT) mechanism; the sirtuin protein regulates mitochondrial dysfunction-related apoptotic pathway [70]. The mitochondrial dysfunction in epilepsy also plays a significant factor in epileptogenesis by increasing the production of reactive oxygen species with long-term elevated pro-inflammatory mediators, further initiating the neuronal apoptotic death [71–73]. Therefore, resveratrol possesses anticonvulsant activity by preventing mitochondrial oxidative stress in epilepsy [74–76]. Furthermore, resveratrol also restores peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha and regulates oxidative stress and mitochondrial dysfunction [77, 78]. Resveratrol also increases the expression of antioxidant Nrf2 protein and erythroid 2-related factor 2, decreasing the reactive oxygen species and preventing neuroinflammation in epilepsy [79–81]. Resveratrol efficiently prevents chronic seizures induced oxidative stress and suppresses neuroinflammation by preventing NF-kB activation that promotes the production of inflammatory molecules such as iNOS, COX-2, and IL-1ß [82–84]. Also, the stimulation of AMP-activated kinase (AMPK) by resveratrol further inhibited the NF-kB activation and the production of pro-inflammatory molecules that initiates hyperexcitability in epilepsy [85, 86].

LPS-Rs, pseudo-peptide BOX A

In LPS-induced neuroinflammation, LPS-Rs, a TLR4 (Toll-like receptors-4) antagonist, suppress inflammatory mediators levels such as IL-6, TNF-α, COX-2, IL-1, iNOS, and NO in a substantial way in tissue. LPS-Rs modulates levels of various signaling pathways like MAPKs, JNK/p38, and p65-NF-kB in neuronal tissue [90]. The activation of the neuroimmune system represented by excessive migration of microglial cells is the progressive events of neuroinflammation mediated neurodegeneration in epilepsy by modulating further intracellular inflammatory pathways exacerbating neurotoxicity. The implication of toll-like receptors (TLRs) in microglial cells further modulating TLR dependent signaling of activation of MAPKs, JNK/p38, and p65-NF-kB cascades mediating neuroinflammation and exacerbated neurodegeneration in epilepsy [91, 92]. The various studies suggested the involvement of microglia cells infiltration of neuroimmune cells (T-cells) that acts as a marker for neuroinflammation or neuronal tissue damage in response to chronic seizure-induced brain injury. Therefore, the elevated levels of pro-inflammatory mediators (IL-1beta, IL-6, TNF-α, COX-2, iNOS, and NO) are seen to be elicited centrally propagating extracellular diffusion pathways involving the activation of NF-kB influencing neuroinflammation in epilepsy [92]. Therefore, the LPS-Rs, a lipopolysaccharide of bacterium *Rhodobacter sphaeroides*, is a potent TLR4 antagonist that has inhibited neuroinflammation and neuronal apoptotic death. TLR4, an endogenous danger signal

protein produced in the CNS by immune cells, neurons, and glia in response to cell injury or neuronal hyperexcitability, can be activated by pro-inflammatory cytokines HMGB1 [89, 91]. The elevated levels of HMGB1 in epileptic brain tissues when seizures are persistent further binds to TLR4, promoting the activity of postsynaptic NMDA receptor and increasing the calcium influx leading to potentiates NMDA-induced excitotoxicity [24, 25]. The hyperactivation of metabotropic glutamate receptors group I (NMDAR) mediates excitatory synaptic transmission in epilepsy. Thus, the TLR4 inhibitor LPS-Rs tends to be a protective strategy in reducing the HMGB1 that prevents postsynaptic NMDA receptor hyperactivation mediated excitotoxicity in epilepsy [9, 24, 92]

Clinical & future prospective

Despite the treatment approaches in epilepsy targeting inflammatory pathways have been explored in the current review suggesting the immunomodulatory treatment in epilepsy indicating inflammatory processes. Several inflammatory targets broadly discuss the consequences like cognitive dysfunction, excitotoxicity, and drug resistance from invasive neuroinflammation in epilepsy. Further in the future, the understanding of mRNAs-based gene therapy in epilepsy is a recent promising strategy in preventing the neuroinflammation-mediated neuronal dysfunction in epilepsy. The epileptic studies suggested the dysregulation of miRNA under pathological state associated with hyperexcitability. The Gene expression data (RNA-Seq) and miRNA suggested the role of miRNAs regulating inflammatory responses neuronal necrosis and apoptosis genes in epilepsy. The inflammatory mediators are the biomarkers for the brain tissue injury in epilepsy that are marked by the upregulated levels of cytotoxic substances like interleukin-1 β (IL1 β), tumor necrosis factor-α (TNF-α), and high mobility group protein (HMGB1) [95]. Further, miRNAs have a role in regulating the genes encoding for proteins controlling the functioning of neuronal and non-neuronal cells and the receptors that seem to be altered under epileptogenesis. Therefore, the microarray studies screened the alterations in miRNAs as an early phase controller for the occurrence of the disease that is responsible for the regulation for pathogenic processes of neuroinflammation destroying the blood–brain barrier and aggravated damages in the brain promoting neuronal excitability in epilepsy [95, 96] (Fig. 2). The miRNAs like miR-34c-5p have been downregulated in epileptic patients of drug resistance, indicating the disruption of the blood–brain barrier and elevated levels of inflammatory mediators (HMGB1, IL-1β) indicates the potential role of neuroinflammation in the development of epileptogenesis. Furthermore, the other upregulation of miR-27a-3p and downregulation of miR-125a5p also found to be altered in epileptic brain tissue, increasing the expression of IL-1, INF-α, and TNF-α) representing the neuroinflammation in epilepsy [95, 96]. Likewise, the miRNA 146a, 155, 221, 122, 22 is upregulated during seizures induced neuronal injury as an indicator of activation of glial cells and providing a future targeted therapy of miRNAs as master regulators of immune responses [95]. The upregulation of miRNA 155 and 122 expression indicates the increase of the neurotrophic factors (BDNF, TGF-beta) promoting glial cells dysfunctioning mediated neuroinflammation by increasing the expression of TNF-alpha mediated excitotoxicity in epilepsy [95]. Therefore, the MRG-106 or Cobomarsen, an inhibitor of miRNA 155, and SPC3649 (miravirsen) an inhibitor of miRNA 122 tend to effectively prevent inflammatory disease, which might be a future targeted therapy for neuroinflammation in epilepsy [95, 98]. The decreased miRNA 122 in epilepsy also indicates the neuroinflammation in epilepsy, as the miRNA 122 has a role in preventing pro-inflammatory cytokines by inhibiting the transcriptional factor (NF-kB) [95, 97].

Conclusion

Elevated inflammatory biomarkers are the evidence of neuroinflammation and structural changes like hippocampal cell degeneration and mossy fiber sprouting, increasing excitability in epilepsy. Neuroimmune responses of activation of glial cells give rise to overproduction of cytokines (IL-1β, IL-6, TNF-α, and reactive oxygen and nitrogen species (ROS)) as well disrupting blood–brain barrier causing drug resistance. The elevated levels of cytokines attributed to the neuronal excitability underlying neuroinflammatory pathways mechanisms causing excitotoxicity in epilepsy. Therefore, the initiators like SC-58236, NS-398, anakinra, resveratrol, etc., are effective therapies by suppressing the cytokines and preventing the neuroinflammation producing secondary seizures, including neuronal dysfunction and providing the correlation of cytokines and various cascades mediated excitotoxicity.

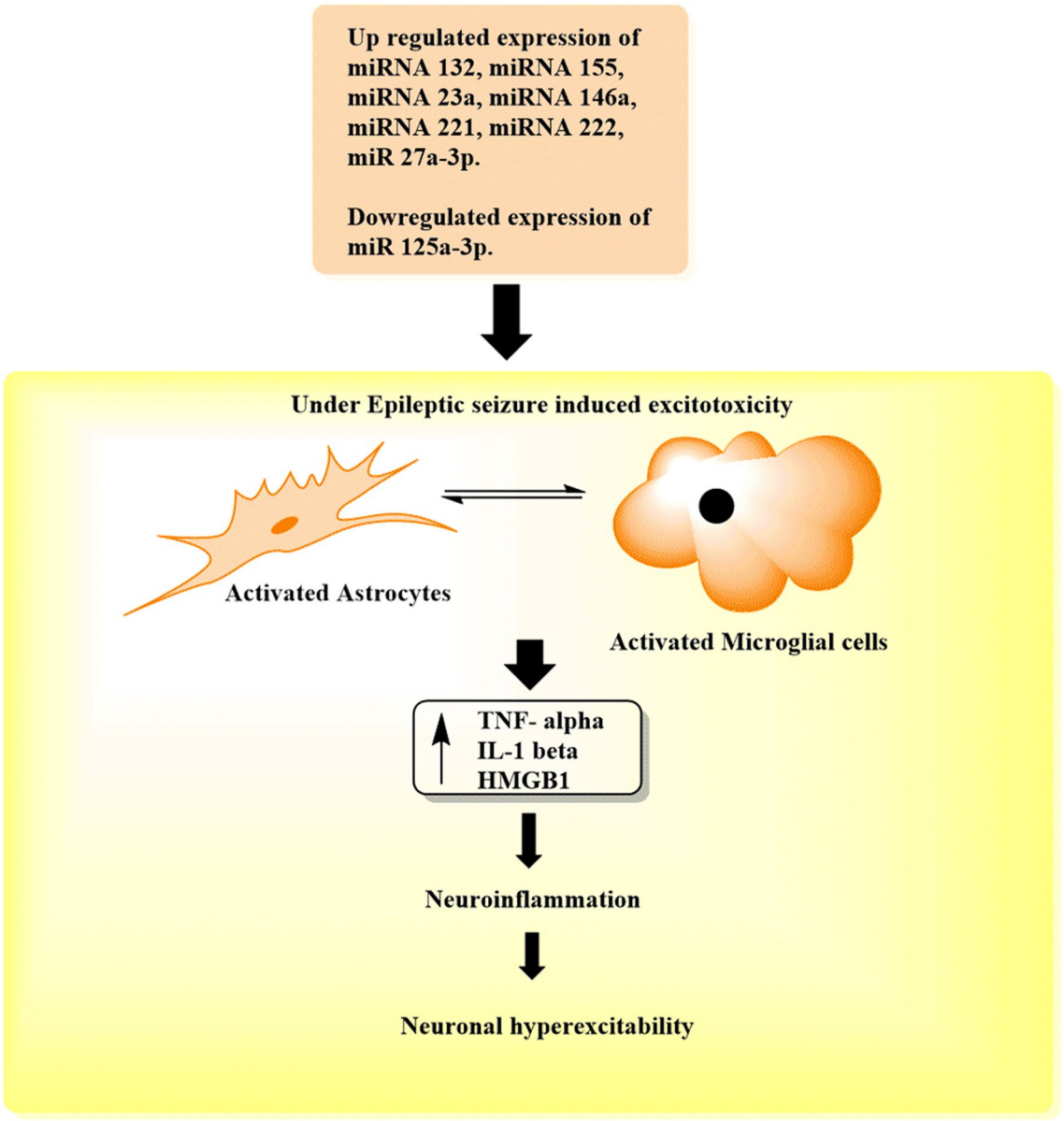

Fig. 2 Alterations in microRNAs and neuroinflammation in epilepsy. Illustration of various microRNAs as regulators of neuroinflammatory processes likely to be unregulated or down-regulated under the pathological condition of epileptogenesis

Acknowledgements The authors are grateful to the Chitkara College of Pharmacy, Chitkara University, Rajpura, Patiala, Punjab, India for providing the necessary facilities to carry out the research work.

Author contribution Conceptualization: Conceived and designed the experiments: TGS. Analyzed the data: SS, TGS Wrote the manuscript: SV, SS Editing of the Manuscript: TGS critically reviewed the article: TGS. All authors read and approved the final manuscript.

Funding Nil.

Data availability Not applicable.

Declarations

Conflict of interest There are no conflicts of interest.

Consent to participate Not applicable.

Ethical approval Not applicable.

References

1. Foresti ML, Arisi GM, Shapiro LA (2011) Role of glia in epilepsy-associated neuropathology, neuroinflammation and neurogenesis. Brain Res Rev 7(966):115–122. https://doi.org/10.1016/j.brainresrev.2010.09.002
2. Rana A, Musto AE (2018) the role of inflammation in the development of epilepsy. J Neuroinflammation 5(1):1–2. https://doi.org/10.1186/s12974-018-1192-7
3. Rehni AK, Singh TG (2013) Selenium induced anticonvulsant effect: a potential role of prostaglandin E1 receptor activation linked mechanism. J Trace Elem Med Biol 27(1):31–39. https://doi.org/10.1016/j.jtemb.2012.05.001
4. Koepp MJ, Årstad E, Bankstahl JP, Dedeurwaerdere S, Friedman A, Potschka H, Ravizza T, Theodore WH, Baram TZ (2017) Neuroinflammation imaging markers for epileptogenesis. Epilepsia 58:11–19. https://doi.org/10.1111/epi.13778
5. Webster KM, Sun M, Crack P, O'Brien TJ, Shultz SR, Semple BD (2017) Inflammation in epileptogenesis after traumatic brain injury. J Neuroinflammation 14(1):1–7. https://doi.org/10.1186/s12974-016-0786-1
6. Rehni AK, Singh TG (2011) Modulation of leukotriene D4 attenuates the development of seizures in mice. Prostaglandins Leukot Essent Fatty Acids 85(2):97–106. https://doi.org/10.1016/j.plefa.2011.04.003
7. Rana A, Musto AE (2018) The role of inflammation in the development of epilepsy. J Neuroinflammation 15(1):1–2. https://doi.org/10.1038/nrneurol.2010.178
8. Lee VL, Shaikh MF (2019) Inflammation: cause or consequence of epilepsy?. In: Epilepsy-Advances in Diagnosis and Therapy. IntechOpen.
9. Choi J, Koh S (2008) Role of brain inflammation in epileptogenesis. Yonsei Med J 49(1):1–8. https://doi.org/10.3349/ymj.2008.49.1.1
10. Vezzani A, Maroso M, Balosso S, Sanchez MA, Bartfai T (2011) IL-1 receptor/Toll-like receptor signaling in infection, inflammation, stress and neurodegeneration couples hyperexcitability and seizures. Brain Behav Immun 25(7):1281–1289. https://doi.org/10.1016/j.bbi.2011.03.018
11. Vezzani A, Balosso S, Ravizza T (2019) Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy. Nat Rev Neurol 15(8):459–472. https://doi.org/10.1038/s41582-019-0217-x
12. Ravizza T, Vezzani A (2018) Pharmacological targeting of brain inflammation in epilepsy: Therapeutic perspectives from experimental and clinical studies. Epilepsia Open 3:133–142. https://doi.org/10.1002/epi4.12242
13. Qian F, Tang FR (2016) Metabotropic glutamate receptors and interacting proteins in epileptogenesis. Curr Neuropharmacol 14(5):551–562. https://doi.org/10.2174/1570159X14666160331142228
14. Zoicas I, Kornhuber J (2019) The role of metabotropic glutamate receptors in social behavior in rodents. Int J Mol Sci 20(6):1412. https://doi.org/10.3390/ijms20061412
15. Pocock JM, Kettenmann H (2007) Neurotransmitter receptors on microglia. Trends Neurosci 30(10):527–535. https://doi.org/10.1016/j.tins.2007.07.007
16. Vezzani A (2014) Epilepsy and inflammation in the brain: overview and pathophysiology: epilepsy and inflammation in the brain. Epilepsy curr 14(2):3–7.
17. Vezzani A (2020) Brain inflammation and seizures: evolving concepts and new findings in the last 2 decades. Epilepsy Curr 20(6):40S-S43.
18. Sanz P, Garcia-Gimeno MA (2020) Reactive glia inflammatory signaling pathways and epilepsy. Int J Mol Sci 21(11):4096.
19. Han T, Qin Y, Mou C, Wang M, Jiang M, Liu B (2016) Seizure induced synaptic plasticity alteration in hippocampus is mediated by IL-1β receptor through PI3K/Akt pathway. Am J Transl Res 8(10):4499
20. Zhang H, Tao J, Zhang S, Lv X (2020) LncRNA MEG3 reduces hippocampal neuron apoptosis via the PI3K/AKT/mTOR pathway in a rat model of temporal lobe epilepsy. Neuropsychiatr Dis Treat 16:2519. https://doi.org/10.2147/NDT.S270614
21. Hixson KM, Cogswell M, Brooks-Kayal AR, Russek SJ (2019) Transcriptomic analysis of the BDNF-induced JAK/STAT pathway in neurons: a window into epilepsy-associated gene expression. BioRxiv 1:577627. https://doi.org/10.1101/577627
22. Tjalkens RB, Popichak KA, Kirkley KA (2017) Inflammatory activation of microglia and astrocytes in manganese neurotoxicity. Neurotoxicity. https://doi.org/10.1007/978-3-319-60189-2_8
23. Shimada T, Takemiya T, Sugiura H, Yamagata K (2014) Role of inflammatory mediators in the pathogenesis of epilepsy. Mediators Inflamm. https://doi.org/10.1155/2014/901902
24. Balosso S, Liu J, Bianchi ME, Vezzani A (2014) Disulfide-containing high mobility group box-1 promotes N-methyl-D-aspartate receptor function and excitotoxicity by activating Toll-like receptor 4-dependent signaling in hippocampal neurons. Antioxid Redox Signal 21(12):1726–1740. https://doi.org/10.1089/ars.2013.5349
25. Paudel YN, Shaikh M, Chakraborti A, Kumari Y, Aledo-Serrano Á, Aleksovska K, Alvim MK, Othman I (2018) HMGB1: a common biomarker and potential target for TBI, neuroinflammation, epilepsy, and cognitive dysfunction. Front Neurosci 11(12):628. https://doi.org/10.3389/fnins.2018.00628
26. Singh S, Singh TG, Rehni AK, Sharma V, Singh M, Kaur R (2021) Reviving mitochondrial bioenergetics: a relevant approach in epilepsy. Mitochondrion. https://doi.org/10.1016/j.mito.2021.03.009
27. Dresselhaus EC, Meffert MK (2019) Cellular specificity of NF-κB function in the nervous system. Front Immunol 9(10):1043. https://doi.org/10.3389/fimmu.2019.01043
28. Simani L, Sadeghi M, Ryan F, Dehghani M, Niknazar S (2020) Elevated blood-based brain biomarker levels in patients with epileptic seizures: a systematic review and meta-analysis. ACS Chem Neurosci 11(24):4048–4059. https://doi.org/10.1021/acschemneuro.0c00492
29. Singh S, Singh TG (2020) Role of nuclear factor kappa B (NF-KB) signalling in neurodegenerative diseases: an mechanistic approach. Curr Neuropharmacol 18(10):918–935. https://doi.org/10.2174/1570159X18666200207120949
30. Rehni AK, Bhateja P, Singh TG, Singh N (2008) Nuclear factor-κ-B inhibitor modulates the development of opioid dependence in a mouse model of naloxone-induced opioid withdrawal syndrome. Behav Pharmacol 19(3):265–269. https://doi.org/10.1097/FBP.0b013e3282febcd9
31. Noe FM, Polascheck N, Frigerio F, Bankstahl M, Ravizza T, Marchini S, Beltrame L, Banderó CR, Löscher W, Vezzani A (2013) Pharmacological blockade of IL-1β/IL-1 receptor type 1 axis during epileptogenesis provides neuroprotection in two rat models of temporal lobe epilepsy. Neurobiol Dis 1(59):183–193. https://doi.org/10.1016/j.nbd.2013.07.015
32. Roseti C, van Vliet EA, Cifelli P, Ruffolo G, Baayen JC, Di Castro MA, Bertollini C, Limatola C, Aronica E, Vezzani A, Palma

E (2015) GABAA currents are decreased by IL-1β in epileptogenic tissue of patients with temporal lobe epilepsy: implications for ictogenesis. Neurobiol Dis 1(82):311–320. https://doi.org/10.1016/j.nbd.2015.07.003
33. Voet S, Srinivasan S, Lamkanfi M, van Loo G (2019) Inflammasomes in neuroinflammatory and neurodegenerative diseases. EMBO Mol Med 11(6):10248. https://doi.org/10.15252/emmm.201810248
34. Wu X, Liao Z, Wang K, Hua W, Liu X, Song Y, Zhang Y, Yang S, Yang C (2019) Targeting the IL-1β/IL-1Ra pathways for the aggregation of human islet amyloid polypeptide in an ex vivo organ culture system of the intervertebral disc. Exp Mol Med 51(9):1–6. https://doi.org/10.1038/s12276-019-0310-7
35. Yan C, Gao N, Sun H, Yin J, Lee P, Zhou L, Fan X, Yu FS (2016) Targeting imbalance between IL-1β and IL-1 receptor antagonist ameliorates delayed epithelium wound healing in diabetic mouse corneas. The Am J Pathol. 186(6):1466–1480. https://doi.org/10.1016/j.ajpath.2016.01.019
36. Dyomina AV, Zubareva OE, Smolensky IV, Vasilev DS, Zakharova MV, Kovalenko AA, Schwarz AP, Ischenko AM, Zaitsev AV (2020) Anakinra reduces epileptogenesis, provides neuroprotection, and attenuates behavioral impairments in rats in the lithium-pilocarpine model of epilepsy. Pharmaceuticals 13(11):340. https://doi.org/10.3390/ph13110340
37. Singh S, Singh TG, Rehni AK (2020) An Insight into Molecular Mechanisms and Novel Therapeutic Approaches in Epileptogenesis. CNS Neuroll Disorders-Drug Targets 19(10):750–779. https://doi.org/10.2174/1871527319666200910153827
38. Dey A, Kang X, Qiu J, Du Y, Jiang J (2016) Anti-inflammatory small molecules to treat seizures and epilepsy: from bench to bedside. Trends Pharmacol Sci 37(6):463–484. https://doi.org/10.1016/j.tips.2016.03.001
39. Sharma VK, Singh TG, Mehta V (2021) Stressed mitochondria: a target to intrude Alzheimer's disease. Mitochondrion. https://doi.org/10.1016/j.mito.2021.04.004
40. Stępień KM, Tomaszewski M, Tomaszewska J, Czuczwar SJ (2012) The multidrug transporter P-glycoprotein in pharmacoresistance to antiepileptic drugs. Drugs Pharmacol Rep 64(5):1011–1019. https://doi.org/10.1016/S1734-1140(12)70900-3
41. Khan H, Gupta A, Singh TG, Kaur A (2021) Mechanistic insight on the role of leukotriene receptors in ischemic–reperfusion injury. Pharmacol Rep. https://doi.org/10.1007/s43440-021-00258-8
42. Rawat C, Kukal S, Dahiya UR, Kukreti R (2019) Cyclooxygenase-2 (COX-2) inhibitors: future therapeutic strategies for epilepsy management. J Neuroinflammation 16(1):1–5. https://doi.org/10.1186/s12974-019-1592-3
43. Rojas A, Jiang J, Ganesh T, Yang MS, Lelutiu N, Gueorguieva P, Dingledine R (2014) Cyclooxygenase-2 in epilepsy. Epilepsia 55(1):17–25. https://doi.org/10.1111/epi.12461
44. Potschka H (2010) Modulating P-glycoprotein regulation: future perspectives for pharmacoresistant epilepsies? Epilepsia 51(8):1333–1347. https://doi.org/10.1111/j.1528-1167.2010.02585.x
45. Chen Y, Cai Z, Ke Z (2017) Antineuroinflammation of minocycline in stroke. Neurologist 22(4):120–126. https://doi.org/10.1097/NRL.0000000000000136
46. Montesinos J, Alfonso-Loeches S, Guerri C (2016) Impact of the innate immune response in the actions of ethanol on the central nervous system. Alcoholism 40(11):2260–2270. https://doi.org/10.1111/acer.13208
47. Yuan X, Fu Z, Ji P, Guo L, Al-Ghamdy AO, Alkandiri A, Habotta OA, Moneim AE, Kassab RB (2020) Selenium nanoparticles pretreatment reverse behavioral, oxidative damage, neuronal loss and neurochemical alterations in pentylenetetrazole-induced epileptic seizures in mice. Int J Nanomed 15:6339. https://doi.org/10.2147/IJN.S259134
48. De Rubeis S, Fernández E, Buzzi A, Di Marino D, Bagni C (2012) Molecular and cellular aspects of mental retardation in the Fragile X syndrome: from gene mutation/s to spine dysmorphogenesis. Synaptic Plasticity. https://doi.org/10.1007/978-3-7091-0932-8_23
49. Singh R, Rao HK, Singh TG (2020) Neuropathic pain in diabetes mellitus: challenges and future trends. Obes Med 18:100215. https://doi.org/10.1016/j.obmed.2020.100215
50. Milatovic D, Montine TJ, Aschner M (2011) Prostanoid signaling: dual role for prostaglandin E2 in neurotoxicity. Neurotoxicology 32(3):312–319. https://doi.org/10.1016/j.neuro.2011.02.004
51. van Vliet EA, Zibell G, Pekcec A, Schlichtiger J, Edelbroek PM, Holtman L, Aronica E, Gorter JA, Potschka H (2010) COX-2 inhibition controls P-glycoprotein expression and promotes brain delivery of phenytoin in chronic epileptic rats. Neuropharmacology 58(2):404–412. https://doi.org/10.1016/j.neuropharm.2009.09.012
52. Katan M, Cockcroft S (2020) Phosphatidylinositol (4, 5) bisphosphate: diverse functions at the plasma membrane. Essays Biochem 64(3):513–531. https://doi.org/10.1042/EBC20200041
53. Yousuf MS, Samtleben S, Lamothe SM, Friedman TN, Catuneanu A, Thorburn K, Desai M, Tenorio G, Schenk GJ, Ballanyi K, Kurata HT (2020) Endoplasmic reticulum stress in the dorsal root ganglia regulates large-conductance potassium channels and contributes to pain in a model of multiple sclerosis. FASEB J 34(9):12577–12598. https://doi.org/10.1096/fj.202001163R
54. Wei LL, Shen YD, Zhang YC, Hu XY, Lu PL, Wang L, Chen W (2010) Roles of the prostaglandin E 2 receptors EP subtypes in Alzheimer's disease. Neurosci Bull 26(1):77–84. https://doi.org/10.1007/s12264-010-0703-z
55. Rawat C, Kutum R, Kukal S, Srivastava A, Dahiya UR, Kushwaha S, Sharma S, Dash D, Saso L, Srivastava AK, Kukreti R (2020) Downregulation of peripheral PTGS2/COX-2 in response to valproate treatment in patients with epilepsy. Sci Rep 10(1):1–4. https://doi.org/10.1038/s41598-020-59259-x
56. Bar-Klein G, Cacheaux LP, Kamintsky L, Prager O, Weissberg I, Schoknecht K, Cheng P, Kim SY, Wood L, Heinemann U, Kaufer D (2014) Losartan prevents acquired epilepsy via TGF-β signaling suppression. Ann Neurol 75(6):864–875. https://doi.org/10.1002/ana.24147
57. Weissberg I, Wood L, Kamintsky L, Vazquez O, Milikovsky DZ, Alexander A, Oppenheim H, Ardizzone C, Becker A, Frigerio F, Vezzani A (2015) Albumin induces excitatory synaptogenesis through astrocytic TGF-β/ALK5 signaling in a model of acquired epilepsy following blood–brain barrier dysfunction. Neurobiol Dis 1(78):115–125. https://doi.org/10.1016/j.nbd.2015.02.029
58. Kaminska B, Kocyk M, Kijewska M (2013) TGF beta signaling and its role in glioma pathogenesis. Glioma Signaling. https://doi.org/10.1007/978-94-007-4719-7_9
59. Van Vliet EA, Aronica E, Gorter JA (2015) Blood–brain barrier dysfunction, seizures and epilepsy. InSeminars in Cell & Developmental Biology 1 (Vol. 38, pp. 26–34). Academic Press. https://doi.org/10.1016/j.semcdb.2014.10.003.
60. Um JW (2017) Roles of glial cells in sculpting inhibitory synapses and neural circuits. Front Mol Neurosci 13(10):381. https://doi.org/10.3389/fnmol.2017.00381
61. Baldwin KT, Eroglu C (2017) Molecular mechanisms of astrocyte-induced synaptogenesis. Curr Opin Neurobiol 45:113–120. https://doi.org/10.1016/j.conb.2017.05.006
62. Naegele JR (2015) Blocking Astrocyte Transformation at the Dysfunctional Blood Brain Barrier: Seizure Suppression by Losartan. Epilepsy Curr 15(2):87–89.

63. Diniz LP, Matias IC, Garcia MN, Gomes FC (2014) Astrocytic control of neural circuit formation: highlights on TGF-beta signaling. Neurochem Int 1(78):18–27. https://doi.org/10.1016/j.neuint.2014.07.008
64. Kang X, Qiu J, Li Q, Bell KA, Du Y, Lee JY, Hao J, Jiang J (2017) Cyclooxygenase-2 contributes to oxidopamine-mediated neuronal inflammation and injury via the prostaglandin E2 receptor EP2 subtype. Sci Rep 7(1):1–4. https://doi.org/10.1038/s41598-017-09528-z
65. Rehni AK, Singh TG (2012) Involvement of CCR-2 chemokine receptor activation in ischemic preconditioning and postconditioning of brain in mice. Cytokine 60(1):83–89. https://doi.org/10.1016/j.cyto.2012.05.009
66. Jiang J, Quan Y, Ganesh T, Pouliot WA, Dudek FE, Dingledine R (2013) Inhibition of the prostaglandin receptor EP2 following status epilepticus reduces delayed mortality and brain inflammation. Proc Natl Acad Sci 110(9):3591–3596. https://doi.org/10.1073/pnas.1218498110
67. Erblich B, Zhu L, Etgen AM, Dobrenis K, Pollard JW (2011) Absence of colony stimulation factor-1 receptor results in loss of microglia, disrupted brain development and olfactory deficits. PLoS ONE 6(10):26317. https://doi.org/10.1371/journal.pone.0026317
68. Nagib MM, Yu Y, Jiang J (2020) Targeting prostaglandin receptor EP2 for adjunctive treatment of status epilepticus. Pharmacol Ther 1(209):107504. https://doi.org/10.1016/j.pharmthera.2020.107504
69. Grewal AK, Singh TG, Sharma D, Sharma V, Singh M, Rahman MH, Abdel-Daim MM (2021) Mechanistic insights and perspectives involved in neuroprotective action of quercetin. Biomed Pharmacother 140:111729. https://doi.org/10.1016/j.biopha.2021.111729
70. Sharma VK, Singh TG (2020) Insulin resistance and bioenergetic manifestations: Targets and approaches in Alzheimer's disease. Life Sci. https://doi.org/10.1016/j.lfs.2020.118401
71. Sharma V, Kaur A, Singh TG (2020) Counteracting role of nuclear factor erythroid 2-related factor 2 pathway in Alzheimer's disease. Biomed Pharmacother 129:110373. https://doi.org/10.1016/j.biopha.2020.110373
72. Carloni S, Favrais G, Saliba E, Albertini MC, Chalon S, Longini M, Gressens P, Buonocore G, Balduini W (2016) Melatonin modulates neonatal brain inflammation through endoplasmic reticulum stress, autophagy, and mi R-34a/silent information regulator 1 pathway. J Pineal Res 61(3):370–380. https://doi.org/10.1111/jpi.12354
73. Ethemoglu MS, Seker FB, Akkaya H, Kilic E, Aslan I, Erdogan CS, Yilmaz B (2017) Anticonvulsant activity of resveratrol-loaded liposomes in vivo. Neuroscience 15(357):12–19. https://doi.org/10.1016/j.neuroscience.2017.05.026
74. Musto AE, Rosencrans RF, Walker CP, Bhattacharjee S, Raulji CM, Belayev L, Fang Z, Gordon WC, Bazan NG (2016) Dysfunctional epileptic neuronal circuits and dysmorphic dendritic spines are mitigated by platelet-activating factor receptor antagonism. Sci Rep 6(1):1–6. https://doi.org/10.1038/srep30298
75. Khan H, Tiwari P, Kaur A, Singh TG (2021) Sirtuin acetylation and deacetylation: a complex paradigm in neurodegenerative disease. Mol Neurobiol. https://doi.org/10.1007/s12035-021-02387-w
76. Lu H, Wang B, Cui N, Zhang Y (2018) Artesunate suppresses oxidative and inflammatory processes by activating Nrf2 and ROS-dependent p38 MAPK and protects against cerebral ischemia-reperfusion injury. Mol Med 17(5):6639–6646. https://doi.org/10.3892/mmr.2018.8666
77. Mannan A, Garg N, Singh TG, Kang HK (2021) Peroxisome proliferator-activated receptor-gamma (PPAR-ɣ): molecular effects and its importance as a novel therapeutic target for cerebral ischemic injury. Neurochem Res. https://doi.org/10.1007/s11064-021-03402-1
78. Madreiter-Sokolowski CT, Waldeck-Weiermair M, Bourguignon MP, Villeneuve N, Gottschalk B, Klec C, Stryeck S, Radulovic S, Parichatikanond W, Frank S, Madl T (2019) Enhanced intercompartmental Ca2+ flux modulates mitochondrial metabolism and apoptotic threshold during aging. Redox Biol 1(20):458–466. https://doi.org/10.1016/j.redox.2018.11.003
79. Kaarniranta K, Kajdanek J, Morawiec J, Pawlowska E, Blasiak J (2018) PGC-1α protects RPE cells of the aging retina against oxidative stress-induced degeneration through the regulation of senescence and mitochondrial quality control: the significance for AMD pathogenesis. Int J Mol Sci 19(8):2317. https://doi.org/10.3390/ijms19082317
80. Hannan M, Dash R, Sohag AA, Haque M, Moon IS (2020) Neuroprotection against oxidative stress: phytochemicals targeting TrkB signaling and the Nrf2-ARE antioxidant system. Front Mol Neurosci 2(13):116. https://doi.org/10.3389/fnmol.2020.00116
81. Ahmed SM, Luo L, Namani A, Wang XJ (1863) Tang X (2017) Nrf2 signaling pathway: Pivotal roles in inflammation. Biochim Biophys Acta Mol Basis Dis Bba-Mol Basis Dis 2:585–597. https://doi.org/10.1016/j.bbadis.2016.11.005
82. Rius-Pérez S, Pérez S, Martí-Andrés P, Monsalve M, Sastre J (2020) Nuclear factor kappa B signaling complexes in acute inflammation. Antioxid Redox Signal 33(3):145–165. https://doi.org/10.1089/ars.2019.7975
83. Abdollahi E, Momtazi AA, Johnston TP, Sahebkar A (2018) Therapeutic effects of curcumin in inflammatory and immune-mediated diseases: a nature-made jack-of-all-trades? J Cell Physiol 233(2):830–848. https://doi.org/10.1002/jcp.25778
84. Thawkar BS, Kaur G (2019) Inhibitors of NF-κB and P2X7/NLRP3/Caspase 1 pathway in microglia: Novel therapeutic opportunities in neuroinflammation induced early-stage Alzheimer's disease. J Neuroimmunol 15(326):62–74. https://doi.org/10.1016/j.jneuroim.2018.11.010
85. Wang S, Liang X, Yang Q, Fu X, Rogers CJ, Zhu M, Rodgers BD, Jiang Q, Dodson MV, Du M (2015) Resveratrol induces brown-like adipocyte formation in white fat through activation of AMP-activated protein kinase (AMPK) α1. Int J Obes 39:967–976. https://doi.org/10.1038/ijo.2015.23
86. Xu L, Botchway BO, Zhang S, Zhou J, Liu X (2018) Inhibition of NF-κB signaling pathway by resveratrol improves spinal cord injury. Front Neurosci 4(12):690. https://doi.org/10.3389/fnins.2018.00690
87. Rehni AK, Singh TG, Singh N, Arora S (2010) Tramadol-induced seizurogenic effect: a possible role of opioid-dependent histamine H1 receptor activation-linked mechanism. Naunyn Schmiedebergs Arch Pharmacol 381(1):11–19. https://doi.org/10.1007/s00210-009-0476-y
88. Thapa K, Khan H, Sharma U, Grewal AK, Singh TG (2020) Poly (ADP-ribose) polymerase-1 as a promising drug target for neurodegenerative diseases. Life Sci. https://doi.org/10.1016/j.lfs.2020.118975
89. Gaikwad S, Agrawal-Rajput R (2015) Lipopolysaccharide from Rhodobacter sphaeroides attenuates microglia-mediated inflammation and phagocytosis and directs regulatory T cell response. J Inflamm Res 17:2015. https://doi.org/10.1155/2015/361326
90. Almeida-Suhett CP, Prager EM, Pidoplichko V, Figueiredo TH, Marini AM, Li Z, Eiden LE, Braga MF (2015) GABAergic interneuronal loss and reduced inhibitory synaptic transmission in the hippocampal CA1 region after mild traumatic brain injury. Exp Neurol 1(273):11–23. https://doi.org/10.1016/j.expneurol.2015.07.028
91. Armada-Moreira A, Gomes JI, Pina CC, Savchak OK, Gonçalves-Ribeiro J, Rei N, Pinto S, Morais TP, Martins RS,

Ribeiro FF, Sebastião AM (2020) Going the extra (synaptic) mile: excitotoxicity as the road toward neurodegenerative diseases. Front Cell Neurosci 24(14):90. https://doi.org/10.3389/fncel.2020.00090
92. Cho YJ, Kim H, Kim WJ, Chung S, Kim YH, Cho I, Lee BI, Heo K (2017) Trafficking patterns of NMDA and GABAA receptors in a Mg2+-free cultured hippocampal neuron model of status epilepticus. Epilepsy Res 1(136):143–148. https://doi.org/10.1016/j.eplepsyres.2017.08.003
93. Sasabe J, Suzuki M, Imanishi N, Aiso S (2014) Activity of D-amino acid oxidase is widespread in the human central nervous system. Front Mol Neurosci 10(6):14. https://doi.org/10.3389/fncel.2018.00052
94. Foresti ML, Arisi GM, Shapiro LA (2011) Role of glia in epilepsy-associated neuropathology, neuroinflammation and neurogenesis. Brain Res 66(1–2):115–122. https://doi.org/10.1016/j.brainresrev.2010.09.002
95. Alsharafi WA, Xiao B, Abuhamed MM, Luo Z (2015) miRNAs: biological and clinical determinants in epilepsy. Front Mol Neurosci 13(8):59. https://doi.org/10.3389/fnmol.2015.00059
96. Wang J, Zhao J (2021) MicroRNA dysregulation in epilepsy: from pathogenetic involvement to diagnostic biomarker and therapeutic agent development. Front Mol Neurosci 12(14):35. https://doi.org/10.1080/17460441.2020.1746266
97. Nakamura M, Kanda T, Sasaki R, Haga Y, Jiang X, Wu S, Nakamoto S, Yokosuka O (2015) MicroRNA-122 inhibits the production of inflammatory cytokines by targeting the PKR activator PACT in human hepatic stellate cells. PLoS ONE 10(12):e0144295. https://doi.org/10.1371/journal.pone.0144295
98. Mahesh G, Biswas R (2019) MicroRNA-155: a master regulator of inflammation. J Interferon Cytokine Res 39(6):321–330. https://doi.org/10.1089/jir.2018.0155
99. Lai YC, Muscal E, Wells E, Shukla N, Eschbach K, Hyeong Lee K, Kaliakatsos M, Desai N, Wickström R, Viri M, Freri E (2020) Anakinra usage in febrile infection related epilepsy syndrome: an international cohort. Ann Clin Transl Neurol 7:2467–2474. https://doi.org/10.1002/acn3.51229
100. Radu BM, Epureanu FB, Radu M, Fabene PF, Bertini G (2017) Nonsteroidal anti-inflammatory drugs in clinical and experimental epilepsy. Epilepsy Res 131:15–27. https://doi.org/10.1016/j.eplepsyres.2017.02.003
101. Maroso M, Balosso S, Ravizza T, Iori V, Wright CI, French J, Vezzani A (2011) Interleukin-1β biosynthesis inhibition reduces acute seizures and drug resistant chronic epileptic activity in mice. Neurother 8:304–315. https://doi.org/10.1007/s13311-011-0039-z
102. Nasr SMB, Moghimi A, Mohammad-Zadeh M, Shamsizadeh A, Noorbakhsh SM (2013) The effect of minocycline on seizures induced by amygdala kindling in rats. Seizure 22:670–674. https://doi.org/10.1016/j.seizure.2013.05.005
103. Wang DD, Englot DJ, Garcia PA, Lawton MT, Young WL (2012) Minocycline-and tetracycline-class antibiotics are protective against partial seizures in vivo. Epilepsy Behav 24:314–318. https://doi.org/10.1016/j.yebeh.2012.03.035
104. Zhou P, Qian L, Chou T, Iadecola C (2008) Neuroprotection by PGE2 receptor EP1 inhibition involves the PTEN/AKT pathway. Neurobiol Dis 29:543–551. https://doi.org/10.1016/j.nbd.2007.11.010
105. Fischborn SV, Soerensen J, Potschka H (2010) Targeting the prostaglandin E2 EP1 receptor and cyclooxygenase-2 in the amygdala kindling model in mice. Epilepsy Res 91:57–65. https://doi.org/10.1016/j.eplepsyres.2010.06.012
106. Löscher W, Potschka H, Sisodiya SM, Vezzani A (2020) Drug resistance in epilepsy: clinical impact, potential mechanisms, and new innovative treatment options. Pharmacol Rev 72:606–638. https://doi.org/10.1124/pr.120.019539
107. Bhuyan P, Patel M (2014) StEPing "EP2" to prevent status epilepticus-induced mortality and inflammation: StEPing "EP2" to prevent status epilepticus. Epilepsy Curr 14:35–37.
108. Shetty AK (2011) Promise of resveratrol for easing status epilepticus and epilepsy. Pharmacol Ther 131:269–286. https://doi.org/10.1016/j.pharmthera.2011.04.008
109. Mishra V, Shuai B, Kodali M, Shetty GA, Hattiangady B, Rao X, Shetty AK (2015) Resveratrol treatment after status epilepticus restrains neurodegeneration and abnormal neurogenesis with suppression of oxidative stress and inflammation. Sci Rep 5:1–19. https://doi.org/10.1038/srep17807