REVIEW ARTICLE

Neuroinflammation in neurological disorders: pharmacotherapeutic targets from bench to bedside

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Abstract

Neuroinflammation is one of the host defensive mechanisms through which the nervous system protects itself from pathogenic and or infectious insults. Moreover, neuroinflammation occurs as one of the most common pathological outcomes in various neurological disorders, makes it the promising target. The present review focuses on elaborating the recent advancement in understanding molecular mechanisms of neuroinflammation and its role in the etiopathogenesis of various neurological disorders, especially Alzheimer's disease (AD), Parkinson's disease (PD), and Epilepsy. Furthermore, the current status of anti-inflammatory agents in neurological diseases has been summarized in light of different preclinical and clinical studies. Finally, possible limitations and future directions for the effective use of anti-inflammatory agents in neurological disorders have been discussed.

Keywords Neuroinflammation · Neurological disorders · Alzheimer's disease · Parkinson's disease · Epilepsy

Introduction

Developing countries (like India) are going through a phase of epidemiological transition with a higher socio-economic burden of non-communicable disease. Among various non-communicable diseases, neurological disorders have been considered significant causes of mortality and morbidity, not only in India but also worldwide (Feigin et al. 2020). Owing to population overgrowth and aging, the absolute number of disabilities and deaths due to neurological diseases is piling up, suggesting prevention and management of primary neurological conditions are ineffective. The major reason could be a lack of clear understanding of the etiopathogenesis of these neurological conditions.

The neuroinflammatory cascade has been identified as a common etiopathogenic factor in different neurological disorders, including stroke, Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), Huntington's disease (HD), migraine, epilepsy, Multiple Sclerosis (MS), ischemic/traumatic brain injury (TBI), spinal cord injury (SCI), and depression. Virtually, neuroinflammation appears to be involved in most neurological and neurodegenerative diseases and poses a common thread that connects their pathologies (Gilhus and Deuschl 2019; Brambilla 2019). The understanding of neuroinflammation is continuously under evolution; therefore, intermittent analysis of the current information is required.

The process of neuroinflammation originated by synchronized neural/non-neural cells, aiming to restore neuronal homeostasis and protect neuronal integrity (Degan et al. 2018). In the acute phase, such inflammatory response poses a protective effect by maintaining neuronal homeostasis, contributing to neurogenesis, repair, and clearance of protein plaques and damaged cells (Russo and McGavern 2016; Shabab et al. 2017). However, during chronic phase, the maladaptive outcome associated with neuroinflammation leads to worsening neuronal damage.

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This review discusses the interrelationships between neuroinflammation and pathologies of several neurological disorders, mainly AD, PD, and epilepsy. We specifically focus on cellular and molecular events as significant players in neuroinflammation, including resident cells, immune cells, pro-inflammatory cytokines, inflammasomes, high mobility group box protein-1 (HMGB1), oxidative stress, mitochondrial dysfunction, neurotransmitters, and ion channel. Furthermore, modulation of neuroinflammation as a plausible therapeutic approach in neurological disorders has been summarized in light of various preclinical and clinical studies.

Molecular mechanism of neuroinflammation

Neuroinflammation may be triggered by different biological mechanisms, including glial reactions and oxidative stress or brain injuries (stroke, trauma, chronic infection, etc.). Basic research to understand the mechanism of neuroinflammation
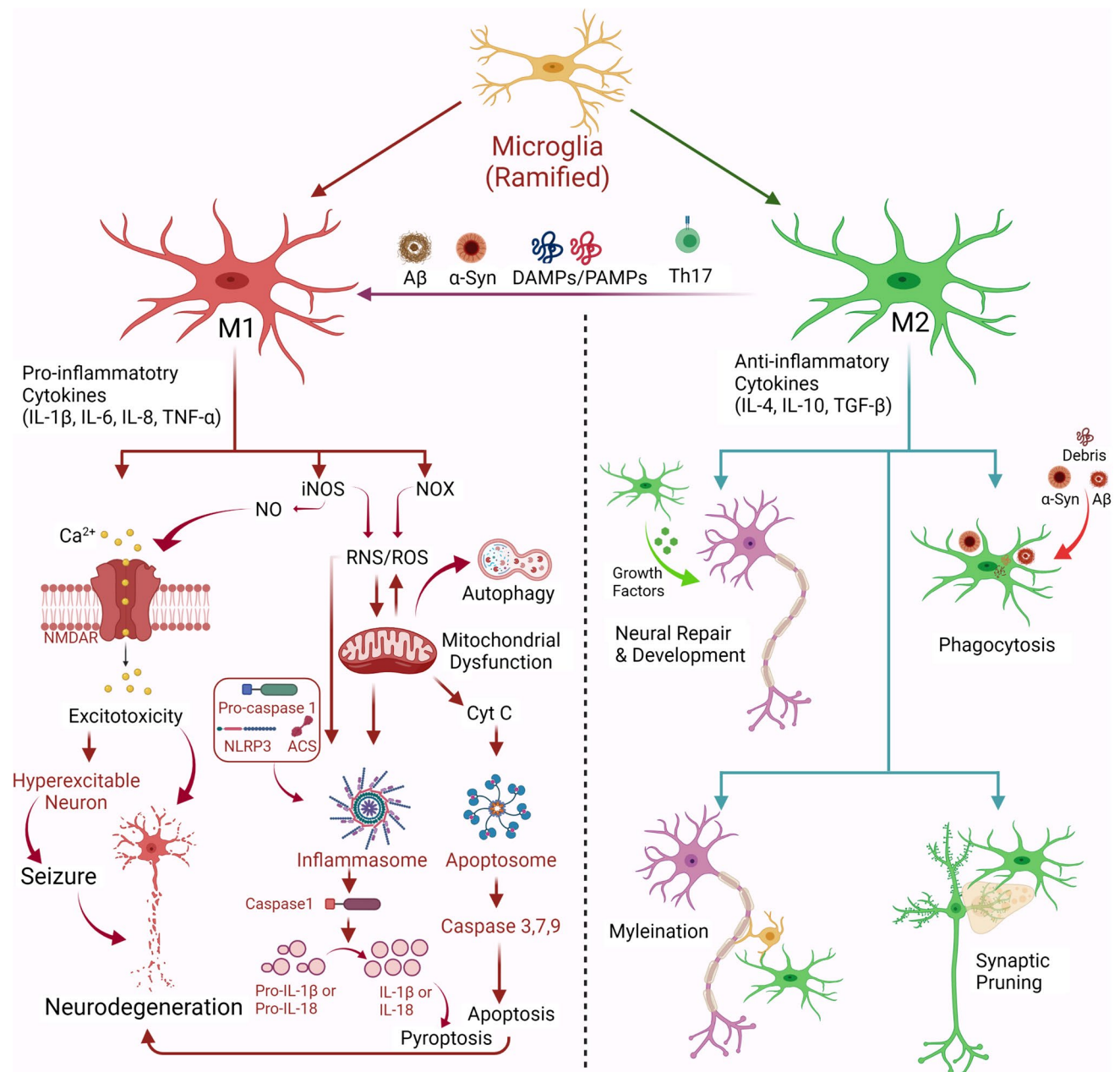

Fig. 1 Role of microglia, cytokines, inflammasome, mitochondrial dysfunction, in neuroinflammation and development of neurological diseases
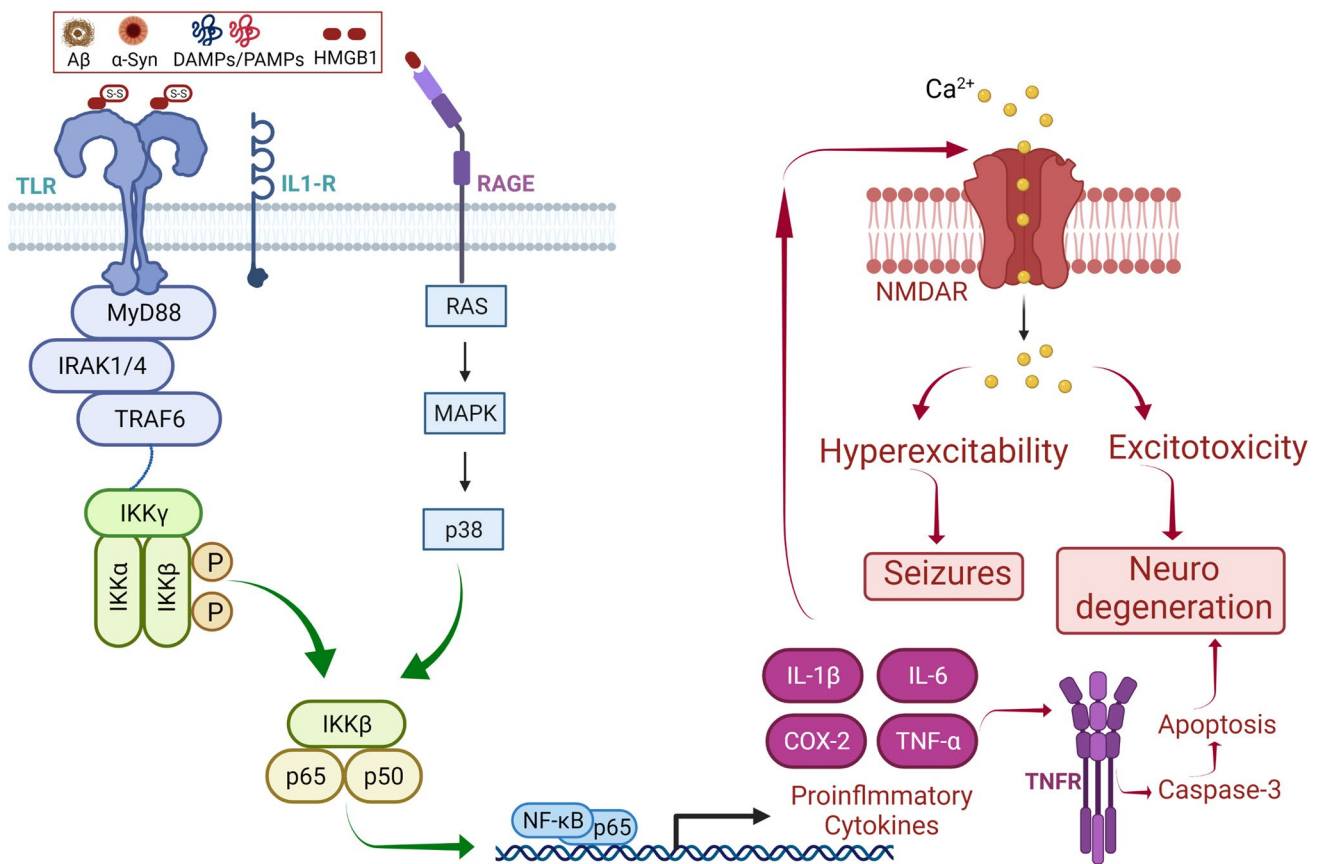
Fig. 2 Role of proinflammatory cytokines, HMGB1, DAMPs/PAMPs in neuroinflammation and associated neuropathological outcome

is over-pouring; however, exact pathogenesis remains unclear. The current information on neuroinflammation and its role in different neurological disorders has been illustrated in Figs. 1 and 2.

Glial cells in neuroinflammation

The CNS microenvironment is closely monitored by ramified microglia by sensing death/damage signals and proliferating microglia at the injury site. Microglial cells are very dynamic and play an essential role in maintaining neuronal homeostasis, neuronal growth, pruning of excess synapses to maintain optimal neuronal plasticity, and clearance of cellular debris, protein aggregates, several pathogens/antigens, and neural plasticity (Katsumoto et al. 2014). Under the influence of exogenous and endogenous factors (pathogen-associated molecular patterns (PAMP), and damage-associated molecular patterns (DAMP)) pattern recognition receptors (PPRs) on microglia may recognize pathogens, protein aggregates, or cellular debris, and lead to microglial activation (Leng and Edison 2021). During acute neuroinflammation, microglial cells get rapidly activated. Microglia activation leads to phagocytosis of pathogenic species and

releases cytokines, chemokines, reactive oxygen/nitrogen species (ROS/RNS), and prostaglandins. Over time, progression to chronic inflammation causes degeneration of neurons and disruption of blood–brain barrier (BBB) possibly via over production of ROS/RNS and recruitment of peripheral immune cells to initiate cellular damage (Garden 2013). Generally, this process usually remains active until the immune response is eliminated.

In normal condition, microglia remains in a quiescent/ resting state with ramified morphology and perform surveillance function in the CNS (Nimmerjahn et al. 2005; Davalos et al. 2005). However, under pathological conditions, dramatic morphological change (amoebic shape) activates the microglia. The activated microglia expresses various surface molecules (like Fc receptor, cluster of differentiation (CD-11b, CD-11c, CD-14), major histocompatibility complex (MHC), toll-like receptor (TLR), scavenger receptor, cytokine, and chemokine receptors), functions as antigen-presenting cells (APC) and attracts various immunological cells (Rock et al. 2004). Thus, activated innate immunity exerts the neuroprotective effect of microglia via maintaining homeostasis, repair, neuroregeneration and, clearance of toxic substances. At first instance, activation of TLR and

scavenger receptors dampens neurotoxicity by sequestering abnormal protein aggregates. At the same time, their downstream signaling (including cytokines/chemokines, excitatory amino acids, nucleic acids, ROS, and several proteases) activates the microglial neurotoxic effects. Overexpression of TLR/scavenger receptors has been reported in several neurological disorders (Cho et al. 2005; Carpentier et al. 2008; Tiwari et al. 2019). Thus, whether activated microglia would elicit a neuroprotective/neurotoxic effect depends on the microenvironment, type, and magnitude of stimuli (Nakanishi and Wu 2009; Sawada 2009).

The assessment of functional phenotype, M1/M2 dichotomy of microglia, was devised for a long, indicating M1 as pro-inflammatory phenotype while M2 as anti-inflammatory phenotype (Mantovani et al. 2002; Henkel et al. 2009). However, the experimental evidence contradicts such a microglia dichotomy. Still, these phenotypic dichotomy is widely used to refer M1 as neurotoxic and M2 as neuroprotective under certain pathological conditions (Ransohoff 2016). The activation of microglia depends on the type of stimuli received. Several experimental evidence has suggested, lipopolysaccharide (LPS) or interferon (IFN) γ may induce activation of detrimental M1 phenotype while IL-4/IL-13 might lead to induction of protective M2 phenotype (Loane and Kumar 2016).

During aging, sustained activation of microglia results in functional impairment and contributes to the emergence of neurodegenerative diseases. Various experimental evidence supports the chronic activation of microglia as a standard pathological marker of neurodegenerative disorders. In the early stage of neurodegeneration, disease-related proteins (Aβ or α-syn) serves as DAMPs and activates pattern recognition receptors. In contrast, soluble oligomers activate several other microglia receptors (CD-47, CD-14, CD-36, α6β1 integrin, TLR) (Fassbender et al. 2004; Tiwari et al. 2019). Activation of such receptors switches microglia from quiescent to the active state which proliferate near extracellular plaque and restrict its further growth (Edwards 2019). Therefore, in the early stage, microglial activation serves a neuro-supportive function by releasing several proteases for clearance of Aβ plaque (Jimenez et al. 2008).

Further, the M2 phenotype helps in phagocytosis of Aβ plaques and creates a physical barrier to prevent further spreading of plaque (Condello et al. 2015). Indeed, acute microglia activation appears neuroprotective, but the sustained chronic microglial activation exerts detrimental changes. Such microglial dysfunction results in the overproduction of pro-inflammatory cytokines leading to polarization of microglia towards M1. Furthermore, owing to M1 polarization, the accumulation of Aβ plaques leads to a neurotoxic effect and causes synaptic loss (Piccioni et al. 2021).

The inflammatory cytokines released from activated microglia may have a bit absolute neurotoxic effect, including most deleterious inflammatory cytokines (TNF-α and INF-γ). In contrast, their downstream signaling involves activation of MAPK and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and exerts neuroprotection (Kamata et al. 2005). Indirectly, these mediators stimulate the glutamate release from activated microglia, resulting in neuronal damage via excitotoxicity (Barger and Basile 2001; Takeuchi et al. 2006, 2008). Such elevation in glutamate level might result from astrocytic glutamate transporters inhibition (critical for extracellular glutamate removal) and its potent neurotoxic effects (Liang et al. 2008; Takaki et al. 2012).

Thus, inhibition of microglial activation and blockade of glutamate signaling have been evaluated for their neuroprotective effect in several neurological disorders. However, such a hypothesis may have some potential side effects which need to be addressed simultaneously (Parsons et al. 2007). Overall, under pathological conditions, harmful impacts of microglia contribute to the development of various neurological disorders. Thus, a better understanding of the precise mechanism of neurotoxic behavior of microglia would support a desirable therapeutic approach inhibiting deleterious effects of microglia without affecting its neuroprotective effect for neurological disorders.

T cells and monocytes in neuroinflammation

The activated microglia and infiltrating T cells lead to Neuroinflammation (Denney et al. 2012). Neuroinflammation does get affected by stimulated testosterone T cells (Massa et al. 2017). The endogenous immune-suppressors are CD4^{+}, Foxp3, and CD25 regulatory T cells (Tregs), suppresses T cell proliferation, and pro-inflammatory cytokine (Reynolds et al. 2010). IL-21 and IL-9 are produced by activation of stimulated CD4^{+} T cells, and it was significantly increasing in AD. The pro-inflammatory cytokines (IL-6, IL-21, IL-23) are involved in the differentiation of Th-17 cells and results in Neuroinflammation (Reynolds et al. 2010). Local administration of IL-17 was reported to enhance dendritic cells (activated) in the experimental model (Niranjan et al. 2016). Further research is required to establish therapeutic potential based on T cells in neuroinflammatory diseases.

According to recent research, monocyte plays crucial role in intitation of neuroinflammation (Jones et al. 2018). In experimental model of PD reported infiltration of monocytes from periphery to CNS results in neurodegeneration (Harms et al. 2018). In contrast, depletion of monocyte results in exacerbation of neurodegeneration in MPTP model of PD suggesting neuroprotective role of monocytes (Cote et al. 2015; Wattananit et al. 2016). Further, CXCL12, a chemokine, causes monocyte mediated stimulation of endothelial cells facilitating lymphocyte transmigration across BBB and deployment of immune cells towards brain

(Schmitt et al. 2012). Monocytes contribute to phagocytosis of faulty proteins and debris in brain. The mediator of inflammation, like saturated fatty acids, causes toxicity towards neuronal cells of human monocytes. Infiltrating monocytes do not contribute to the resident microglia pool, but they trigger experimental autoimmune encephalitis progression (Ajami et al. 2011). The constitutive function of macrophages and monocytes in autoimmune neuroinflammation may be defined by activation of NF-κB (Karlmark et al. 2012).

Cytokines in neuroinflammation

Cytokines are a considerably more prominent, heterogeneous group of glycoproteins released from microglia, astrocytes, macrophages, monocytes, etc., and work in an autocrine and paracrine manner. Any infection, trauma, or ischaemic brain damage commences cellular responses that hold various hallmarks of neuroinflammation and are majorly responsible for neuronal repair and restoration of homeostasis (Alyu and Dikmen 2016). In such conditions, activation of glial cells, typically mediated via astrocytes and microglia, embrace enhanced production of an array of cytokines and chemokines.

Generally, cytokines mediate signaling is of two types: pro-inflammatory (IL-1β, IL-6, IFN-γ, and TNF-α) and anti-inflammatory cytokines (IL-4, IL-10, IL-13), which either facilitate or inhibit inflammatory responses. The equilibrium between these cytokines eliminates the underlying cause in acute phase, while the chronic release of pro-inflammatory cytokines appears as a critical pathogenic mechanism of various neurological diseases. In the acute stage, activation of astrocytes has been shown to integrate the signals from several cytokines (IL-4, IL-10, IL-13) and chemokines, including interferon-γ (IFN-γ), interleukin-17 (IL-17), IL-1β, and CC-chemokine ligand 2 (CCL2). Furthermore, administration of pro-inflammatory cytokine has been reported to induce depression-like behavior, while antidepressant treatment has been found to reduce cytokine production (Himmerich et al. 2019).

Neuroinflammation is mainly triggered by blood-borne leukocytes invading CNS. Thus infiltrated leukocytes enhance the production of various cytokines, which further recruits more leukocytes and aggravates neuroinflammation. Cytokines produced by microglia and astrocyte activation, like- IL-1β, IL-6, TNF, IL-18, IL-12, IL-23, and IL-33, induce neuroinflammation and neurodegeneration (Becher et al. 2017).

APCs in secondary lymphoid tissues contain IL-12 and IL-23, which polarize differentiating T cells against different effecter function phenotypes. Initially, IL-12 was considered critical in the development of MS (Segal and Shevach 1996). Later role of IL-23 is recorded in migrating secondary lymphoid tissues in Neuroinflammation (Becher et al. 2002). After the pathogenic invasion of TH cells, the resident microglia release IL-23, which initiates Neuroinflammation (Li et al. 2007). Thus, IL-23 has emerged as a critical player in generating pathogenic TH cell phenotypes. There are both the genesis and maintenance of pathogenic TH cells, which function in both the peripheral immune compartment and the CNS. Both IL-1 and IL-6 appear to play critical peripheral roles in promoting pathogenic activity in TH cells capable of causing CNS inflammation. IL-6 is another crucial cytokine essential for the progression of neuroinflammation by inhibiting FoxP3 expression in differentiating TH cells (Eugster et al. 1998; Sonderegger et al. 2008). On the other hand, IL-6 induces the expression of IL-1 receptors on TH cells which helps them recognizing local IL-1 production in CNS (Chung et al. 2009).

Inflammasome in neuroinflammation

Inflammasomes are intracellular multi-protein complexes that recognize harmful substances (microbial pathogens or host-derived harmful substances) and activate inflammatory cascade and immune response against them. Upon detecting these dangerous signals, they induce host immune mechanisms by secreting inflammatory mediators like IL-1β and IL-18. They also induce pyroptosis (alytic cell death process), resulting in release of inflammatory mediators, thus potentiating the inflammasomes induced inflammatory response by many folds. Neuroinflammation and neurodegeneration are mostly a result of the deposition of aggregated host proteins like amyloid-β (Aβ), α-synuclein, and prions (Qi et al. 2018). These aggregations activate inflammasomes which in turn triggers neuroinflammation and neurodegeneration (Holbrook et al. 2021; Saresella et al. 2016).

Recognition of harmful pathogens and host-derived aggregation is mainly mediated by PRRs that sense PAMPs and host or environment-derived DAMPs (Lampron et al. 2013). PRRs can be of two types: membrane-bound PRRs (detects extracellular signals) and intracellular PRRs like-NLR and ALR families of receptors (Walsh et al. 2014). Detection of priming signals by these DAMPs and PAMPs and the detection of toxins and harmful chemicals by NLR and ALR activate the formation of various proteins that finally aggregate and form inflammasomes. Inflammasomes activate caspase-1 and induce secretion of pro-IL-1β, pro-IL-18, and gasdermin D. Caspase-1 cleaves them and produce IL-1β, IL-18, and gasdermin D N-terminal domain, which further activates the pyroptosis process (Fig. 1) (Lamkanfi and Dixit 2014; Shi et al. 2017). IL-1β and IL-18 have a vital role in CNS infections, cell death, brain injury, and neurodegenerative disease. Higher concentrations of IL-1β, IL-18 are observed in various neurodegenerative disorders (Broz and Dixit 2016).

Neuroinflammation-associated neuronal degeneration is a significant event in many neuronal disorders like- AD, PD, HD, TBI, SCI, etc. There is an increased expression of inflammasome markers like apoptosis-related speck-like protein containing a CARD (ASC), caspase 1, NLRP1, and NLRP3 levels in the CSF of patients (Wallisch et al. 2017). There is a steep increase in IL-1β levels initially during the disease development, whereas IL-18 levels gradually increased over several days. Thus, suggesting possible involvement of IL- 1β at early stages, while IL-18 might be involved in later stages of disease progression (Yatsiv et al. 2002). In spinal cord injury, higher levels of NLRP1, ASC, caspase1, IL-1β, and IL-18 are responsible for inflammasome activation and disease progression (de Rivero Vaccari et al. 2008).

The deposition of misfolded Aβ plaque is the main reason for AD development. Along with this, high expression of IL-1β in the microglia cells surrounding Aβ plaques was observed in AD patients (Simard et al. 2006). Also, high levels of inflammasome markers such as NLRP3, ASC-1, NLRC4, caspase 1, caspase 5, and cytokines IL-1β, IL-18 were reported in AD patients (Saresella et al. 2016). ALS, another fatal neurodegenerative disease, is associated with inflammasomes activation. NLRP3, ASC-1, NLRC4, caspase 1, and IL-18 levels increased in ALS patients (Gugliandolo et al. 2018). The pathology of this disease was proven to be driven by IL-18 or by DAMPs via pyroptosis (Maier et al. 2015). Higher expression of IL- 1β and NLRP3 is also associated with Parkinson's disease. The pathology of PD is driven by progressive death of dopaminergic neurons in substantia nigra induced by IL- 1β and NLRP3 inflammasome activation (Ferrari et al. 2006; Mouton-Liger et al. 2018). HD has also been associated with higher expression of inflammasome, while treatment with caspase 1/3 inhibitor (tetracycline-derived minocycline) showed a delay in HD patients' disease progression (Voet et al. 2019).

HMGB1 proteins in neuroinflammation

HMGB1, a DAMP family protein, is a highly abundant protein released upon inflammasome activation by glial cells and neurons (Ravizza et al. 2018). They activate receptors for advanced glycine and end products (RAGE) and TLR4 on target cells. Thus, the HMGB1/TLR4/RAGE signaling axis plays an essential role in initiating neuroinflammation (Paudel et al. 2018).

During brain injury, HMGB1 acts as an inflammatory cytokine in case of brain injuries (Richard et al. 2017; Aucott et al. 2018). DAMPs influence synaptic organization and function within the hippocampus and might initiate epileptogenesis (Ravizza et al. 2018). It has been reported that immediately after neuronal injury, the amount of HMGB1 in the neuronal extracellular space gets increased several folds (Scaffidi et al. 2002).

HMGB1 may interact with numerous receptors (RAGE, TLR2/4/9, integrin, a-synuclein filaments, proteoglycans, T-cell immunoglobulin, TIM-3, TREM1, CD-24, etc.), present on extracellular domain (Kang et al. 2014). Among these receptors, RAGE and TLR4 play the leading role in the pathology of neuronal diseases via initiation of NF-κB mediated inflammatory cascade (Bianchi and Manfredi 2007). The role of HMGB1 within the growth and ailment of CNS has been well explained (Fang et al. 2012). At the site of neuronal injury, the released HMGB1 may get partially oxidized to give disulfide form of HMGB1 which further activate TLR/NF-κB mediated inflammatory cascade and generates free radicals leading to BBB damage and functional impairments (Gu et al. 2014; Paudel et al. 2018). Thus, HMGB1/TLR4/RAGE/NF-κB cell signaling activation causes neuroinflammation, hyperexcitability in neurons, development of seizures and neurodegeneration.

Mitochondrial dysfunction and oxidative stress in neuroinflammation

Mitochondria is a vital cell organelle that produces the energy required for almost all types of biological functions. Mitochondrial dysfunction can cause energy imbalances inside the cell, which leads to inflammation and cell death. There are several factors which induce mitochondrial damage.

The redox imbalance is one of the main reasons for mitochondrial damage. Oxidative stress refers to an imbalance favoring the development of ROS over antioxidant defenses factors. The generation of ROS (superoxide anions and hydrogen peroxide) is a result of electron transport system via mitochondrial oxidative phosphorylation (OXPHOS) complexes (H_2O_2). ROS are essential mediator of redox-sensitive signaling pathways, and may lead to oxidative damage to protein, lipids, and nucleic acids (West and Shadel 2017). Complex I/III of the OXPHOS chain are the most favourable sites of mitochondrial ROS processing (Chrysostomou et al. 2013). Oxidative stress is caused by interruption in one or more fuctions of mitochondria leading to increased mitochondrial membrane permeability resuting in lipid peroxidation, apoptosis and neuronal death (Kanamori et al. 2010; Karumuri et al. 2019; Quamar et al. 2019; Maan et al. 2020; Mandal et al. 2020a; Mandal et al. 2020b; Jaiswal et al. 2020).

Another consequence of oxidative stress is the accumulation of neurotoxic glutamate levels which may initiate autophagy (Lin and Kuang 2014). Deprivation of oxygen and nutrient makes the retinal ganglionic cells energy-deficient, which further dramatically increases ROS level. This rise is due to slower electron transport in the OXPHOS,

which increases the reduction state of electron carriers and favors superoxide production at low oxygen levels (Chidlow et al. 2017). Abnormal cellular calcium influx also has been related to oxidative stress (Guo et al. 2013). Extensive genome-wide association studies (GWAS) have established susceptibility loci linked to mitochondrial dysfunction with mixed results (Van Bergen et al. 2015). Polymorphism in thioredoxin reductase 2, a mitochondrial protein necessary for redox homeostasis, is one example (Bailey et al. 2016). Mitophagy dysfunction is also a cause of mitochondrial disfunction, which leads to neuroinflammation. Mitophagy is the mechanism by which the autophagy system degrades damaged mitochondria. This process is essential for clearing debris and aggregating proteins from cells, shielding them from potentially harmful proteins. Association of PINK1 and Parkin activity helps recognize damaged mitochondria (Wu et al. 2015). Thus, defects in PINK1 and Parkin can cause impairment in mitophagy and cease inflammation.

As a result of mitochondrial dysfunction, mitochondrial membrane damage leads to release of DAMPs which initiates multiple inflammatory cascades resulting in chronic inflammation. These mitochondrial DAMPs are recognized by microglial PRRs which further activate TLR/ NF-κB inflammatory pathway promoting release of pro-inflammatory cytokines and chemokines. The inflammation caused by mitochondrial DAMPs can further lead to mitochondrial dysfunction and exacerbating the inflammatory cycle (Tezel and Wax 2000; Duarte 2021).

When PRRs recognize stress products like mitochondrial DAMPs like TLRs, TNF receptors, and inflammasomes, unique pathways involving NF-κB cascades are activated. One of the most important regulators of inflammatory immune responses is NF-κB. TLRs stimulate downstream transcription factors MyD88/TRIF. Various ligands may interaction with PRRs including TNF-α, IL-1, IL-6, and variety of chemokines (CCL2, CXCL1, and CXCL10) (Glass et al. 2010). The NOD-like receptors, which form protein complexes known as inflammasomes, are another group of PRRs that can modulate the microglial inflammatory response. The maturation and release of cytokines like IL-1 and IL-18 can be triggered by cooperative downstream cross-talks between TLRs and NOD-like receptors (Gurung et al. 2015).

Mitochondria can cause activation of inflammasome signaling directly. ROS generated by mitochondria or DAMPs activates the NLRP3 inflammasome pathway (Liu et al. 2018). Activated NLRP3 is further redistributed to membranes of nucleus and mitochondrial, where it conjugates with ASC and procaspase-1 and develops into NLRP3 inflammasome (Gurung et al. 2015). NLRP3 is usually associated with the endoplasmic reticulum membrane. Activated NLRP3 inflammasome results in caspase-1-dependent conversion of pro-IL1β/ pro-IL-18 into active IL-1β/ IL-18 and

initiates inflammation meaditated cell death known as pyroptosis (Liu et al. 2018). The NLRP3 inflammasome senses mitochondrial dysfunction and blockade of mitophagy.

The activation of TLR/NLRP3/MyD88.NF-κB pathway leads to generation of cytokine storm. When NF-κB is activated, the IL-1 cytokine family is produced, which amplifies inflammatory signal manyfolds by inducing a progressive release of pro-inflammatory cytokines in astrocytes and microglia (Yang et al. 2011). TNF-α production is markedly increased in mitochondrial disfunction, indicating a pro-inflammatory imbalance. TNF-α release can impair the function of mitochondrial components, reduce ATP content, increase ROS, and depolarize the mitochondrial membrane potential, all of which can affect mitochondrial function. Increased ROS may then have even more negative consequences by keeping NF-κB activated and producing pro-inflammatory signaling. Thus, the activation of neuroinflammation may negatively impact mitochondrial function, resulting in a vicious cycle (Wilkins et al. 2017). The complement system is also activated in mitochondrial disfunction, which leads to induction in the production of pro-inflammatory factors like IL-1β and TNF-α. It augments the release of mtDAMPs from mitochondria, thus, causing Neuroinflammation (Duarte 2021).

Autophagy in neuroinflammation

Autophagy is a biological process of degradation of cellular proteins and organelles inside the lysozyme in multicellular organisms. The damaged organelles and proteins are incorporated inside a membrane structure, known as an autophagosome. This autophagosome then binds to the lysozymes and results in the degradation of cellular organelles. There are mainly three types of autophagy, macroautophagy, microautophagy, and chaperone-mediated autophagy (Trempe and Fon 2013). Macroautophagy (also known as autophagy) is a conserved eukaryotic cell pathway that allows for the bulk degradation of cytoplasmic components. The goal components are kept apart from the rest of the system by an autophagosome (Glick et al. 2010).

Autophagy machinery consists of various steps, including initiation, elongation, and maturation of autophagic vesicles and ultimately fusion with lysosomes to form an autolysosome (Alavian et al. 2011). The procedure entails ULK complexes with ATG1, ATG13, ATG17, and ATG9, regulatory class III PI3 kinase complexes with beclin-1 (ATG6), and ATG5-ATG12-ATG16 multimerization complexes are formed de novo. ATG9, a transmembrane protein required for lipidation of phagophore membrane, is recruited by the ATG1-ATG13 complex (Ravikumar et al. 2010). Depending on the interaction ligands, the PI3 kinase-beclin1 complex may activate or suppress the autophagy and further engage other ATG proteins necessary for phagosome growth.

When ultraviolet radiation absorption group (UVRAG) is combined with activating molecule in beclin-1-regulated autophagy (AMBRA) and ATG14, it promotes autophagy by interacting with the beclin-1 complex (Ghavami et al. 2014). On the other hand, UVRAG complexed with RUN domain and cysteine-rich domain-containing (RUBICON) interaction, on the other side, inhibits autophagy (Ghavami et al. 2014).

At the endoplasmic reticulum, Bcl2 releases beclin-1 which forms a complex with UVRAG/AMBRA, and initiates the development of the multimeric complex (ATG5-ATG12-ATG16) (Glick et al. 2010). The LC3bII, a lipidated product of LC3bI (ATG8), is cleaved by ATG4 and further complexed with phosphatidylethanolamine unevenly on both sides of the membrane ATG9 of the ULK complex, and then incorporated into the initiating membrane (Ghavami et al. 2012). During elongation and development of autophagosomes, around the selected complex for degradation, the membrane of mitochondria, and endoplasmic reticulum, are recruited (Ghavami et al. 2014). The release of LC3bII from the exterior membrane surface signifies the completion of the autophagosome. As a result, LC3bII appears as a standard marker for autophagic flux monitoring (Glick et al. 2010). The newly developed autophagosome merges with the lysosome and turn into autophagolysosome. The momentary formation of amphisomes offers the requisite pH for proper lysosomal protease activity. The merger of lysosome and autophagosome is mediated through cytoskeletal microtubules which helps transferring autophagosomes to various lysosomal membrane proteins (Atlashkin et al. 2003; Lee et al. 2007).

Neuroinflammation has been a common feature in almost all lysosomal storage diseases with a neurological component (Farfel-Becker et al. 2011). Autophagy is essential in the regulation of inflammation and immunity. Autophagy selectively degraded catalase, resulting in ROS generation and macrophage non-apoptotic death (Yu et al. 2006). As a result, therapeutic strategies targeting autophagy mediated inhibition of neuroinflammation may be helpful in the quest to develop a novel target for the management of neurodegenerative diseases. Neuroinflammation and oxidative stress have been implicated in the development of AD. They are interested in the advancement of cognitive destruction in AD because they can promote Aβ and neurofibrillary tangles (NFT) development and thus contribute to progressive cognitive decline in AD (Cai et al. 2013; Guan et al. 2018). Rapamycin, autophagy inducer, has shown improvement in learning and memory via reduction in Aβ,tau aggregation, oxidative stress, and neuroinflammation signaling cascades (Liu et al. 2013; Ji et al. 2018).

Neurotransmitters in neuroinflammation

Glutamate, most abundant excitatory neurotransmitter in CNS, is known to play a vital role in astrocyte activation (Perea et al.

2009). Excitatory amino acid transporters (EAATs) present on neuron and astrocyte cells maintain the glutamate release (Bak et al. 2006). Astrocytes maintain the glutamate level in the synaptic cleft by Glutamate Aspartate Transporter (GLAST), and the excess glutamate is primarily regulated by GLU transporters on astrocytes (Chaudhry et al. 2002). Animal studies suggested that knockdown of GLAST results in increased expression of glutamate in the synaptic cleft, which activates the astrocyte cell to maintain the glutamate levels by GLU transporters (Danbolt 2001). This astrocyte activation plays a central role in the neuroinflammation process. Further, glutamate toxicity leads to increased expression of inflammatory markers, microglial activation in the brain leading to neuroinflammation (Boka et al. 1994; Tsai et al. 2012).

Recent studies suggested that peripheral and central neuroinflammation is associated with an altered GABAergic system (Montoliu et al. 2015; Dadsetan et al. 2016). This study indicated an increased expression of GABA transporter GAT-3 in the cerebellum of rats having neuroinflammation. Also, there was an increase in the extracellular GABA concentration in the cerebellum. This increased GAT-3 and GABA expression lead to neuroinflammation and motor disfunction in the rats. However, the neuroinflammation gets reversed when the expression of GAT-3 and GABA gets normalized (Dadsetan et al. 2016).

Dopamine is associated with cytokine production. Decrease dopamine release leads to increase cytokine production, thus, results in neuroinflammation (Abd Wahab et al. 2019). Serotonin (5-HT) plays an essential role in innate and adaptive immunity and modulates neuroinflammation process. 5-HT can trigger the lymphocyte and monocytes and impact cytokines' secretion (Dürk et al. 2005). They modulate the release of IL-1β, IL-6, IL-8/CXCL8, IL-12p40, and TNF- α. Activation of the 5-HT$_3$ receptor upregulates IL-1β, IL-6, IL-8/CXCL8 cytokines, which leads to Neuroinflammation (Dürk et al. 2005). In contrast, activation of 5-HT$_{2A}$ has been reported to inhibit TNF-α release and cause reduction of Neuroinflammation (Vanover et al. 2008). The expression of 5-HT$_{2B}$ receptor has been widely recognized in microglia cells which play an essential role in their activation and proliferation, resulting in Neuroinflammation (Kolodziejczak et al. 2015).

Role of neuroinflammation in various neurological diseases

Given chronic neuroinflammation, anti-inflammatory medications in neurological diseases have shown efficacy with varying observations in clinical investigations. Non-steroidal anti-inflammatory drugs (NSAIDs) have been found to inhibit prostaglandin synthesis by inhibiting the COX-2 enzyme. On the other hand, they have also been found to regulate mitochondrial calcium homeostasis. PPARs,

inflammasome, HMGB1, and thus might limit the disease progression. Neuroinflammation in the pathogenesis of AD, PD, epilepsy, and miscellaneous neurological conditions has been elaborated.

Neuroinflammation in Alzheimer's disease

AD is one of the highly prevalent chronic neurodegenerative disorders, contributing around 60–70% of dementia worldwide. According to prevailing amyloid and tau cascade hypotheses, the accumulation of Aβ deposits and neurofibrillary tangle containing hyperphosphorylated Tau in the brain initiates the cellular events in AD (Leng and Edison 2021; Cummings 2021).

AD is characterized by an intracellular deposition of NFTs, extracellular deposition of Aβ plague, and microglial activation. NFTs are paired helical filaments made up of hyperphosphorylated tau proteins, and Aβ is derived from Amyloid precursor proteins (APP) by the action of β and γ secretase. Beta-site APP cleaving enzyme 1 (BACE1) is one major β-secretase enzyme found in the human brain (Webers et al. 2020). There are mainly two types of Aβ proteins $Aβ_{1-40}$ and $Aβ_{1-42}$, containing 40 and 42 amino acid residues. Among these two types, $Aβ_{1-42}$ is more amyloidogenic and tends to aggregate to form Aβ plague. The Aβ plagues are cleared by microglia cells. Microglia cells remove the Aβ aggregates by uptake, local degradation, or degradation by releasing a neprilysin enzyme. So, there is a delicate balance between the removal and synthetic pathways of Aβ proteins (Webers et al. 2020). Disruption of this balance by neuronal insult or overproduction leads to aggregation of Aβ proteins and formation of plaques in the extracellular compartment in the brain. A wide variety of receptors, like the different toll-like receptors (TLR4 and TLR6) and the NACHT, LRR, CD36, and pyrin-protein-containing (NLRP3) domains, are resent in microglia, which can bind to Aβ. They are stimulated by DAMPs, including adenosine triphosphate (Calsolaro and Edison 2016; Rivers-Auty et al. 2020). When Aβ binds to CD36, TLR4, or TLR6 receptors, microglia get activated, and proinflammatory cytokines and chemokines are produced. The cytokines released by the activation of microglia cells are mainly TNF-α and IL-1β (Kaur et al. 2019). TNF-α binds to the TNF receptor on the cell membrane, induces the extrinsic pathway of apoptosis. Extracellular Aβ can stimulate pro-inflammatory gene expression by activation of the MAPK/NF-kB pathway (Solito and Sastre 2012).

Aβ can also induce NADPH oxidase-mediated priming in microglial cells, leading to generation of ROS. Production of ROS leads to increased oxidative stress and mitochondrial dysfunction (Simpson and Oliver 2020). This mitochondrial dysfunction increased the cell membrane permeability of mitochondria and leads to the secretion of mitochondrial DAMPs, and cytochrome-c. Mitochondrial DAMPs leads to activation of NF-kB, which promotes the development of pro-inflammatory cytokines and chemokines (pro-IL-1 and TNF-α). The release of cytochrome-c further initiates the apoptosis cascade (Duarte 2021). Microglia can also interact with astrocytes to activate them. Although TNF-α and IL-1β can also directly stimulate and activate astrocytes. Activation of astrocytes leads to the formation of iNOS, thus can cause prolonged neuroinflammation. The C-terminal 100 amino acid of bAPP in Aβ plaques can cause astrogliosis and neurodegeneration in the existence of amyloid pathology (Tiwari et al. 2019).

Aβ itself can initiate a cascade of relations which leads to cytokine release and neuroinflammation. Aβ induces the release of various pro-inflammatory cytokines like IL-1α, IL-1β, IL-6, and TNF-α. Aβ sensitizes astrocytes and microglia cells to secrete IL-1, which influences the production of Aβ plagues. Thus, by this mechanism, Aβ induces its own production several-folds resulting in intensified cytokine mediated neuroinflammation. IL-1β induces astrogliosis in Aβ treated astrocytes by activating IL-1R. The IL-1β was primarily triggered by astrocytes APP and neurotoxic Aβ manufacturing by neurons.IL-1β also activates astrocytes and microglia cells and induces them to secrete various pro-inflammatory cytokines like- IL-1β, IL-6, and IL-18. IL-1β shows cell-specific activity; like in glia cells, IL-1β activates the NF-kβ mediated cytokine production. It stimulates the cascading mitogen-activated protein kinases (MAPK)-p38, enhances the secreted APP fragment clamped with BACE1 (Sawikr et al. 2017). IL-6, synthesized by astrocytes, microglia, neuron, and endothelial, on the other hand, increased IL-1β mediated inflammatory response, and elevated IL-6 mRNA concentration was found in the brain of AD patients (Fernandes et al. 2017).

Tau protein is also one of the significant drivers of AD pathogenesis. Tau corresponds to the microtube-associated protein (MAP) family and is mainly expressed in axon-preferred neurons. Hyperpolarization of tau protein is associated with the prognosis of AD. IL-1β can cause tau protein phosphorylation and NFT creation via the MAPK-p38 pathway. The neuronal hyperphosphorylation of Tau protein, is engaged in the IL-1β-induced up-regulation of MAPK-p38. in AD, hyperphosphorylated Tau exists in coupled helical filaments, dystrophic neuritis, and NFTs. This finding demonstrated a loss of axonal integrity as well as a decrease in synapse connection, which is the reason for dementia in AD. AD observes a loss of synaptophysin in triangular neurons, and the activated microglia correlates with the neuronal disease (Laurent et al. 2018). The anti-inflammatory approaches targeting neuroinflammation have been bolstered by several preclinical findings listed in Table 1.

Table 1 Experimental evidences suggesting role of anti-inflammatory agents in Alzheimer's disease

Sr. No	Anti-inflammatory agent (dose; route)	Experimental model	Animal/Cell lines	Standard drug	Outcome	References
1	Dexpanthenol (1000 mg/kg/day, i.p.) for 3 weeks	STZ induced sporadic AD animal model	Sprague–Dawley rats	–	Neuroprotection in hippocampus, and reduction in cholinergic deficiency and neuroinflammation	Erdogan et al. (2021)
2	Linalool (50 and 100 mg/kg, i.p.) for 21 days	Aβ induced animal model of AD	Sprague–Dawley rats (260–280 g)	–	Neuroprotective effect via reducing oxidative stress and neuroinflammation	Yuan et al. (2021)
3	Kaempferol (10 mg/kg, i.p.) for 21 days	STZ induced sporadic AD animal model	Wistar rats	–	Improvement in acquisition and retrieval of spatial memory via mitigating oxidative stress and neuroinflammation	Babaei et al. (2021)
4	Alirocumab (4, 8 and 16 mg/kg/week)	High-fat-cholesterol-diet – induced-AD-like condition	Wistar Rats	–	Amelioration of cognitive deficit, cholesterol hemostasis and reduction of neuro-inflammation via inhibition of HMGB1/RAGE/TLR4 axis	Abuelezz and Hendawy (2021)
5	Crocin (50, 100 mg/kg, i.p.) for 4 weeks	LPS-induced neuroinflammation and memory impairments in a rat model	Male Wistar rats (220–250 g)	–	Improvement in spatial memory impairment via mitigating oxidative stress and neuroinflammation	Azmand and Rajaei (2021)
6	Betalain (10, 20 mg/kg, p.o.) for 4 weeks	AlCl₃ induced rat model of AD	Sprague Dawley (SD) rats (7–9 weeks, 170–190 g)	–	Attenuation of learning and memory impairment, suppression of oxidative stress via inhibition of AchE, Na⁺/K⁺ ATPase, NF-κB expression	Shunan et al. (2021)
7	OLT1177 (3.75, 7.5 g/kg, in feed pallet) for 3 months	Transgenic mouse model of AD	Male C57BL/6 J WT mice and APP/PS1 ΔE9 mice (6 months)	–	Improvement in memory function, reduction in plaques, and neuroinflammtion by inhibiting NLRP3 inflammasome	Lonnemann et al. (2020)
8	Sinapic Acid (20 mg/kg, p.o.) for 3 weeks	STZ induced sporadic AD animal model	Male Wistar rats		Improvement in cognitive impairment and neuroprotection via alleviating oxidative stress, neuroinflammation and cholinergic dysfunction	Verma et al. (2020)

Table 1 (continued)

Sr. No	Anti-inflammatory agent (dose; route)	Experimental model	Animal/Cell lines	Standard drug	Outcome	References
9	Baicalein, Wogonin, Oroxylin A (10, 50, or 100 μM)	$A\beta_{25-35}$ induced neurotoxicity	PC-12 cell lines	—	Neuroprotection via inhibition of apoptosis and neuroinflammation through downregulating NF-κB/MAPK pathway	Ji et al. (2020)
10	Benfotiamine (150 mg/kg, p.o.) for 30 days	STZ induced sporadic AD animal model	Male Wistar rats (~350 g)	—	Improvement of cognitive deficit, mitochondria enzymes and insulin signaling pathway, with inactivation of GSK3α/β and ERK1/2 and reduced neuroinflammation	Moraes et al. (2020)
11	Cotinine and 6-Hydroxy-L-Nicotine (0.3 mg/kg, i.p.) for 33 days	$A\beta_{25-35}$ induced animal model of AD	Male Wistar rats (350±10 g, 4–5 months)	Donepezil (5 mg/kg, i.p.)	Improvement in memory deficit via modulation of *BDNF*, arc and *IL-1β* gene expression	Boiangiu et al. (2020)
12	Miconazole (40 mg/kg, i.p.) for 7 days	LPS-induced neuroinflammation and memory impairments in a rat model	Male C57BL6/N mice (20–25 g, 8 week)	—	Attenuation of cognitive impairment via mitigating neuroinflammation	Yeo et al. (2020)
13	Celecoxib (1–10 μM)	$A\beta_{1-42}$ induced neurotoxicity	SH-SY5Y neuroblastoma cells	—	Neuroprotective effect via effectors of downstream of HO-1 activation (carbon monoxide, and bilirubin)	Mhillaj et al. (2020)
14	Oxymatrine (40 mg/kg, i.p.) for 8 week	Transgenic mouse model of AD	Male hAPP transgenic mice (8 months)	—	Reduction in Aβ plaques density, and proinflammatory cytokines	Chen et al. (2019)
15	Etodolac and α-tocopherol (10 mg/kg, i.p./drinking water) for 1 month	Transgenic mouse model of AD	Female 5XFAD mice (4 months)	—	Improved BBB integrity, and reduced Aβ load, oxidative stress and neuroinflammation	Elfakhri et al. (2019)
16	Adalimumab (1 mg/kg; i.p.) for 3 weeks	$A\beta_{1-42}$ induced animal model of AD	Male ICR mice (30–35 g, 7 weeks)	—	Improvement in memory impairment, attenuation of neuronal damage, BDNF expression and neuroinflammation, BACE-1 expression via inhibition of NF-κB/TNF-α, IL-6	Park et al. (2019)
17	Celecoxib (15 mg/kg, s.c.) for 8 days	sAβ induced animal model of AD	Male Wistar rats (275–300 g)	—	Prevention of behavioral dysfunction, and neuroprotection via COX-2 inhibition and elevation of NA and BDNF	Mhillaj et al. (2018)

Table 1 (continued)

Sr. No	Anti-inflammatory agent (dose; route)	Experimental model	Animal/Cell lines	Standard drug	Outcome	References
18	Ibuprofen (375 ppm) in chow pallet for 5 month	Transgenic mouse model of AD	Male APP/PS1 mice (15–25 g)	–	Reduction in Aβ plaques, via inhibiting neuroinflammation	Zhang et al. (2018)
19	JC-124 (50 mg/kg, i.p., 5 times a week) for 4 weeks	Transgenic mouse model of AD	CRND8 mice (9 months)	–	Reduction in Aβ deposition, reduced in microglia activation, oxidative stress, neuroinflammation by NLRP3 inhibition	Yin et al. (2018)
20	Xamoterol (6 mg/kg, p.o., 5 times a week) from 4–6.5 months of age	Transgenic mouse model of AD	Male 5XFAD mice (3 months)	–	Reduction amyloid and tau pathology, via reduction of neuroinflammation	Ardestani et al. (2017)
21	Punicalagin (1.5 mg/kg, through drinking water) for 4 week	LPS induced neuroinflammation and AD in mouse	Male ICR mice (10 weeks)	–	Suppression of iNOS/COX-2, neuroinflammation, and downregulation of APP/ BACE-1 via direct inhibition of NF-κB	Kim et al. (2017)
22	Curcumin (25, 50, 100 mg/ kg, p.o.) for 30 days	STZ induced sporadic AD animal model	Male Wistar rats (300–340 g)	–	Prevention of recognition memory deficit, improvement in neuroinflammation and hippocampal/ subventricular neurogenesis	Bassani et al. (2017)
23	Glycyrrhizin (30 mg/kg, p.o.) for 3 days	Splenectomy induced cognitive Impairment in Aged Mice	Male C57BL mice (9 and 18 months)	–	Reduction of postoperative neuroinflammation via HMGB1 inhibition	Kong et al. (2017)
24	Minocycline (50 mg/kg p.o.) for 17 days	Aβ$_{1-42}$ induced animal model of AD	Male BALB/c mice (30–40 g, 100 days)	–	Improvement in spatial memory impairment and proinflammatory cytokines	Garcez et al. (2017)
25	Mefenamic acid (25 mg/kg, intracranially) for 28 days	Transgenic mouse model of AD	Male 3xTgAD mice (13–14 months)	–	Neuroprotective effect via inhibition of inhibiton of NLRP3 inflammasome	Daniels et al. (2016)
26	Valdecoxib (5, 10 mg/kg, i.p.), Zafirlukast (15 and 30 mg/kg, i.p.) for 21 days	Aβ induced animal model of AD	Male Wistar rats (230–250 g)	–	Improvement in cognitive function, reduction in oxidative stress and neuroinflammation via inhibition of COX/LOX pathway	Kalra et al. (2016)
27	Thalidomide (50 mg/kg/day, i.p. for 21 days), Etanercept (0.3 mg/kg ICV), Infliximab (5 mg/kg ICV)	STZ induced sporadic AD animal model	Male Sprague Dawley rats (250–300 g)	–	Improvement in spatial and fear based memory deficit	Kübra Elçioğlu et al. (2015)

Table 1 (continued)

Sr. No	Anti-inflammatory agent (dose; route)	Experimental model	Animal/Cell lines	Standard drug	Outcome	References
28	Lycopene (1, 2, 4 mg/kg, p.o.) for 14 days	Aβ$_{1-42}$ induced animal model of AD	Male Wistar rats (200–230 g)	–	Improvement in memory function, and reduction in neuroinflammation (TNF-α, IL-1β, TGF-β, NF-κB) and apoptosis (caspase-3)	Sachdeva and Chopra (2015)
29	Neproxane (5, 10 and 20 mg/kg, p.o) for 15 days	Colchicine induced Rat Model of AD	Male Charles Foster Rat (200–250 g)	–	Reduced in number of plaques via inhibition of COX-induced neuroinflammation	Sil et al. (2014)
30	Thalidomide (100 mg/kg, i.p.) for 3 days	Transgenic mouse model of AD	APP23 transgenic mice and C57BL/6 mice	–	Reduction in activation of astrocytes/microglia, Aβ load and BACE-1 and neuroinflammation	He et al. (2013)
31	Ibuprofen (50 mg/kg, osmotic pump) for 4 weeks	Transgenic mouse model of AD	Male APP23 mice (6 weeks)	–	Improvement in spatial memory performance	Van Dam et al. (2010)
32	Naproxane/ Ibuprofen (375 ppm) in chow pallet for 6 month	Transgenic mouse model of AD	Male and female R1.40 mice (3–6 months)	–	Blockade od neuronal CCEs and alterations in brain microglia without altering APP	Varvel et al. (2009)
33	Curcumin (83 mg/kg, through diet) for 4 month	Transgenic mouse model of AD	Tg2576 moue (3–4 months)	–	Reduction of plaque, amyloid burden, and neuroinflammation	Begum et al. (2008)
34	Ibuprofen (375 ppm) in chow pallet for 6 month	Transgenic mouse model of AD	huAPPsw (Tg2576) mice (10 months)	–	amyloid reduction via inhibition of neuroinflammation (IL-1β and its downstream target ACT)	Morihara et al. (2005)
35	Indomethacin (10 mg/L) in drinking water for 7 months	Transgenic mouse model of AD	Tg 2576 mice (8 months)	–	Reduction in amyloid burden and amyloidopathy via inhibiting NF-κB signaling	Sung et al. (2004)

STZ: Streptozotocin; NA: Noradrenaline

Neuroinflammation in Parkinson's disease

PD is the second most common neurodegenerative disease majorly affecting the geriatric population and is characterized by various motor and non-motor symptoms. Major motor manifestations include bradykinesia, rigidity, and tremor, while these symptoms are preceded by premotor symptoms, including constipation, bladder disorders, hyposmia, autonomic dysfunction, depression, and sleep disorders (Angelopoulou et al. 2021; Hirsch and Standaert 2021; Mann et al. 2020).

The main characteristic of PD pathology is the accumulation of α-synuclein and neuroinflammation. The primary role of α-synuclein is to maintain synaptic vesicle dynamics, mitochondrial function, intracellular trafficking, and act as a chaperon. When soluble α-synuclein monomers start aggregating, it gives rise to large insoluble α-synuclein fibers and Lewy body formation (Rocha et al. 2018). Generally, the insoluble α-synuclein is removed from cells by majorly two pathways, ubiquitin–proteasome pathway and lysosomal autophagy system (LAS). LAS seems even more significant to concise oligomeric assemblies than the ubiquitin–proteasome system (Panicker et al. 2021). It has been proposed that LAS mediates α-synuclein degradation with chaperone-mediated autophagy as well as macroautophagy. Alteration of this process leads to the accumulation of α-synuclein inside the cell (Brás and Outeiro 2021).

Aggregation of α-synuclein fibers leads to the formation of toxic β-plated sheets, which ultimately leads to the formation of Lewy bodies. These β-plated sheets further block the LAS system, thus, induce the aggregation of α-synuclein. The appearance of β-plated sheets further increases the production of α-synuclein inside the cell (Poewe et al. 2017). This trans-synaptic transmission of β-plated sheets spreads the pathology to other unaffected cells.

Aggregation of toxic oligomers leads to mitochondrial dysfunction by inhibiting mitochondrial complex-I/III. This further leads to the downregulation of mitochondrial master transcriptional regulator, peroxisome proliferator-activated receptor-gamma coactivator 1-α (PGC-1α) (Das et al. 2021). The downregulation of PGC-1α leads to the genetiaon of ROS, further adding to more misfolding of α-synuclein and reduction in its proteolysis. In addition, oxidative stress increases the calcium ion influx into the cell, which leads to impaired calcium homeostasis. This imbalance leads to caspase activation and cell death via apoptosis (Bose and Beal 2016). Toxic oligomers can also activate microglia. Activated microglia then releases a pro-inflammatory cytokine (TNF-α, IL-1β), which can induce the inflammatory process in the brain. TNF-α then acts on the TNF receptor and activates the extrinsic pathway of apoptosis (Duarte 2021), resulting in neuronal cell death. Inflammation can also induce the misfolding of α-synuclein and can disturb

proteolysis of α-synuclein, thus influencing the whole cycle many-fold a lead to dopaminergic cell death (Poewe et al. 2017).

The activation of M1 type of microglia cells, various pro-inflammatory cytokines are released like- iNOS, IL-1β, IL-6, TNF-α, IFN-γ, C1q, IL-1α, and IL-1β (Janda et al. 2018). The release of these cytokines leads to inflammatory reactions inside the brain. Activated microglia then interacts with astrocytes and triggers them to produce pro-inflammatory factors. Furthermore, α-synuclein can also directly induce astrocytes and increase the production of pro-inflammatory cytokines and chemokines such as CCL2, CCL20, CXCL1, CX3CL1, IL-1β, IL-6, TNF-α (Miyazaki and Asanuma 2020). Overall, the release of these pro-inflammatory mediators results in the degeneration of dopaminergic neurons. Preclinical evidence supporting the role of various anti-inflammatory agents against the experimental model of PD has listed in Table 2.

Neuroinflammation in epilepsy

Epilepsy is one of the common neurological disorders characterized affecting around 70 million people worldwide with identified causes like acute brain injury (stroke, neurotrauma, tumor, and status epilepticus), chronic CNS infection, and metabolic altercations or idiopathic (Akyuz et al. 2021; Vezzani et al. 2019; Mishra and Goel 2016, 2019). Neuroinflammation has been conversed as one of the plausible pathogenmic feature in partial, generalized and refractory seizures (Vezzani et al. 2019; Vezzani 2020; Löscher et al. 2020; Terrone et al. 2020).

Neuroinflammation has been recorded in CNS before the onset of epilepsy in the human brain (Prabowo et al. 2013; Pauletti et al. 2019) and experimental models (Ravizza et al. 2008). In refractory epilepsy brain, activation of TORC1 pathway was associated with increased expression of inflammatory markers such as MHC-I/II, TLR-2/4 for advanced glycation end products (RAGE), IL-1β, HMGB1, and inducible nitric oxide synthase (iNOS) (Pauletti et al. 2019; Shi et al. 2017; Prabowo et al. 2013; Ravizza et al. 2008; Gorter et al. 2006; Turrin and Rivest 2004). These pro-inflammatory mediators cause BBB damage and recruit peripheral immune cells (Vezzani and Friedman 2011).

Systemic inflammatory cascade causing peripheral inflammation can contribute further to developing inflammatory mediators and the accumulation of leukocytes, neutrophils around the BBB (Rana and Musto 2018). Then leukocytes secrete chemokine CCL2 and inflammatory mediator IL-1β, which leads to upregulation of MMP9 (Bronisz and Kurkowska-Jastrzębska 2016). MMP-9 has different roles in the brain, from structural changes to inflammatory processes. Chronic MMP-9 levels lead to dilution and dendritic spine elongation, leading to morphological synapse

Table 2 Experimental evidences suggesting role of anti-inflammatory agents in Parkinson disease

Sr. No	Anti-inflammatory agent (dose; route)	Experimental Model	Animal	Standard drug	Outcome	References
1	DA-CH5 (10 nmol/kg; i.p.) for 30 days	6-OHDA induced rat model of PD	Male Sprague–Dawley rats (220–250 g, 8 weeks)	–	Prevention of dopaminergic neuronal loss in SNpc, reduction of α-synuclein and proinflammatory cytokines	Zhang et al. (2021)
2	Camptothecin (1 mg/kg, p.o.) for 24 days	LPS induced PD mouse model	Male C57BL/6 mice (25–30 g)	–	Neuroprotection by regulating microglia polarization via activating AKT/Nrf2/HO-1 and inhibiting NF-kB pathways	He et al. (2021)
3	Indole-3-Carbinol (12.5, 25 and 50 mg/kg, p.o.) for 21 days	LPS induced PD model	Male Wistar rats (220–280 g)	Levodopa: Carbidopa (25:2.5 mg/kg i.p. twice a day) for 21 days	Reduced motor and memory impairment via alleviating oxidative stress neuro-inflammation (NF-κB inhibition)	Saini et al. (2020)
4	Estradiol benzoate (100 µg) at 48 h for 11 days	MPP+ induced rodent model of PD	Male Wistar rats (200 g)	–	Dopaminergic neuroprotection via reduction in proinflammatory cytokines	Aguirre-Vidal et al. (2020)
5	Dexrazoxane (10 mg/kg,i.p.) for 5 weeks	6-OHDA and MPTP induced rodent model of PD	Male Sprague–Dawley rats (180–220 g) and Mice (10 weeks)	L-DOPA (10 mg/kg)	Dopaminergic neuroprotection by suppression of oxidative stress, endoplasmic reticulum stress, and neuroinflammation	Mei et al. (2019)
6	Astragaloside IV (40 mg/kg, p.o.) for 7 days	MPTP induced rodent model of PD	Male C57BL/6 mice (8 week, 25–30 g)	–	Dopaminergic neuroprotection from oxidative stress and neuroinflammation	Yang et al. (2019)
7	Mulberrin (15, 30 mg/kg, p.o.) for 7 days	MPTP induced rodent model of PD	Male Sprague Dawley rats (~200 g)	–	Improvement in motor coordination by suppressing oxidative stress and neuroinflammation via promoting Wnt/β-catenin signaling	Cao et al. (2019)
8	Cordycepin (10, 20 mg/kg) for 15 days	MPTP induced rodent model of PD	Male Sprague–Dawley rats (~200 g, 5–7 weeks)	–	Reduction of dopaminergic neuronal loss via inhibiting TLR/NF-κB signaling pathway	Cheng and Zhu (2019)
9	Atorvastatin n (10 mg/kg, p.o.) for 7 days	MPTP induced rodent model of PD	Male Wistar rats (300–350 g, 4 months)	–	Dopaminergic neuroprotection in striatal region via modulation of oxidative and inflammatory responses	Marques et al. (2018)

Table 2 (continued)

Sr. No	Anti-inflammatory agent (dose; route)	Experimental Model	Animal	Standard drug	Outcome	References
10	Epigallocatechin-3-gallate (25, 50 mg/kg, p.o.) for 20 days	MPTP induced rodent model of PD	C57BL/6 J mice (16–25 g, 6–8 weeks)	–	Dopaminergic neuroprotection in SNpc by reduction in peripheral inflammatory factors (TNF-α, IL-1β)	Zhou et al. (2018)
11	Tangeretin (50, 100 or 200 mg/kg, p.o.) for 20 days	MPTP induced rodent model of PD	Male Sprague–Dawley rats (320–380 g, 10–12 weeks)	–	Reduction in motor and cognitive impairment and dopaminergic neurodegeneration via reducing expression of pro-inflammatory cytokines	Yang et al. (2017)
12	Paeonol (20 mg/kg, p.o.) for 21 days	MPTP induced rodent model of PD	Male C57BL/6 mice (18–20 g)	–	Reduction in dopaminergic neurodegeneration via reduction of oxidative stress and neuroinflammation and elevating BDNF level	Shi et al. (2016)
13	Thiacremonone (10 mg/kg) in drinking water for 1 month	MPTP induced rodent model of PD	ICR mice (8 weeks)	–	Reduction of neurodegeneration and neuroinflammation through inhibition of p38 activation	Hwang et al. (2016)
14	Dimethylfumarate (50 mg/kg, p.o.) and monomethylfumarate (50 mg/kg, p.o.)	MPTP induced rodent model of PD	C57BL/6 mice and Nrf2 knock-out mice	–	Neuroprotection via Nrf2-mediated antioxidant, anti-inflammatory, and mitochondrial functional/biogenetic effects	Ahuja et al. (2016)
15	Morin (5 or 50 mg/kg, i.p.) for 12 days	MPTP induced rodent model of PD	Male C57BL/6 mice (18–21 g, 6 weeks)	–	Amelioration of motor dysfunction, dopaminergic neuronal loss via inhibiting astrocyte activation and neuroinflammation	Lee et al. (2016)
16	Clozapine N-oxide (1 mg/kg, s.c.) for 21 days	MPTP induced rodent model of PD	C57BL/6 J (gp91$^{phox+/+}$) and phagocytic NADPH oxidase (NOX2)-deficient (gp91$^{phox-/-}$) mice	–	Attenuation of dopaminergic neurodegeneration, motor deficits, and reactive microgliosis via inhibiting NOX-2 activation	Jiang et al. (2016)
17	PPARγ agonist MDG548 (2, 5 or 10 mg/kg i.p.) for 4 days	MPTP induced rodent model of PD	Male C57BL/6 J mice (3 months)	–	Reduction of dopaminergic neuronal loss in SNc, by inhibiting activated microglia and iNOS induction	Lecca et al. (2015)
18	DPTP (20 mg/kg, p.o.) for 7 days	MPTP induced rodent model of PD	Male C57BL/6 mice (6 weeks)	–	Amelioration of glial activation and behavioral impairments via inhibition of JNK/ERK/NF-κB pathway	Lim et al. (2015)

Table 2 (continued)

Sr. No	Anti-inflammatory agent (dose; route)	Experimental Model	Animal	Standard drug	Outcome	References
19	Tanshinone IIA (25 mg/kg, i.p.) for 6 days	MPTP induced rodent model of PD	Male C57BL/6 mice (25–30 g, 3–4 months)	–	Neuroprotection was associated with suppression of microglial activation and reduced expression of NADPH oxidase and iNOS	Ren et al. (2015)
20	α-Asarone (10 mg/kg, p.o.) for 15 days	MPTP induced rodent model of PD	Male C57BL/6 mice (25–28 g, 8–9 weeks)	–	Improvement in behavioral impairments by suppressing microglial activation and neuroinflammation	Kim et al. (2015)
21	Nobiletin (25, 50 mg/kg, i.p.) for 14 days	MPTP induced rodent model of PD	Male C57/BL6N mice (8–9 weeks)	–	Reduction in motor and cognitive impairment via enhancement of DA in striatum and hippocampus	Yabuki et al. (2014)
22	AL-1 (30, 60 or 120 mg/kg/day) for 14 days	MPTP induced rodent model of PD	Male C57BL/6 mice (20 ± 2 g, 6–8 weeks)	–	Protection of Dopaminergic neurons and neuroinflammtion in SN via inhibition of NF-κB	Zhang et al. (2014)
23	Fenofibrate (100 mg/kg, p.o.) for 21 days	MPTP induced rodent model of PD	Male Wistar rats (280–320 g)	–	Reduction in hypolocomotion, depression like behavior, by improving DA level and reducing oxidative stress	Barbiero et al. (2014)
24	S-allyl cysteine (120 mg/kg, i.p.) for 5 days	MPTP induced rodent model of PD	male C57BL/6 mice (25–30 g)	–	Dopaminergic neuroprotection via reducing oxidative stress via upregulation of Nrf-2 in SN	García et al. (2014)
25	6-shogaol (10 mg/kg, p.o.) for 3 days	MPTP induced rodent model of PD	Male C57BL/6 mice (22–23 g, 7 weeks)	–	Dopaminergic neuroprotection in SNpc and striatum via inhibition of f TNF-α, NO, iNOS, and COX-2	Park et al. (2013)
26	Atorvastatin (10 mg/kg, p.o.) for 7 days	MPTP induced rodent model of PD	Male Wistar rats (4 months, 300–350 g and 25–30 days)	–	Improvement in motor deficit via modulating neuroinflammation and NGF level in hippocampus and striatum	Castro et al. (2013)
27	Rosiglitazone (3 mg/kg, i.p.)	6-OHDA induced PD mode	Male Sprague–Dawley rats (225–250 g)	–	Reduction of dopaminergic neuronal loss by mitigating microglial activation in striatum via inhibition of COX-2 and TNF- expression	Lee et al. (2012)

Table 2 (continued)

Sr. No	Anti-inflammatory agent (dose; route)	Experimental Model	Animal	Standard drug	Outcome	References
28	Nimesulide (5 or 10 mg/kg, po) for 12 days	MPTP induced rodent model of PD	Male Wistar rats (250–300 g)	–	Recovery in behavioral impairment and neuroprotection by mitigating oxidative stress	Gupta et al. (2010)
29	Chunghyuldan (50 mg/kg, p.o.) for 5 days	MPT+ induced rodent model of PD	Male C57BL/ 6 mice (8 weeks)	–	Improvement in motor symptoms and reduction in dopaminergic neurodegeneration via inhibition of oxidative stress and mitochondrial dysfunction	Kim et al. (2010)
30	Rofecoxib (2–8 mg/kg, p.o.), Celecoxib (10–40 mg/kg, p.o.), Nimesulide (2.5–10 mg/kg, p.o.), Naproxen (7–20 mg/kg, p.o.)	Perphenazine-induced catatonia and MPTP induced rodent model of PD	Male Wistar rats (250–300 g)	–	Reduction in motor dysfunction by modulating dopaminergic neurotransmission and/or oxidative stress	Gupta et al. (2009)
31	Parecoxib (2 mg/kg) for 21 days	MPTP induced rodent model of PD	Male Wistar rats (280–320 g)	–	Reduction in motor and memory impairment, neuroprotective effect	Reksidler et al. (2007)
32	3-Hydroxymorphinan (12 or 24 mg/kg, i.p.) for 7 days	MPTP induced rodent model of PD	Male C57BL/6 J mice (25 ± 3 g)	–	Reduction in motor impairment and dopaminergic neuronal loss via inhibition in microgliosis	Zhang et al. (2006)

DPTP: 3-(3,4-Dihydroxy-phenyl)-2-[4-(3-trifluoromethylphenyl)phenyl)-but-2-enoylaminol)-propionic acid methyl ester, MPTP:, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, SN: Substantia Nigra

modifications and related to affected person plasticity of synaptic (Acar et al. 2015). In addition, MMP-9 weakens the BBB by destroying the tight junction interconnections directly. Thus, BBB becomes weak, which allows the migration of leucocytes by traffic cups. The elevated CD44, VCAM-1, and ICAM-1 levels support trans-endothelial migration of leucocytes through the BBB (Acar et al. 2015).

Albumins like serum proteins also infiltrate the loosened BBB and enter into the CNS. Albumin enhances the production of TGF-β1 via activation of astrocytes. This binding also activates the astrocytes and induces secretion of TGF-β1 and MMP9. Produced MMP9 further loosens the BBB, and TGF-β1 impairs the potassium glutamate buffer system inside the cells (Webster et al. 2017). TGF-β1 additionally induces excitatory synaptogenesis, thus helps in the development of hyperactivity of neurons. A pro-inflammatory, platelet-activating factor (PAF) is released from the postsynaptic neurons. PAF induces the per synaptic sites to release glutamine, and it also upregulates COX2 release from microglia and astrocytes by acting upon the PAF receptor present on them (Hammond et al. 2016; Guan and Wang 2019).

Microglia are activated by various cytokines present in the brain like TNF-α, IL-1β, and partly by PAF. Induction of COX2 mediated production of PGE2 level stimulates astrocytic glutamate causing hyperexcitability mediated neuronal death (Shimada et al. 2014). COX2 also upregulates various chemokines like CCL2 and CXCL12 in the brain, further weakening the BBB and stimulating TNF-α release from microglial cells (Sharma et al. 2019). The released TNF-α from microglia then induces neuroinflammation, cell death and upregulates AMPA receptors (Takeuchi et al. 2006; Galic et al. 2012). IL-1β upregulates NMDA receptor expression (Viviani et al. 2003) and reduces GABA$_A$ current (Roseti et al. 2015) results in ictogenesis. In addition, activation of TLR, present in astrocytes and microglia, induces the release of pro-inflammatory cytokines like TNF-α, IL-1β from microglial cells (Iori et al. 2017; Rana and Musto 2018; Li et al. 2021). IL-1β also induces the production of MMP-9 by upregulating its transcription (Bronisz and Kurkowska-Jastrzębska 2016). Thus, IL-1β plays a role in epileptogenesis and BBB damage. Activation of TLR3 potentiates TNF-α level and induces endocytosis of GABA receptors, leading to epileptogenesis (Rana and Musto 2018). Results of various anti-inflammatory agents supporting the protective effect against experimental models of epilepsy are listed in Table 3.

Limitations of anti-inflammatory approaches

Various anti-inflammatory approaches have illustrated neuroprotection against degenerating neurons in experimental models of AD, PD, and epilepsy by mitigating neuroinflammation, however clinical relevance of NSAIDs in neurological diseases appears conflicting. Summary of few clinical investigations exploring the role of anti-inflammatory agents in neurological disorders in clinical samples has been mentioned in Table 4.

Chronic treatment with selective/nonselective COX2 inhibitors in placebo-controlled clinical trials has suggested no protective effect on mild-moderate AD symptoms (Aisen et al. 2003; Reines et al. 2004). In addition, rofecoxib treatment has shown discouraging findings in patients with mild cognitive impairment reported in a secondary preventive study (Thal et al. 2005). Meanwhile, some preclinical investigations suggested the protective effect of NSAIDs and raised hope for futuristic clinical investigations (Varvel et al. 2009). However, randomized clinical trials have failed to corroborate these findings in AD patients (Ali et al. 2019). Anti-inflammatory agents have also exhibited protective effect in PD patients. A meta-analysis suggested pronounced protective effect of nonaspirin NSAIDs (ibuprofen) as compared to aspirin in PD patients (Gagne and Power 2010). In contrast, a recent meta-analysis suggested no association of NSAIDs and risk of PD (Poly et al. 2019). Overall, the clinical impact of anti-inflammatory agents (NSAIDs) remain ambiguous. In epilepsy, pre-clinical and clinical studies supported targeting the anti-inflammatory approach as a complementary approach for symptomatic treatment of recurrent seizures from conventional and refractory seizures (Radu et al. 2017). Till date only low dose aspirin had suggested protection against seizures. Moreover, limited information is available regarding the use of anti-inflammatory agents in clinical epilepsy.

NSAIDs have been negated to have protective role in various neurological disorders and thus, should not be used as a therapeutic option in the clinical setup (Miguel-Álvarez et al. 2015). In a clinical trial, minocycline, an antibiotic with anti-inflammatory properties, failed to exert disease-modifying or delay traverse disease progression in patients with mild AD (Howard et al. 2020). Howard and colleagues explained the first reason as "neuroinflammation might be a reaction to pathological characteristics of the disease rather than important factor in neurodegeneration" and second reason as microglial activation and neurodegeneration is a complex phenomenon, whose inactivation might interfere with its supportive function (Howard et al. 2020). Gyengesi and Münch suggested the future trials to be more specific for cytokine-suppressive anti-inflammatory drugs, which can directly inhibit the production of cytotoxic cytokines (TNF-α, IL-1β, iNOS), and free radicals (Gyengesi and Münch 2020).

The possible explanations behind these varied outcomes may incorporate anti-inflammatory agents organization, selectivity of COX variant, improper utilization of anti-inflammatory agents for a given neurological condition and their severity, inappropriateness in the target site, or

Table 3 Experimental evidences suggesting role of anti-inflammatory agents in epilepsy

Sr. No	Anti-inflammatory agent (dose; route)	Experimental model	Animal	Standard drug	Outcome	References
1	Edaravone (1, 10, and 30 mg/kg, i.p.) for 14 days	Penicillin-induced focal onset seizure model in rats	Wistar Rats	–	Pretreatment suppressed epileptiform activity	Kurt and Aygun (2021)
2	Etanercept for 8 weeks	WAG/Rij rat model of absence epilepsy	WAG/Rij rats, 8 months	–	Reduction in cognitive impairment, despair like behavior and SWD	Karson et al. (2021)
3	Ibuprofen (30 mg/kg, i.p., at 48 h) for 29 days	PTZ induced chronic epilepsy	Sprague Dawley Rats	–	Antiepileptic effect via inhibition of COX-2/NLRP3/IL-18 Pathway	Liu et al. (2020)
4	Tocilizumab (10 and 30 mg/kg, i.p.) acute and chronic (17 weeks)	LPS induced changes in WAG/Rij rat model of absence epilepsy	WAG/Rij rats (6 months)	–	Reduction in development of absence seizure along with reduction of comorbid depression and anxiety like behavior	Leo et al. (2020)
5	Inverse agonist of CB2 SMM-189 (6 mg/kg, i.p., b.i.d.)	Kainate induced status epilepticus	Male C57BL/6 mice (8–9 weeks)	Diazepam (10 mg/kg, i.p.)	Reduction of seizure induce cytokine surge	Yu et al. (2020)
6	Hyperoside (50 mg/kg, intra-gastric) for 14 days	Mouse model of Kainic acid induced epilepsy	Male ICR mice (8 weeks, 30–35 g)	–	Reduction in seizure induced hippocampal (CA3 region) neuronal damage via inhibiting PI3K/AKT and MAPK pathways	Cao et al. (2020)
7	Rev-Erbα specific agonist SR9009 (100 mg/kg, i.p.) for 7 days	Pilocarpine induced status epilepticus	Male C57 BL/6 mice (21–24 g)	Diazepam (10 mg/kg, i.p.)	Antiinflammatory and neuroprotective effect via inhibition of NLRP3/ IL-1β, IL-18, IL-6, and TNF-α/ astrocytosis, microgliosis in hippocampus	Yue et al. (2020)
8	Dexamethasone (3 mg/kg, i.p.)	Immature rat model of febrile status epilepticus	Sprague Dawley rat pups (postnatal 10/11 days)	–	Reduction in spike series prevalence and frequency, cytokine production, and BBB leakage	Garcia-Curran et al. (2019)
9	Nilotinib (25 mg/kg, p.o.) for 1 week	PTZ-induced epilepsy in rats	Male rats (200–250 g)	Pregabaline (30 mg/kg, p.o.) for 1 week	Neuroprotective and antiepileptic effects via promoting antioxidant (NRF-2), antiinflammatory, antiapoptotic pathways (reduction of BDNF, GFAP, beclin-1, NF-κB and BAX expression) and inhibiting autophagy	Attia et al. (2019)

Table 3 (continued)

Sr. No	Anti-inflammatory agent (dose; route)	Experimental model	Animal	Standard drug	Outcome	References
10	Ibuprofen (30 mg/kg, i.p., at 48 h) for 29 days	PTZ induced chronic epilepsy	Male Sprague Dawley rats	—	Reduction of astrocytes proliferation by enhancing autophagy	Peng et al. (2019)
11	Arthrocen (10, 30, 75, 100 mg/kg, p.o.)	PTZ-induced seizure threshold and Maximal Electroshock Seizure Models	Male NMRI mice	—	Enhancement of seizure threshold by elevating GABAergic neurotransmission	Goudarzi et al. (2019)
12	Paeonol (20, 40, 60 mg/kg, i.p.)	PTZ induced kindling in rats	Male Wistar rats (180–200 g, 8–10 weeks)	—	Neuroprotective and anticonvulsant effect via inhibiting oxidative stress and apoptosis	Liu et al. (2019)
13	Ferulic Acid (60 mg/kg, i.p.) for 28 days	PTZ induced kindling in rats	Male Wistar rats (240±20 g)	—	Neuroprotective and anticonvulsant effect via inhibiting oxidative stress and apoptosis	Zhang et al. (2019)
14	TLR3 ligand Poly I:C (0.1, 1, 10 and 33 µg, i.c.v.)	Kainic acid induced seizure	Male C57BL/6 N mice, (~ 50 days, 20–25 g)	—	Inhibition of seizure via activation the TLR3-IRF3/IFN-β axis	Kostoula et al. (2019)
15	Sulfasalazine (250 µmol/L)	4-amino pyridine induced epileptiform discharge in cortical brain slices	C57BL6 mice (6 week)	—	Reduction in cortical hyperexcitability via inhibition of cystine/glutamate antiporter system xc	Alcoreza et al. (2019)
16	Glycyrrhizin (50 mg/kg, i.p.) for 3 days	Traumatic brain injury model	Male C57Bl/6 mice (3 weeks)	—	Reduction in seizure severity and improvement in memory impairment via HMGB1 inhibition	Webster et al. (2019)
17	Rosmarinic acid (8 and 16 mg/kg)	4-aminopyridine and picrotoxin induced seizures in mice	Male CF1 mice (2–3 months, 30–40 g)	Diazepam, Valproic acid	Reduction in seizure induced neuronal damage via improving oxidative stress parameters and mitochondrial respiratory chain activity	Luft et al. (2019)
18	Isoliquiritigenin (20 mg/kg, i.p.)	Kainic acid-induced epilepsy in rats	Male Wistar rats (55±3 g)	—	Neuroprotective and anti-inflammatory effect via attenuation of IBα1-labeled microglia and blocking TLR4/MyD88/IκBα/NF-κB pathway	Zhu et al. (2019)

Table 3 (continued)

Sr. No	Anti-inflammatory agent (dose; route)	Experimental model	Animal	Standard drug	Outcome	References
19	Baicalein (40 mg/kg, i.p.) for 2 weeks	Pilocarpine-induced epileptic rat model	Male Sprague–Dawley rats (200±20 g)	Diazepam (10 mg/kg, i.p.)	Improvement in cognitive deficit, delay in recurrent seizure, and neuroprotection via suppressing oxidative stress, inflammation, regulation of the glucocorticoid pathway and actin-associated protein	Qian et al. (2019)
20	Lycopene (50 mg/ml, intragastric)	Kainic acid-induced seizures in mice	Male Kunming mice (20–22 g)	–	Reduction in seizure score via regulating oxidative stress, inflammatory markers and $GABA_A$ receptor expression	Li et al. (2019)
21	Celecoxib (20 mg/kg, p.o.) for 5 days	Kainic acid induced recurrent seizures	Sprague Dawley Rat (20–25 g, 10 days old)	Pentobarbital (10 mg/kg, i.m.)	Neuroprotective effect via inhibition of proinflammatory cytokines via HMGB1/TLR4 pathway	Morales-Sosa et al. (2018)
22	Nimesulide, Celecoxib, Etoricoxib (0.2, 2 or 20 mg/kg)	PTZ induced seizures	Male Swiss mice (28±3 g)	–	Reduction of neuroinflammation by reducing level of IL-1β, IL-6, IFN-γ, TNF-α in cortex and hippocampus	Temp et al. (2017)
23	Etoricoxib (5, 10 and 20 mg/kg, i.p.)	WAG/Rij rat model of absence epilepsy	Male WAG/Rij rats (3–4 weeks)	–	Reduction in number and duration of SWD	Citraro et al. (2015)
24	Etoricoxib (1, 10 mg/kg, i.p.) for 9 days	PTZ induced kindling in rats	Male Wistar rats	–	Lower dose exhibited anticonvulsant effect while higher dose worsen seizure control and impair learning & memory	Katyal et al. (2015)
25	COX inhibitor NS398 (10 mg/kg, i.p.) + Diazepam (10 mg/kg, i.p.)	Lithium-pilocarpine induced status epilepticus in rats	Male Sprague–Dawley rats (250–400 g)	Diazepam (10 mg/kg; i.p.)	Reduction of SE induced hippocampal neuronal damage while no significant change in vEEG	Trandafir et al. (2015)
26	Parecoxib (10 mg/kg i.p.) for 17 days	Lithium-pilocarpine induced status epilepticus in rats	Female Sprague Dawley rats (200–220 g)	–	Severity of SRS was reduced and prevented hippocampal neuronal damage	Polascheck et al. (2010)
27	Celecoxib (20 mg/kg, p.o.) for 6 days	Rat model of pharmacoresistant epilepsy	Female Sprague Dawley rats (200–224 g)	–	Restoration of pharmacosensitivity	Schlichtiger et al. (2010)
28	Nimesulide (2.5 mg/kg; ip) and Rofecoxib (2 mg/kg, ip)	Bicuculline, picrotoxin, electroshock induced convulsions	Male Laka mice	–	Reduction in seizure severity possibly via COX-2 inhibition and GABAergic modulation	Dhir et al. (2006a)

Table 3 (continued)

Sr. No	Anti-inflammatory agent (dose; route)	Experimental model	Animal	Standard drug	Outcome	References
29	Aspirin (10, 20 mg/kg), naproxen (7, 14 mg/kg, i.p.), nimesulide (1, 2.5, 5 mg/kg, i.p.) or rofecoxib (1, 2, 4 mg/kg, i.p.)	PTZ induced convulsions in mice	Male Laka mice (22–30 g)	Diazepam (0.1 mg/kg, i.p.)	Dose dependent protection against PTZ induced convulsions, Rofecoxib and nimesulide enhanced protective effect of Diazepam	Dhir et al. (2006b)
30	Celecoxib (6 mg/kg i.p.) for 5 days	Kainic acid-induced seizures in rats	Male Wistar rats (250–300 g)	–	Post-treatment enhances functional recovery by increasing BDNF level	Gobbo and O'Mara (2004)

PTZ: Pentylenetetrazole, SWD: Slow wave discharge; vEEG: Video Electroencephalogram

limited entry to the CNS through BBB. This way, the plan of new anti-inflammatory approach for targeting neurological disorders, in view of improved BBB permeability, may deduce a viable treatment option. However, the anti-inflammatory agents (especially with COX inhibitors) have been considered as major sources of drug induced complications (renal and gastro-intestinal side effects). Use of specific COX2 inhibitor (rofecoxib and valdecoxib) have been associated with vascular complications along with higher risk of stroke (Auriel et al. 2014). Moreover, use of such agents in elderly, asthama, pregnant, breastfeeding. patients with liver/kidney/heart diseases are contraindicated. Furthermore, more research is expected to comprehend the mechanism devoid of such adverse outcomes.

Conclusion and future perspective

Neuroinflammation plays a significant role in the development of neurological disease. The concept of neuroinflammation theory covers a wide range. The glial cells, cytokines, inflamosome, autophagy, ion channels, monocytes function as a sensor for homeostasis of disrupted brain tissue and accumulate locally in response to neuronal injury or foreign pathogen entry into the brain. Still, it is very arduous to give a universal conclusion. Preclinical evidences appear commendable suggesting utilization of anti-inflammatory approach to alleviate neurological disease progression, either alone or as combination therapy. However, the finding of clinical investigations is obscure in their result. Thus, until authoritative clinical evidence is established, used of anti-inflammatory agents should be restricted to the approved drugs. Simultaneously exploration of novel anti-inflammatory approaches (other than COX inhibitors) may be given due considereation in the management of disease progression. Further, use of nanoformulation approach also attact attention of researchers for improved brain delivery of anti-inflammatory agents.

Table 4 Clinical investigations suggesting role of Anti-inflammatory agents in different neurological conditions

Sr. No	Anti-inflammatory agent (dose; route)	Patients	Study design (duration)	Number of participants	Outcome	References
Alzheimer's disease (AD)						
1	Naproxen (200 mg, b.i.d.)	AD patients	24 months	195 (> 55 years)	Naproxen slow progress of presymptomatic Alzheimer disease	Breitner and Meyer (2020)
2	Simvastatin (80 mg/day)	AD patients	18 months	80 (> 50 years)	Improvement in cognitive function with reduction in neuroinflammation	Sánchez-Sarasúa et al. (2020)
3	Diclofenac, Etodolac, and Naproxen	AD patients	Retrospective, observational cohort study	–	Reduction in AD frequency with diclofenac	Stuve et al. (2020)
4	Minocycline (200, 400 mg)	Mild AD patients	24 months	544 (303 M, 241F; 74.3 ± 8.2 years)	No delay in the progression of cognitive or functional impairment	Howard et al. (2020)
5	Medium-chain triglyceride based ketogenic diet	20 Japanese patients with mild-to-moderate AD	12 weeks	20 (11 M, 9F)	Improvement in cognitive function	Ota et al. (2019)
6	Resveratrol, SIRT1 activator (1 g, b.i.d.)	AD patients	52 weeks	119	Reduction in CSF MMP9, neuro-inflammation, and induces adaptive immunity	Moussa et al. (2017)
7	Ibuprofen (400 mg, b.i.d.) + Esomeprazol (20 mg, o.d.)	Mild-to-moderate AD patients	RCT, DB, placebo controlled trial (12 months)	132	Negative effect on cognitive decline	Pasqualetti et al. (2009)
8	Tarenflurbil (800 mg/day)	Mild-to-moderate AD patients	24 months	210	Dose-related effect on measures of daily activities and global functions	Wilcock et al. (2008)
9	Rofecoxib (25 mg)	Patients with mild cognitive impairment	RCT, DB, (48 months)	725	Failed to delay the diagnosis of AD	Thal et al. (2005)
10	Rofecoxib (25 mg)	Mild to moderate AD patients	RCT, blinded, (12 months)	692 (> 50 years)	Failed to delay the AD progression	Reines et al. (2004)
11	Rofecoxib (25 mg) or Naproxen (220 mg, b.i.d.)	Mild to moderate AD patients	RCT (12 months)	351	No protective effect on cognitive decline	Aisen et al. (2003)
Epilepsy						
12	Methylprednisolone (30 mg/kg/day) for 3 days	Refractory epilepsy	Retrospective study	31	Improvement in cognitive function and behavioral comorbidities	Kimizu et al. (2020)
13	Pyridoxine + Prednisolone	Infantile spasms	5 months	62 (3 month—3 years)	Reduction in infantile spasms	Kunnanayaka et al. (2018)
14	Aspirin (133 mg)	Partial epilepsy	Retrospective study, 2–8 days	23 (11 M, 12F; 49–76 years)	Reduction in seizure observed in vEEG	Godfred et al. (2013)

Table 4 (continued)

Sr. No	Anti-inflammatory agent (dose; route)	Patients	Study design (duration)	Number of participants	Outcome	References
15	Prednisolone (2 mg/kg per day)	Patients with cryptogenic epileptic encephalopathies	6 weeks	41	73% (30/41) of patients showed a reduction in seizure frequency of > 50%, and 59% (24/41) became seizure free	You et al. (2008)
16	Ibuprofen (5 mg/kg, orally; every 6 h until the child was afebrile for 24 h)	Febrile seizure recurrences	RCT, DB, 24 h	230 (1–4 years)	Reduction in fever but no effect against febrile seizure recurrence	van Stuijvenberg et al. (1998)
Parkinson Disease (PD)						
17	Celecoxib (200 mg/day)	PD patients	One month	14	Slightly higher microglial activation in PD patients	Bartels et al. (2010)
Multiple Sclerosis (MS)						
18	Tabalumab (4, 12, 40, or 120 mg every 4 weeks, or 4 or 120 mg every 12 weeks)	Relapsing–remitting MS	RCT, DB, 73 weeks	245	Failed to exert any protective effect	Silk and Nantz (2018)
19	Atacicept (25, 75, or 150 mg, s.c.; weekly)	Relapsing–remitting MS	Phase II, RCT, DB, 5 years	225 (18–60 years)	Phase II was terminated due to negative results	Kappos et al. (2014)
20	Rituximab (1 g/day, i.v.)	Primary-progressive MS	RCT, DB, 96 weeks	439	No change in disease progression, appearance of severe infection	Hawker et al. (2009)
21	Rituximab (1 g, i.v.)	Relapsing–remitting MS	Placebo-controlled trial, 48 weeks	69	Reduction in inflammatory brain lesions	Hauser et al.(2008)
22	Recombinant human erythropoietin (high-dose; 48,000 IU and low-dose; 8000 IU)	MS patients	48 weeks	8	Improvement in motor and cognitive functions	Ehrenreich et al. (2007)

Declarations

Ethics approval and consent to participate This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that there is no conflict of interest related to this work.

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