Review

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An Insight into the Molecular Mechanisms of Neuroinflammation

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A variety of events, including infection, traumatic brain damage, neurodegenerative illnesses, and autoimmune disorders, can cause neuroinflammation, a complicated biological reaction in the central nervous system. Glial cells, especially microglia and astrocytes, are activated as part of this complex event, which also results in the production of pro-inflammatory cytokines, chemokines, and reactive oxygen species. In this review, the role of microglia and astrocytes in neuroinflammation, as well as the important neuroinflammatory factors including their pathways, and positive and negative aspects of neuroinflammation are discussed. It was earlier documented that microglial cells and astrocytes play a notable role in immune and inflammatory diseases. Various pro-apoptotic pathways like nuclear factor kappa B (NF-κB), cytokines, cyclooxygenases, reactive oxygen species (ROS), and mitogen-activated protein kinase (MAPK) are responsible for the induction of neuroinflammation. Neuroinflammation may also lead to many neurodegenerative diseases like Alzheimer's disease, multiple sclerosis, and Parkinson's disease. It has also been reported that inflammasomes and multi-protein oligomers are also responsible for neuroinflammation.

Keywords: neuroinflammation; microglia; inflammasome; NF-κB; cytokines; reactive oxygen species

Introduction

Inflammation is a biological condition that gets triggered when cells or tissues are damaged, infected, or traumatized. Invading pathogens are eliminated by an effective inflammatory response mechanism, which further triggers wound recovery and tissue regeneration [1]. The neuroprotective functions performed by neurons in the brain include the removal of cellular wreckage and regulation of inflammatory cytokines secretion, neurotrophic factors, and proteases. Inflammation can be beneficial at times, but it can also be harmful, especially during brain injuries [2].

Neuroinflammation is a complex, dynamic, defensive feature that separates injured neurons from unaffected brain tissue. It destroys injured and injury-prone cells and restores the extracellular matrix. The extracellular matrix plays a crucial role in the development and course of many illnesses. The remodeling process and changes to its constituent parts affect the inflammatory microenvironment. Microglia and astrocytes work together to regain the homeostasis in the brain. A variety of factors activate microglia and extremely intricate neuroinflammatory pathways like the initial assault or stimulation, genetic makeup, external factors, and age or previous experiences [3,4]. The severity of neuroinflammation is determined by the condition of the primary stimulus, timeframe, and pathway. Neuroinflammation is the most prominent feature of many neurological disorders, including Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease, autism, and narcolepsy etc. [1].

Acute neuroinflammation is linked to strokes, whereas chronic neuroinflammation is linked to Alzheimer's and Parkinson's diseases, but oxidative assault is the common factor for both. Pattern recognition receptors (PRRs) recognize damage-associated molecular patterns (DAMPs) and pathogen-specific molecular patterns (PAMPs) on bacterial cell walls and perform a critical role in the innate immune response. Glial cells, macro-phases, and oligodendrocytes are expressed in the brain, so they can recognize membrane-bound (toll-like receptors) or bound to cytoplasmic Nod-like receptors (NLRs). The activation of such NLRs causes the formation and activation of inflammasomes, which are

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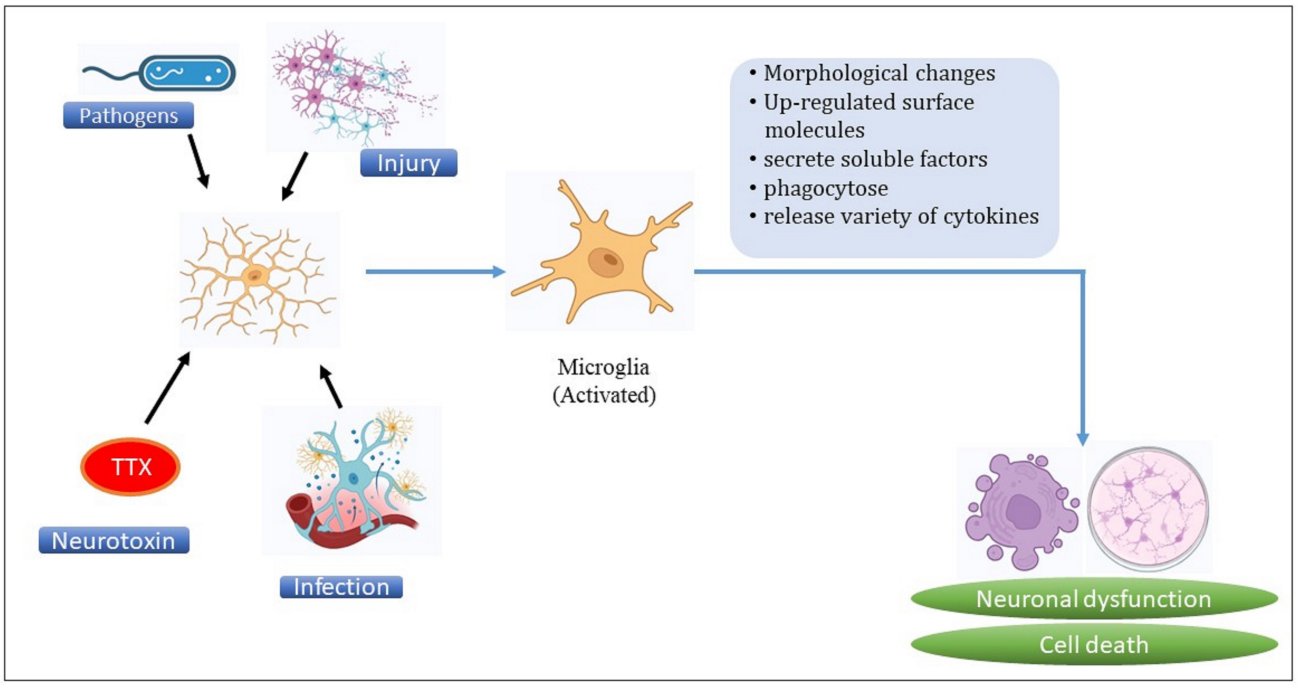

Fig. 1. Microglia activation in neuroinflammation. Microsoft PowerPoint Version 2019 (Chicago, IL, USA) and https://www.bioren der.com/ version 4.0, Science Suite, Inc., Toronto, Canada were used for constructing this Figure. Some elements are from literature [4]. TTX, tetrodotoxin.

cytosolic structural proteins. All such inflammasomes are multi-protein oligomers that encourage the maturation and discharge of interleukin-1 (IL-1), interleukin-18 (IL-18), and interleukin-33 (IL-33) by activating proinflammatory caspases, notably caspase-1 [5,6]. Numerous innate immune psychological processes, including inflammation, autoimmune illnesses, and infectious disease [7], as well as neuroinflammation and important brain diseases [8–13], are impacted by inflammatory indicators. This review discusses the various levels of neuroinflammation and elaborates both positive and negative aspects of it.

Microglial Cells Play a Role in Neuroinflammation

In the grey matter, white matter, and spinal cord, microglial cells are tenant macrophages or collective neuroglia. Microglia account for 10–12 percent of the overall glial cells present in the central nervous system. During embryogenesis, these cells originate from the yolk sac, penetrate the brain's tissue, and spread throughout the brain on an internal level [14]. Unlike other yolk sac-derived macrophages, they are not cleared by bone marrow- or liver-derived macrophages, not even in the neonatal period or later in life. They play a role in both tissue remodeling and regeneration as well as an organism's defense.

When microglial cells are activated, their morphology changes to a transitional and amoeboid form which results in a round morphological appearance like phagocytes. Increased expression of toll-like receptors, purinergic receptors (P2X7), cluster of differentiation (CD4 and CD8), and various/many enzymes, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the cytoplasm, are the causes of the morphological changes. Additionally, there is advanced up-regulation of major histocompatibility complex (MHC), including Class I and II, complement c3, Fc, thrombin, scavenger receptors (CD36, SR-A, CD204, SR-BI), cytokines, and nuclear factor kappa B (NF-κB), as well as several other MHC molecules. Superoxide is generated as P2X7 purinergic receptor and NADPH oxidase are powered up. Activated microglial cells rarely release neurotoxic molecules like IL-1, IL-6, tumor necrosis factor (TNF)-α, glutamate, aspartate, quinolinic acid, nitric oxide (NO), and reactive oxygen species (ROS), but they also end up making inflammasomes easier to assemble and activate [6]. The release of IL-1, IL-6, and TNF-α causes a significant increase in Phospholipase A2 (PLA-2), cycloxygenases (COX)-2, and 5-lipoxygenase (5-LOX) activities, as well as the production of pro-inflammatory eicosanoids and platelet-activating factors. Neuroinflammation is exacerbated by these proinflammatory mediators, as well as proteinases and complement proteins. Microglial cells may continue to stay activated for a long duration of time in chronic neuroinflammation, liberating cytokines and neurotoxic molecules. This contributes to fairly long neurodegeneration [15]. As a result, a therapeutic approach should be aimed at preventing the progression of neurodegenerative diseases by blocking pro-inflammatory media-

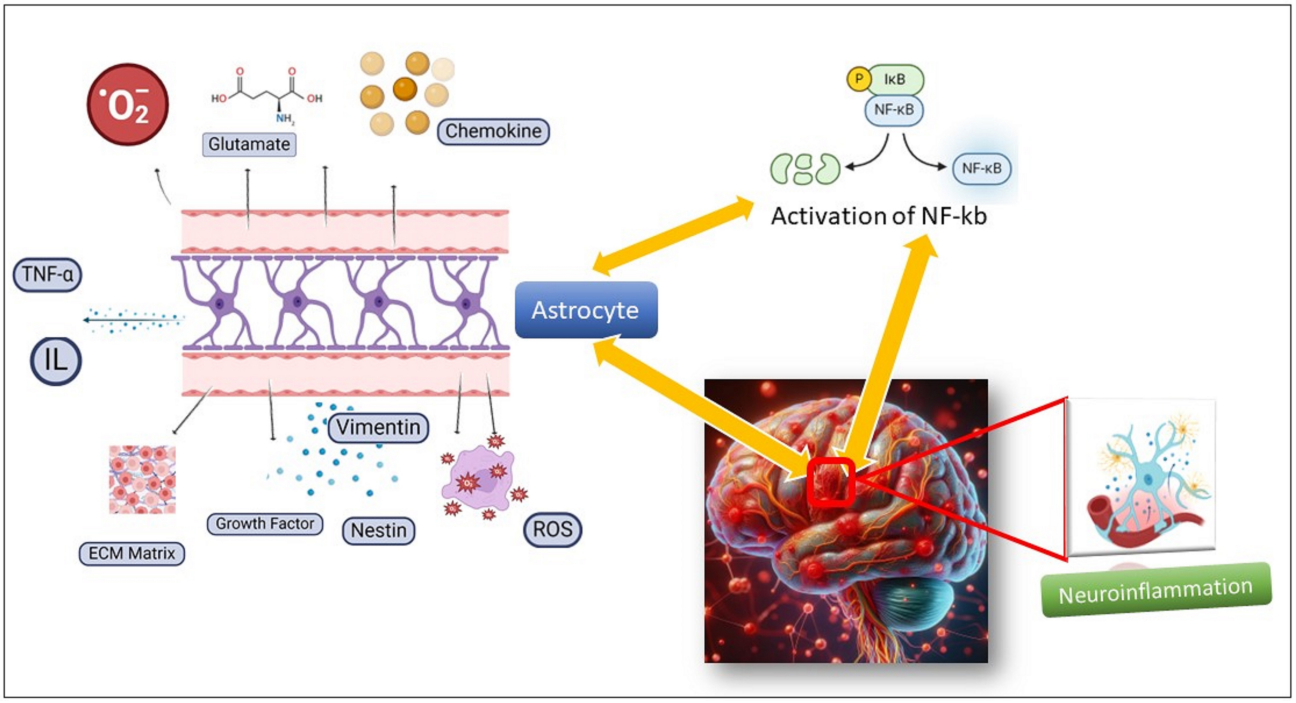

Fig. 2. Activation of astrocytes leading to neuroinflammation. Microsoft PowerPoint Version 2019 (Chicago, IL, USA) and https://www.biorender.com/ version 4.0, Science Suite, Inc., Toronto, Canada were used for constructing this Figure. Some elements are from literature [17,18]. NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; TNF, tumor necrosis factor; IL, interleukin; ECM, extracellular matrix.

tors caused by microglial activation would be impactful [16]. Microglia that have been activated have the potential to destroy neurons. They can, however, involve eradicating pathogens to perform neuroprotective tasks. Fig. 1 (Ref. [4]) depicts the role of microglia activation in neuroinflammation [4].

Astrocytes Play a Role in Neuroinflammation

Astrocytes are glial cells in the brain and spinal cord tissue that are extremely differentiated, and star-shaped. According to studies, the proportion of astrocytes varies in various regions and it accounts for 20 to 40 percent of all glia. They provide biochemical support for endothelial cells and provide nutrition to nerves. They are also involved in the restoration and scarring of the brain and spinal cord. Astrocytes also maintain extracellular ion harmony. They have a reactive astrogliosis response to neurotraumatic and neurodegenerative injuries.

Astrocytes are activated during the astrogliosis process, which produces several inflammatory mediators like cytokines and chemokines, glutamate, reactive oxygen species (ROS), and prostanoids. During the astrogliosis process, transitional filaments (viz., vimentin, glial fibrillary acidic protein, and nestin), provocative stress markers, extracellular matrix (ECM) molecules, growth factors, and cytokines are expressed. Due to this, astrocytes become hypertrophic. Astrogliosis eventually results in the formation of a glial scar, which further becomes a barrier to axonal regeneration. This mechanism is primarily responsible for masterminding the assault response as well as controlling inflammation and restoration [17,18]. Further, astrocytes interact with microglia and contribute to neuroinflammation. They have both pro- and anti-inflammatory properties.

Glutamate is produced by astrocytes and binds to glutamate receptors like metabotropic glutamate receptors (mGluRs) and N-methyl-D-aspartate receptors (NMDARS). A PLC-mediated signaling pathway is activated releasing the neurotransmitters. An astrocytic scar serves as a neuroprotective barrier against inflammatory cells and infectious agents, as well as promotes reorganization and structural modifications. Inhibitors of 5-LOX or cysteinyl leukotrine receptors are used to block glial scar formation. Toll-like receptors (TLRs), nucleotide-binding oligomerization domains, double-stranded RNA-dependent protein kinase, mannose receptors, scavenger receptors, and complement system components all play a role in local innate immune responses. The astrocytes secrete soluble mediators such as C-X-C motif ligand (CXCL)10, C-C motif ligand 2 (CCL2), IL-6, and BAF, which play an important role in neuroinflammation and tissue repair. These receptors are in charge of downstream signaling that causes the main transcription factor (NF-κB) activation resulting

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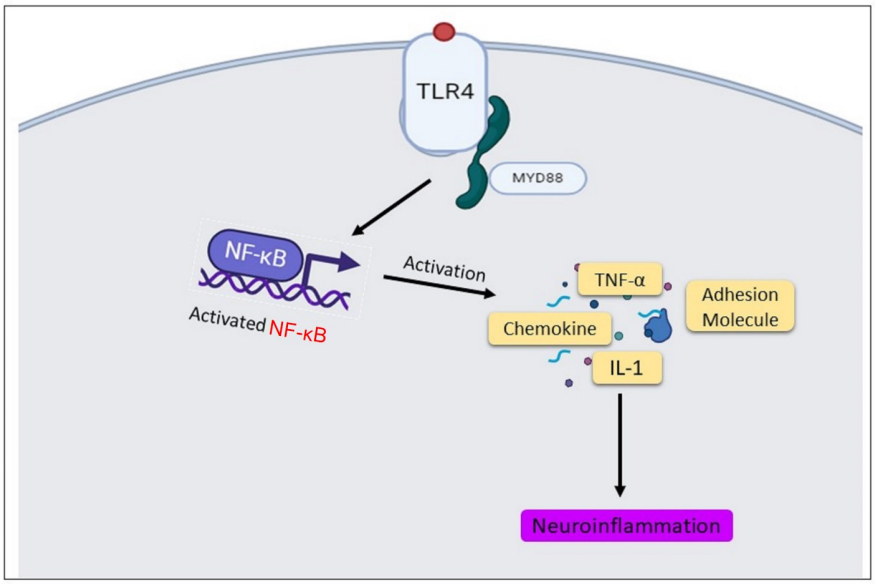

Fig. 3. Myeloid differentiating NF-κB factor that induces neuroinflammation. Microsoft PowerPoint Version 2019 (Chicago, IL, USA) and https://www.biorender.com/ version 4.0, Science Suite, Inc., Toronto, Canada were used for constructing this Figure. Some elements are from literature [16]. TLR4, toll-like receptor 4; MyD88, Myeloid differentiating factor 88.

in the production of inflammatory cytokines [17,18] which further leads to involvement in the development of neuroinflammation as shown in Fig. 2 (Ref. [17,18]).

Neuroinflammation Pathways

Neuroinflammation Pathway Mediated by NF-κB

TLRs are involved in signaling pathways. These membrane proteins, when activated, destroy the invading pathogens. The cytoplasmic region of TLRs contains an extracellular leucine-rich repeat domain (LRR) and a Toll/IL-1 receptor (TIR) domain. TIR is in charge of the signaling pathway, while LRR is in charge of the specific pathogen recognition process.

Myeloid differentiating factor 88 (MyD88) is an adaptor protein that connects to TLRs via their TIR domains, causing NF-κB proteins to get activated. This NF-κB protein causes inflammation by activating pro-inflammatory genes viz., cytokines (IL-1, TNF-α), chemokines, and adhesion molecules. MyD88 activates all TLRs except TLR3. Besides MyD88 pathway is important in microbial infection of the brain. Optic nerve injuries, Alzheimer's disease, and Parkinson's disease are all linked to MyD88 [19,20]. The TLR4/MyD88/NF-κB signaling pathway may be considered as a constructive therapeutic target for mending neuroinflammatory concussions with drugs as indicated in Fig. 3 (Ref. [16]) [16].

Pro-Inflammatory Cytokines Mediated Neuroinflammation Pathway

Activated macrophages produce proinflammatory cytokines. Certain pro-inflammatory cytokines, *viz*., TNF-α, IL-(1 and 6), play a pivotal role in neuroinflammation. Particularly, IL-1 is an important factor in the occurrence of long-term neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, brain stroke, and trauma which are acute neuroinflammatory circumstances [17]. Interleukins (IL-1β and IL-6) bind with the interleukin-1 receptor (IL-1R1) and produce prostaglandin E2 (PGE-2) in the neuronal as well as glial cells which cause neuroinflammation.

TNF-α is a cachectin which is a multipotent inflammatory cytokine. It can trigger apoptosis by triggering receptors with a homologous cytoplasmic sequence that acknowledges intracellular death domains. This includes the death ligands for TNF receptor-1 (TNFR-1) and CD95 (APO-1/Fas). TNF-α attaches to TNFR-1 and activates it. Through Caspase -3 mediated pathways, TNFR-1 stimulation can trigger neuronal apoptosis, causing neuronal cell death. Inside the cell, the death complexes like activator protein-1 (AP-1), NF-κB, and caspases are found. They cause apoptosis through membrane-bound receptors which are involved in the bereavement of neurons. Fig. 4 (Ref. [18,21]) shows the TNF-α induced neuroinflammation [18,21].

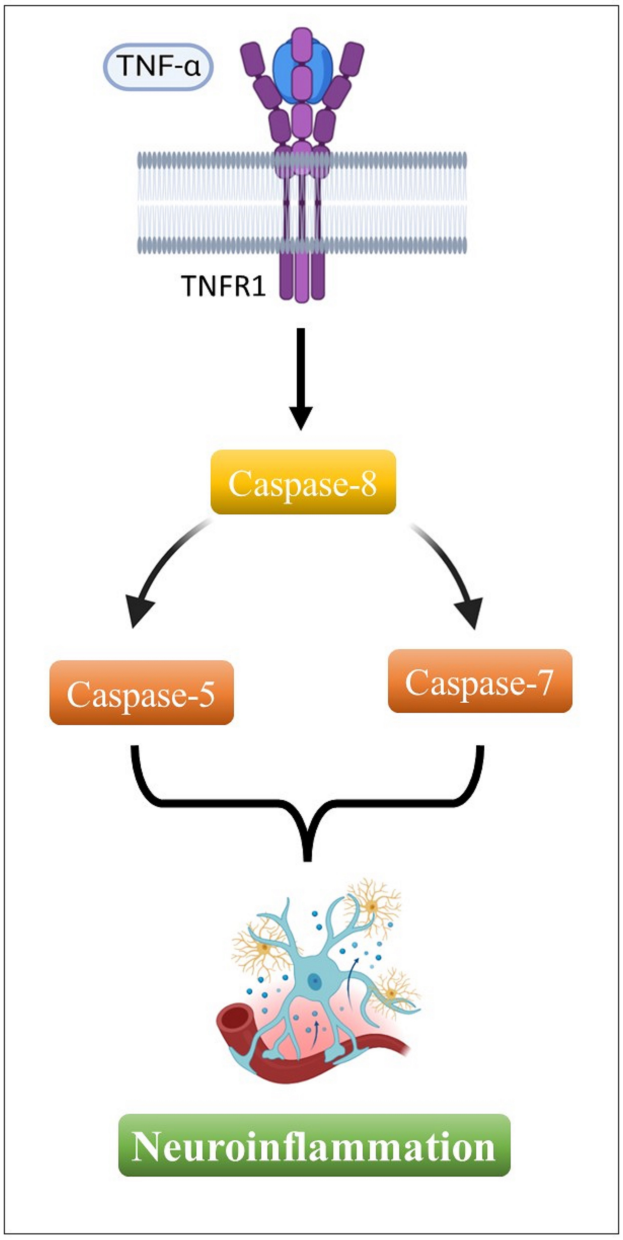

Fig. 4. TNF-α induced neuroinflammation. Microsoft PowerPoint Version 2019 (Chicago, IL, USA) and https://www.biorender.com/ version 4.0, Science Suite, Inc., Toronto, Canada were used for constructing this Figure. Some elements are from literature [18,21]. TNFR1, TNF receptor-1.

ROS-Mediated Neuroinflammatory Pathway

ROS are multipotent, soluble, or diffusible chemical atoms with an unpaired electron that can carry out a signaling process in the cell via extracellular or environmental stimuli. They can cause an inflammatory reaction by activating several genes responsible for the inflammatory signaling cascade. The metabolism of amino acids and neurotransmitters in neuronal tissue generates ROS [22]. They can cause oxidative damage, mitochondrial dysfunction, and tissue injury. This mitochondrial dysfunction activates NF-κB proteins which are responsible for neuroinflammation. Mitochondrial dysfunction is usually pragmatic in many types of neurodegenerative diseases like Huntington's, Alzheimer's, and Parkinson's disease. Further, it is also common in alcohol-linked dementia. Mitochondria-targeted anti-oxidants reduce systemic inflammation and neuroinflammation. The ROS-induced neuroinflammation is shown in Fig. 5 (Ref. [19,23]) [19,23].

NO-Mediated Neuroinflammatory Pathway

NO is a gaseous signaling molecule that regulates the nervous system as well as the immune system. It is generated by three NO synthase (NOS) isoforms: endothelial NO synthase (eNOS), neuronal NO synthase (nNOS), and inducible NO synthase (iNOS). Microglia are present in the neuritic plaques in Alzheimer's brain and can be revealed by iNOS. Bacterial lipopolysaccharide (LPS), interferon-gamma (IFN-γ), TNF-α, and IL-1 are just a few of the stimuli that can cause iNOS expression [20]. Where iNOS causes the formation of NO from l-arginine. This NO can directly influence neuronal apoptosis [14,24].

After exposure to neurotoxic agents, increased levels of superoxide anion and NO can be produced, resulting in nitro-oxidative stress in the brain. When NO and superoxide anions coexist, more cytotoxic agents are produced. These are linked to neuronal artifacts and death [19].

ROS production is responsible for the activation of iNOS, which increases NO production in glial and endothelial cells. NO and ROS regulate cell proliferation at low concentrations. But at a very high level, they are primary cytotoxic molecules that can cause neurodegenerative diseases, as shown in Fig. 6 (Ref. [20]) [20].

Cyclooxygenases Mediated Inflammation of Neurons

COX-1 and COX-2 are two types of cycloxygenases (COX) with inflammatory features [14,25]. The same reaction of deoxygenating arachidonic acid to create prostaglandin G2 (PGG-2) and then transforming PGG-2 to prostaglandin H2 (PGH-2) is catalyzed by these two different isoforms [26]. PGH-2 is transformed into PGE-2, which leads to neuroinflammation [25]. During TNF-α or LPS-induced neuroinflammation, COX-1 inhibition reduces BBB distraction. COX-2 may play an anti-inflammatory role, but this is dependent on the stimulus and the cell type that is being harmed [25]. High generation of COX-2 in neurons has been linked to memory formation and synaptic function as observed in Fig. 7. Up-regulation of COX-2, on the other hand, causes neuronal damage and leads to neurodegenerative diseases.

PI3K/AKT/mTOR Mediated Neuroinflammation Pathway

Inflammatory responses, cell stimulation, and cell death are all controlled by the phosphatidylinositol 3-kinase (PI3K)/serine/threonine protein kinase (AKT) path-

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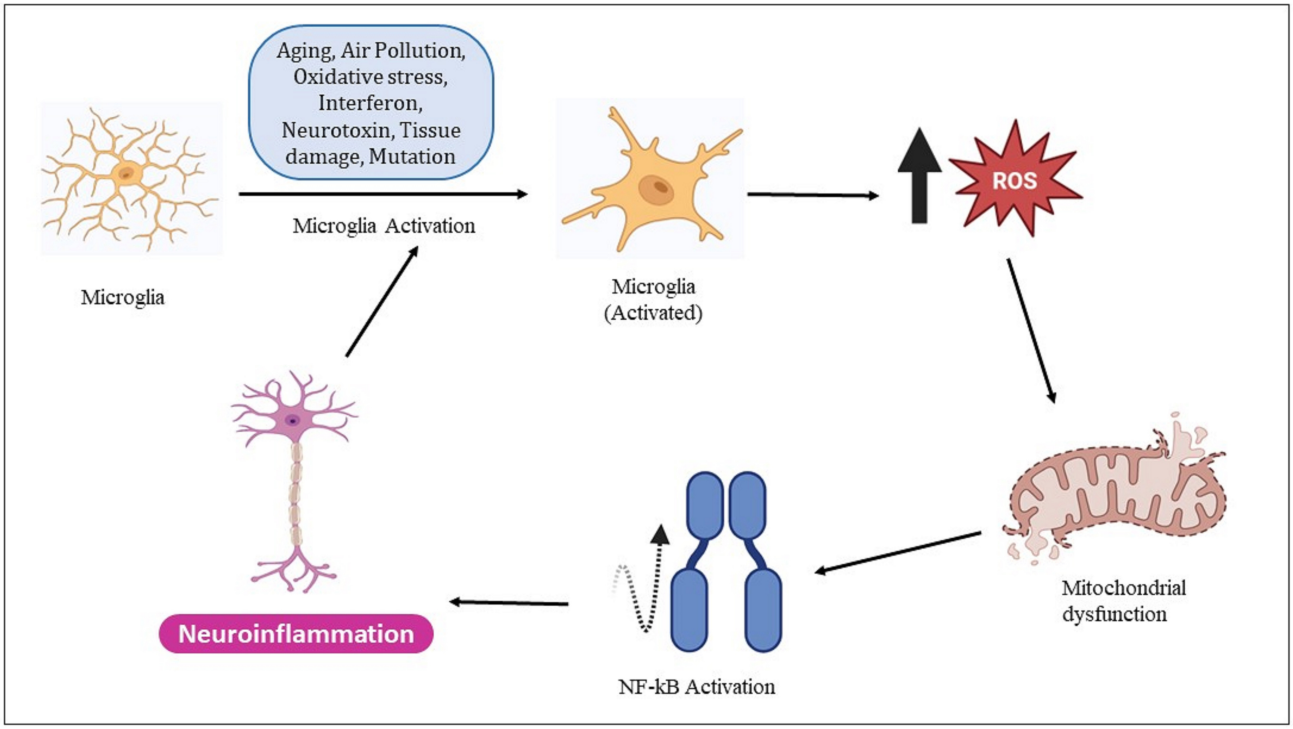

Fig. 5. Reactive oxygen species (ROS)-induced neuroinflammation. Microsoft PowerPoint Version 2019 (Chicago, IL, USA) and https://www.biorender.com/ version 4.0, Science Suite, Inc., Toronto, Canada were used for constructing this Figure. Some elements are from literature [19,23].

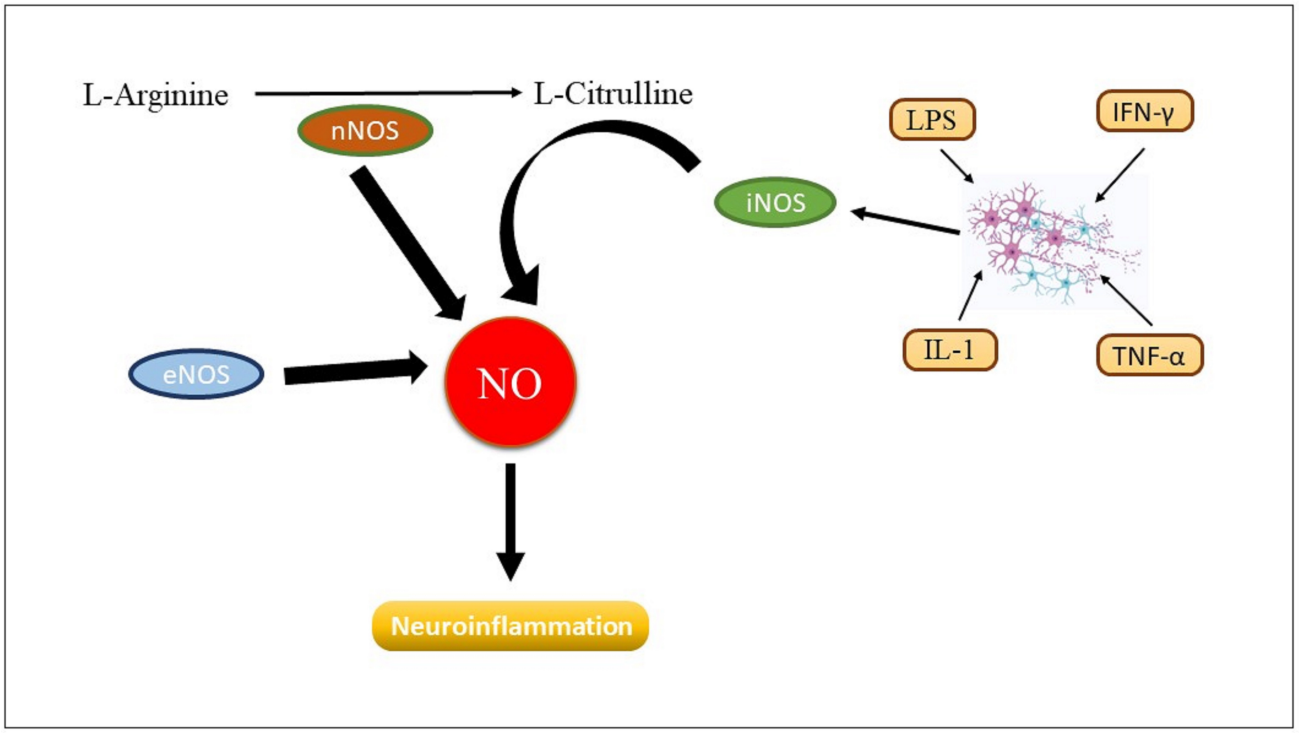

Fig. 6. Nitric oxide-induced neuroinflammation. Microsoft PowerPoint Version 2019 (Chicago, IL, USA) and https://www.biorender.com/ version 4.0, Science Suite, Inc., Toronto, Canada were used for constructing this Figure. Some elements are from literature [20]. eNOS, endothelial NO synthase; LPS, lipopolysaccharide; IFN-γ, interferon-gamma; iNOS, inducible NO synthase; nNOS, neuronal NO synthase.

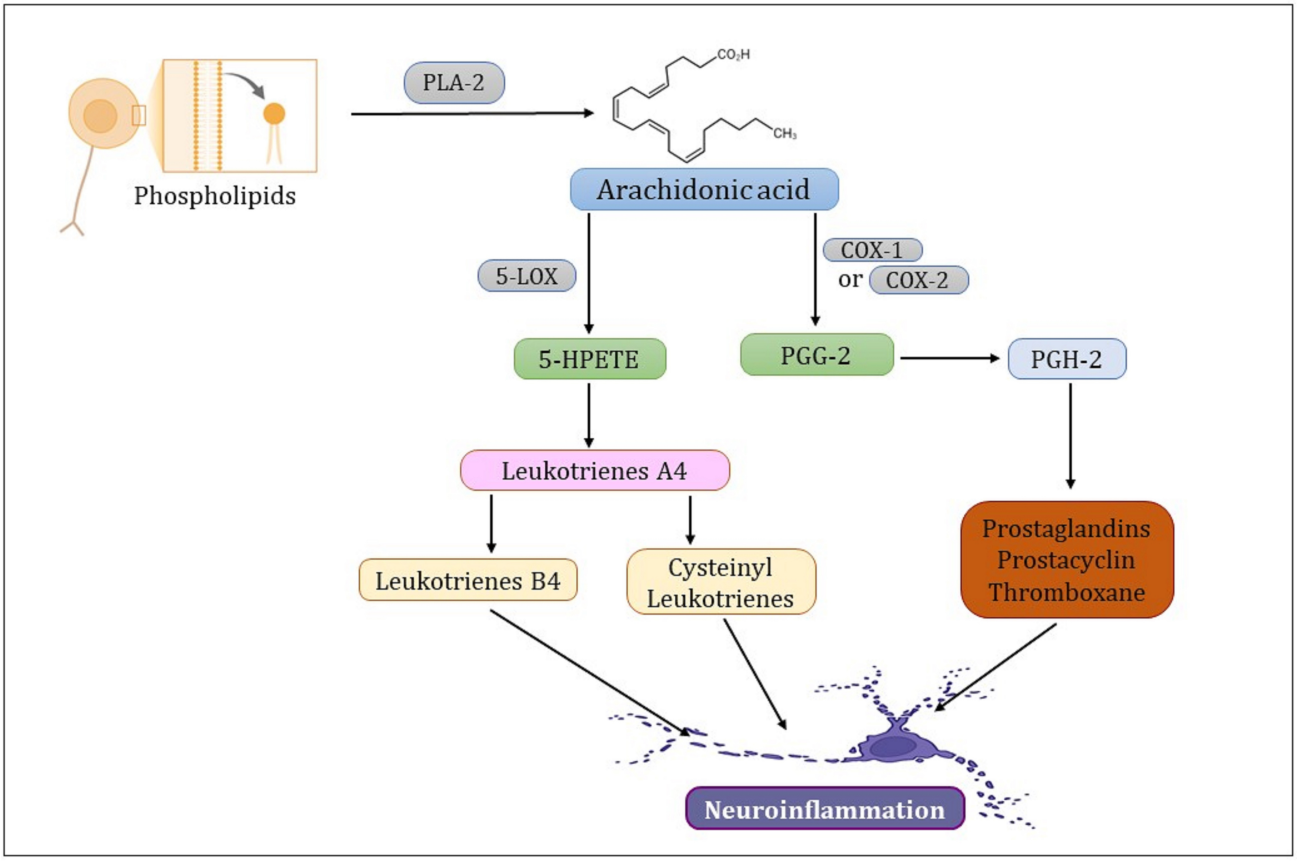

Fig. 7. Cycloxygenases (COX) mediated neuroinflammation. Microsoft PowerPoint Version 2019 (Chicago, IL, USA) and https://www.biorender.com/ version 4.0, Science Suite, Inc., Toronto, Canada were used for constructing this Figure. 5-LOX, 5-lipoxygenase; PLA-2, Phospholipase A2; PGG-2, prostaglandin G2; PGH-2, prostaglandin H2.

way. When PI3K is activated, it initiates a signaling cascade that results in NF-κB translocation. AKT and mammalian target of rapamycin (mTOR) are both activated by PI3K, which is a lipid kinase. AKT activation leads to PI3K pathways and starts a flow of downstream signaling via different targets [27]. The mTOR is an uncharacteristic serine/threonine protein kinase (PI3K) which fits in the family of PI3K. PI3K stimulation promotes AKT which activates mTOR. Microglia is activated when mTOR is phosphorylated. Activated mTOR causes neuroinflammation by increasing the action of NF-κB and promoting the uphill expression of certain markers like COX-2 which are involved in inflammation. Fig. 8 (Ref. [28]) depicts the PI3K/AKT/mTOR-mediated neuroinflammation [28].

MAPK-Mediated Neuroinflammation Pathway

The mitogen-activated protein kinase (MAPK) family is activated when microglia are energized or stimulated. As a reaction to LPS stimulation, MAPKs like p38 MAPK and stress-activated protein kinases/Jun amino-terminal kinases (SAPK/JNK) activate the proinflammatory cytokine cascade [29,30]. p38 MAPK and JNK activate NF-κB. This causes neuronal death (apoptosis) and neuroinflammation by producing cytokines and proinflammatory mediators similar to TNF-α and IL-6. NF-κB also activates COX-2 and iNOS which are responsible for neuroinflammation (Fig. 9).

Positive Aspects of Neuroinflammation

Sickness Behavior Caused by Cytokines

One consequence of neuroinflammatory cytokine production is a peripheral immune response that contributes to the disease's behavior. A similar response, facilitated by the neurovascular unit and resident glia [31,32], tends to produce cytokine and secondary signals. This causes functional or behavioral parts of the sickness response like fever, hypophagia, and reduced activity, along with lowered social interaction [33]. IL-1, TNF-α, and IL-6 are neuroinflammatory cytokines that are implicated in the initiation and upkeep of neuroimmune connectivity, signal formation, and behavioral outcome. The timeframe of cytokine exposure is brief, and the impact is transient, with both microglia and astrocytes activating briefly. This reaction is short-lived, signifying that the central nervous system (CNS) is built to handle neuroinflammation as an advantageous reaction (Fig. 10 (Ref. [31,34])). These changes in behavior caused by sickness are highly adaptable and necessary

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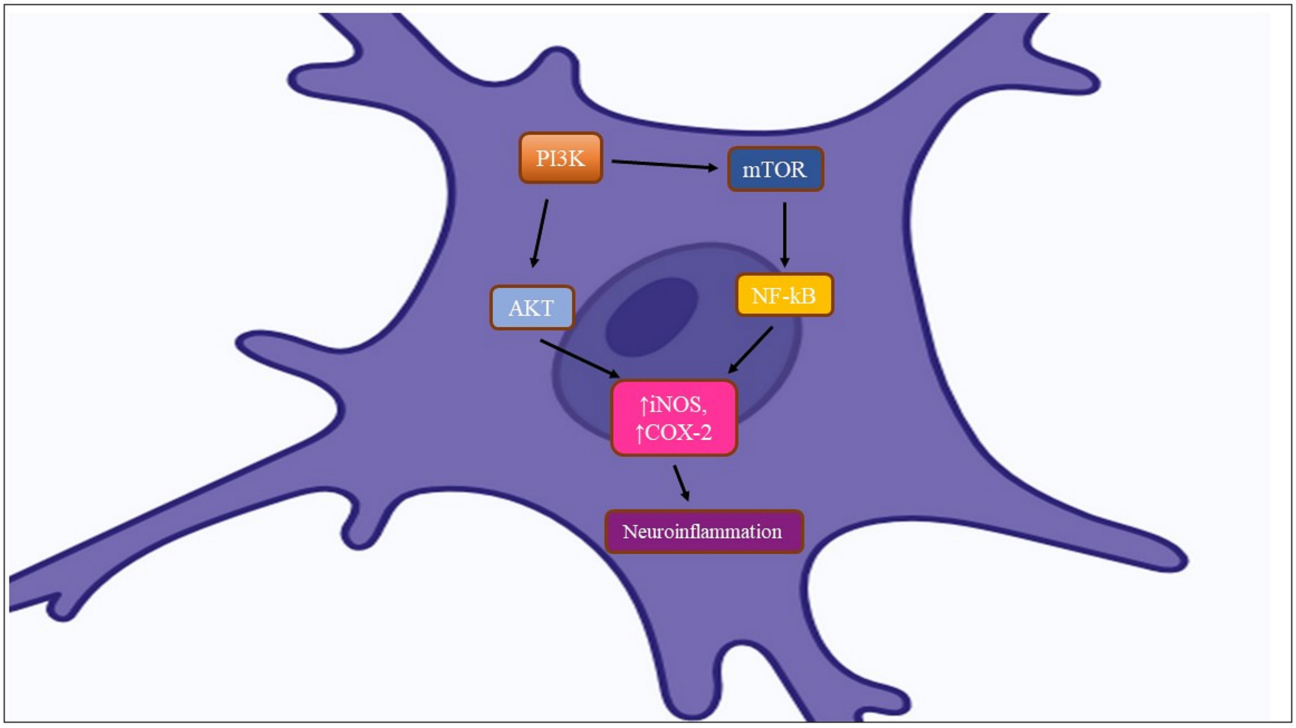

Fig. 8. PI3K/AKT/mTOR mediated neuroinflammation. Microsoft PowerPoint Version 2019 (Chicago, IL, USA) and https://www.biorender.com/ version 4.0, Science Suite, Inc., Toronto, Canada were used for constructing this Figure. Some elements are from literature [28]. PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin; AKT, serine/threonine protein kinase.

in the battle against infection [35]. Morbidity and mortality are negatively impacted by the breakdown of these responses. The transmission of information between immune cells and brain neurons results in a responsive and helpful acute inflammatory reaction to the human host. This way the information is transmitted between immune cells and neurons of the brain. It results in favorable acute inflammatory reaction.

Euflammation or Immune Conditioning

Immune conditioning, also known as euflammation, is another benefit of neuroinflammation. The initiation of peripheral inflammation without illness behavior is known as inflammation. This is caused by three days of subthreshold *Escherichia coli* I.P. injections, which results in the formation of a euflammation induction locus (EIL). 2.0×10^7, 25×10^7, and 100×10^7 CFUs of *E.coli* I.P. injections are used. Upon subsequent immune stimulation, the immune system and leukocytes in the EIL release fewer cytokines [36]. It causes inflammatory signal generation, which is countered by macrophages' enhanced phagocytic possibility within the EIL. Myeloid cell's Phenotype changes in the Myeloid cells and a decline in their inflammatory characteristics were attributed to the euflammatory care. Immune-related cells (CD11b+/MHCII+, CD11b+/TLR4+, CD11b+/CD86+) were found to be reduced in the EIL, but continued to increase in the spleen as well as in the systemic circulation [37]. In addition, when energized with LPS, cultured peritoneal leukocytes produced less *IL-1*, *IL-6*, and *IL-10* mRNA [37]. This is a pretty similar phenotype to endotoxin sensitivity. Blood leukocytes increased their synthesis of IL-1, IL-10, and TNF-α outside of the EIL, phenotypic traits similar to properly trained immunity. This ambivalence is associated with euflammation and results in neuroprotection, as shown in Fig. 10, the preconditioning can be accomplished through several methods, including LPS injections, the use of anesthetics like isoflurane, and hypo and hyperthermia [38]. After a distressing brain artifact with cold or cryo-injury, conditional microglial stimulation can lead to cortical neuron ensheathing cells. A decline in inhibitory axosomatic synapses indicates a neuroprotective role. As a result, this preconditioning leads to/causes neuroprotective effects.

Signaling in Memory

The growth and plasticity of the brain are governed by neuroinflammatory signaling. An incredibly complex cytokine system is implicated in neuroinflammation according to recent studies in memory and learning [39]. IL-1, IL-6, and TNF-α, the major cytokines analyzed in these studies, are generated by a diversified/various cell types, including immune cells. These cells include neurons which maintain synapses both inside and outside the hippocampus, as well as astrocytes [40].

The survey of IL-1R3 can shed light on the impact of IL-1 on neuroinflammation. In contrast to the classical IL-

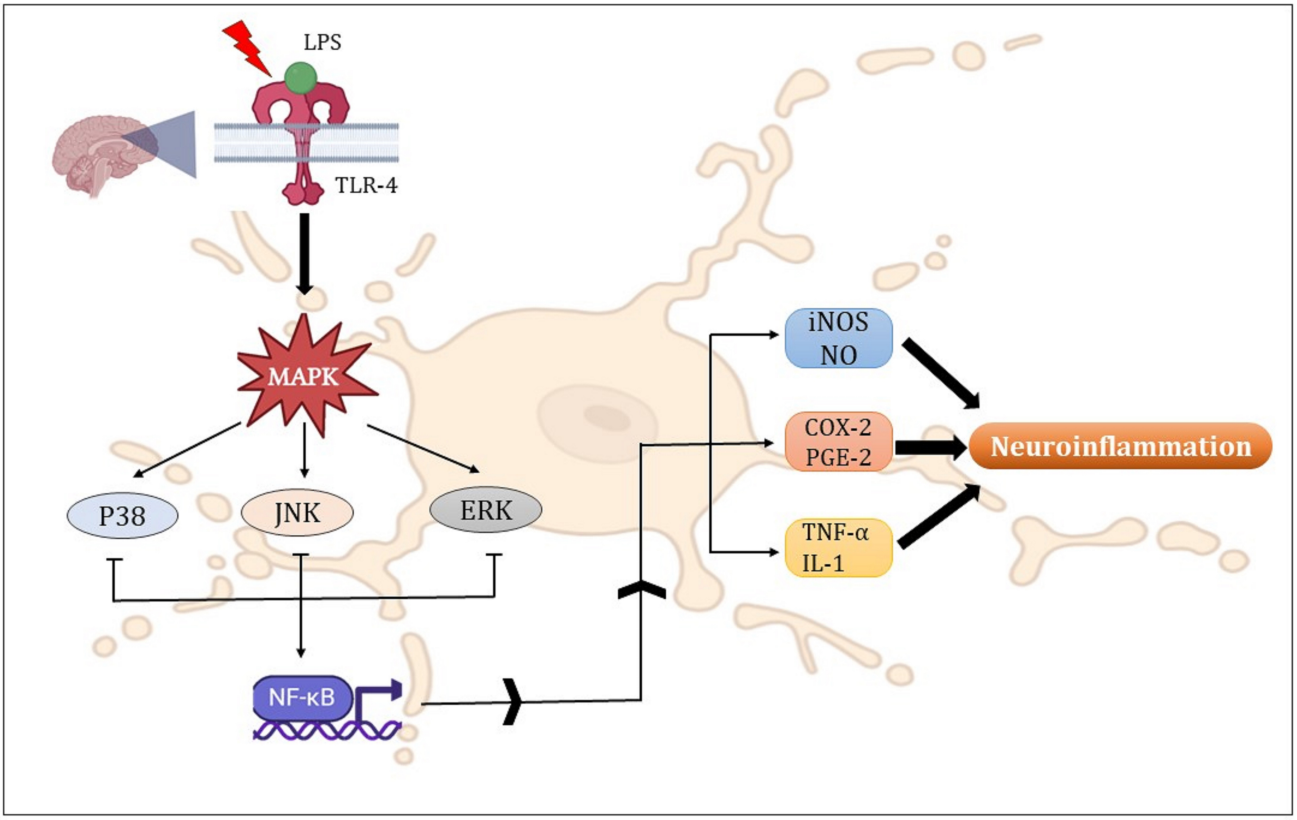

Fig. 9. MAPK-mediated neuroinflammation. Microsoft PowerPoint Version 2019 (Chicago, IL, USA) and https://www.biorender.com/ version 4.0, Science Suite, Inc., Toronto, Canada were used for constructing this Figure. MAPK, mitogen-activated protein kinase; JNK, Jun amino-terminal kinases; PGE-2, produce prostaglandin E2.

R1 present in the immune cells, this truncated protein is produced in neurons [41]. IL-1R3 is stimulated and tends to increase voltage-gated potassium current once it is conjugated with interleukin-1 receptor accessory protein B also known as IL-1RACPb. As a result, the activity of IL-1R3 and IL-1R1 aids memory and learning establishment.

Besides, IL-1β and IL-6 are involved in memory as well as the learning experience. To create an impact on neuronal plasticity, astrocytes earn neuronal signals and stimulate NF-κB pathways [39]. IL-1 promotes AMPA or NMDA-mediated transmission, whereas IL-6 suppresses glutamate secretion and synaptic plasticity [42]. Furthermore, IL-1 triggers the release of aminergic compounds in the hippocampus. Immune cells, particularly T-cells, communicate with inhabitant cells and are involved in memory and cognition [43]. Thus, neuroinflammation signaling pathways play a significant role in neurodevelopment, memory, and learning.

Promotion of Repair Process

Neuroinflammation is active, and intrinsic repair responses as seen in Fig. 10 [34]. A key finding from spinal cord injury (SCI) and traumatic brain injury (TBI) is neuroinflammation and intrinsic repair responses are active. As a result, injury triggers both inflammatory responses and restores them simultaneously. Microglial and macrophage activation, cytokine release, tissue damage, and deterioration all contribute to neuroinflammation in severe trauma. Despite this, a balance exists. A microglia/macrophage "alternative activation" (M2) profile has been identified since 1992 [44]. The neuronal tissue repair and maintenance process requires a delicate balance of classic (M1) and alternative (M2) stimulation. IL-4 and IL-3 induce M2-type macrophages, which encourage angiogenesis and repress the inflammation provoked by SCI. CD4+ cells that enter the injured tissue may generate IL-4. T-cells that produce IL-4 send a neuroprotective signal to neurons and may provide some IL-4 to native microglia. By stimulating TLR4 receptors and feeding the formation of oligodendrocytes these M2 cells can promote lengthy axon regeneration even in inhibitory surroundings [45]. To sum up, alternative microglia and macrophage activation are critical for the intrinsic repair process following SCI.

Negative Features of Neuroinflammation

Stress

Although neuroinflammation is helpful as it involves signaling from the brain to the immune system as an information exchange, it can also be considered to know

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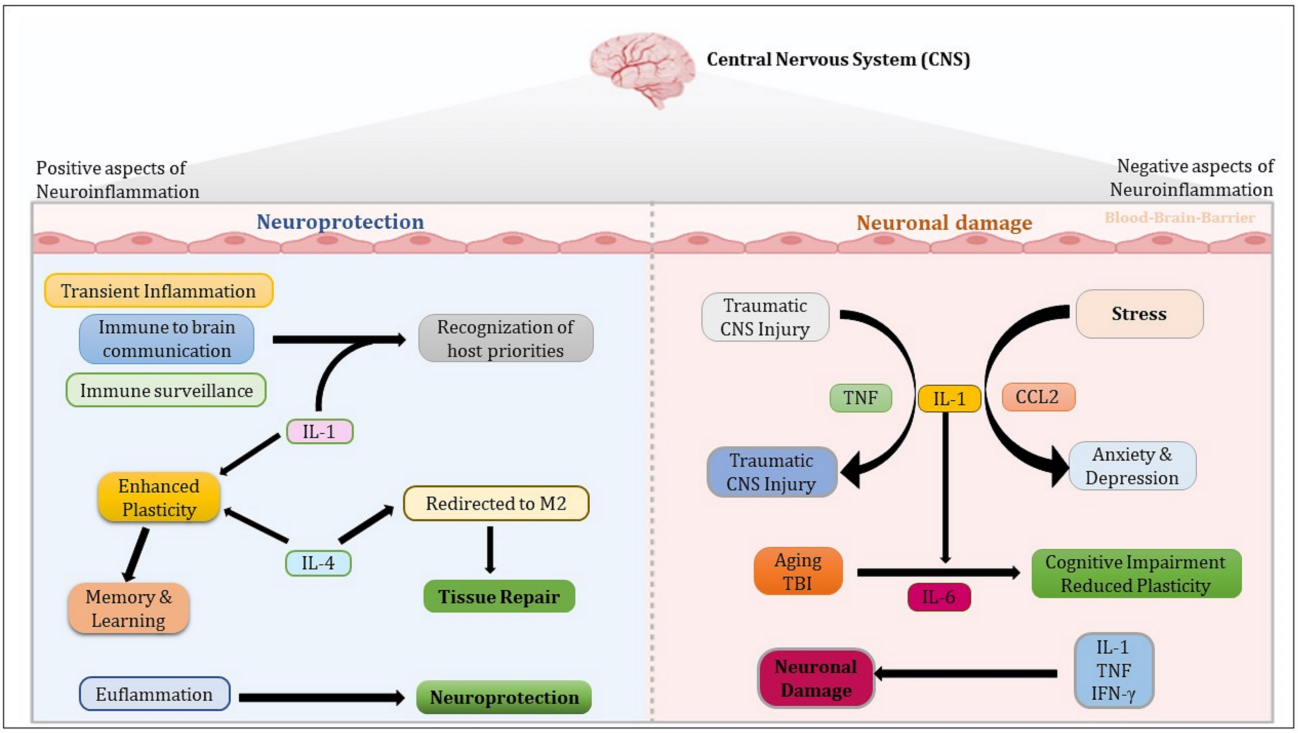

Fig. 10. Positive Vs negative aspects of Neuroinflammation. Microsoft PowerPoint Version 2019 (Chicago, IL, USA) and https://www.biorender.com/ version 4.0, Science Suite, Inc., Toronto, Canada were used for constructing this Figure. Some elements are from literature [31,34]. CNS, central nervous system.

the progression of the brain disease. The reaction to chronic or traumatic sources of stress is a perfect example of this (Fig. 10). Microglia triggers inflammatory responses as a result of chronic or traumatic stress [46–48]. In the brain, social defeat activates microglia and increases proinflammatory cytokine and chemokine formation [48]. These inflammatory processes are accompanied by increased microglia Iba1-immune reactivity, particularly in stress-responsive brain regions. Other stressors include foot shock, which is an unexpected stress that activates resident microglia [46]. The link between stress assessment and microglia stimulation has been credited to noradrenergic signaling, inflammasome stimulation, and ATP release. Sympathetic activation causes the production of proinflammatory monocytes (Ly6Chi/CD45+) that enter the bloodstream and travel to specific stress-responsive regions of the brain in the case of repeated social defeat (RSD). These monocytes encourage stress and anxiety-like behavior for a long time [48].

Aging

Aging is a good example of how interaction and the brain-immune system relationship can be harmed. MHCII, CD68, CD11b, and CD11c, TLRs, and CD86 are the mediators linked with the immune system that are significantly amplified [47,49]. Microglia, in old age, have different morphological identities. These include de-ramification, shortened processes, and fewer branching arbors [50], as well as a large number of inflammatory genes for cytokines like IL-1β and IL-6 and a corresponding significant decline in anti-inflammatory genes for cytokines like particularly IL-4 and IL-10 [51]. The 'priming' profile of microglia is signified in three ways: (1) overexpression of inflammatory molecules, (2) lowered activation threshold and time especially, and (3) enhanced responding and inflammation after stimulation. It is undeniable that as people get older, their inflammatory status rises. Terms locator proteins known as TSPO receptors are expressed in the cellular organelle, particularly in the mitochondria of the activated microglia. The ligand binds to it. TSPO levels were higher in older people as was observed in PET imaging. It represents that as age increases, the activation of microglia also rises [52]. The combination of a rise in cytokines involved in inflammation and a change in microglia phenotype with age suggests that microglia build up a primed phenotype. The aged or older brain becomes more inflammatory as a result of this.

When compared to adult controls, microglia isolated from aged or older mice have higher levels of *TNF-*α, *IL-1*β, *IL-6*, *IL-12*, *TLR2*, and indoleamine 2, 3 dioxygenase (*IBO*) mRNA after LPS (Fig. 10) [31]. Aged mice exhibit these changes in cytokine production. TNF-α, IL-1β, IL-6, IL-12, and TLR2 are cytokine factors that cause aging, memory deficits, and minimization in plasticity. In addition, IL-1β induction was elevated in MHCII+ microglia of aged mice compared to MHCII– microglia after the immune challenge [31]. These findings show that after peripheral

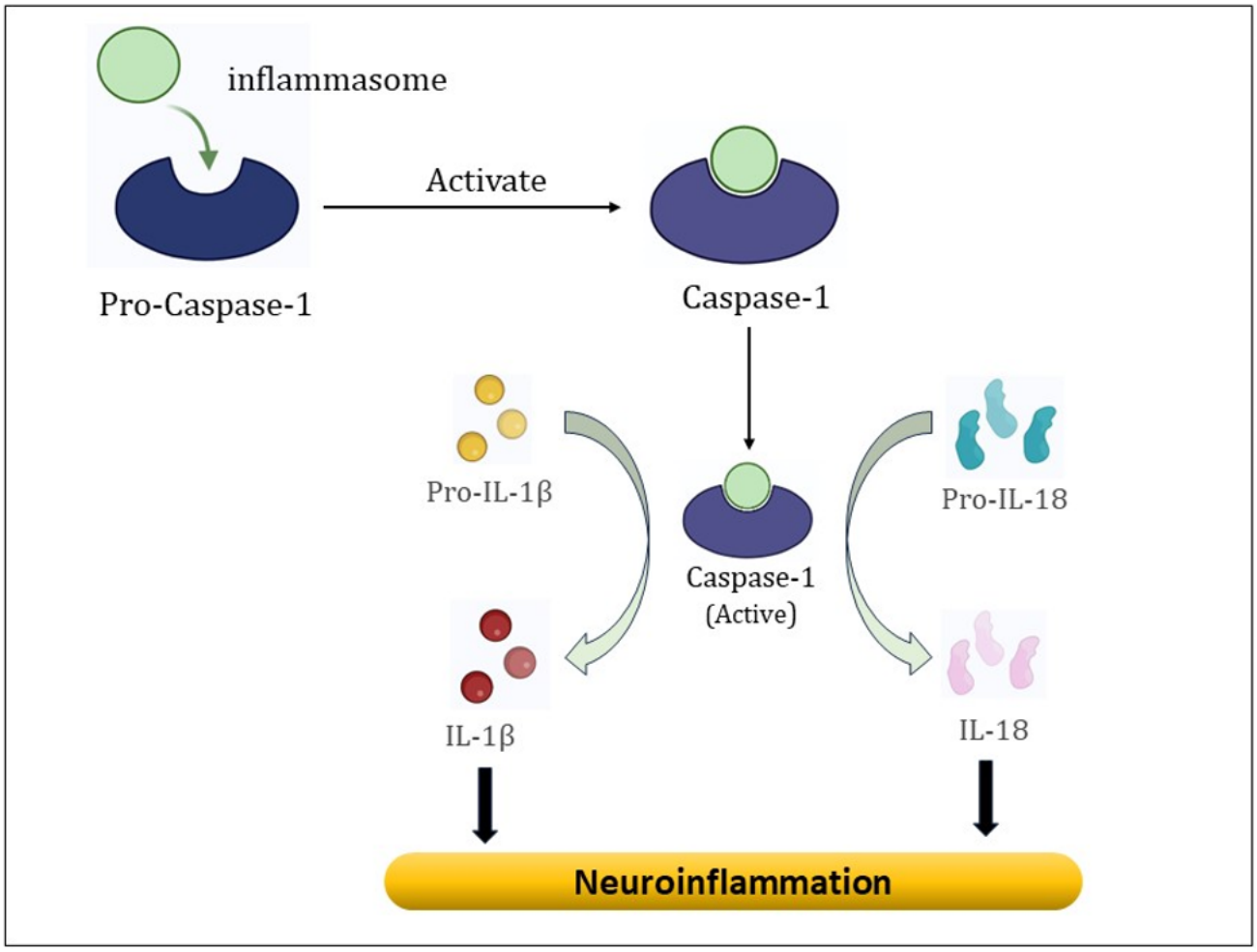

Fig. 11. Role of inflammasomes. Microsoft PowerPoint Version 2019 (Chicago, IL, USA) and https://www.biorender.com/ version 4.0, Science Suite, Inc., Toronto, Canada were used for constructing this Figure.

immune stimulation, primed MHCII+ microglia yield inflammatory cytokines in an ex-aggregated and long-lasting manner.

Traumatic Brain Injury Causes Chronic Microglial Activation

After a penetrating TBI, controlled cortical impact (CCI) causes long-term changes in microglia and astrocytes, such as enhanced MHCII expression observed in rats sixteen days later. In the cortex and thalamus, microglia near the lesion boundary express higher levels of proinflammatory mediators such as MHCII, CD68, and NADPH oxidase (NOX2), which persists twelve months post-injury. Furthermore, CCI causes an increase in the production of inflammatory cytokines in the macrophages and microglia, which is linked to augmented lesion area and neuron massive loss in the hippocampus. Such tissue damage is fairly reliable with the other experimental procedures of focal or penetrating brain trauma in that it continues over time. Midline fluid percussion injury (mFPI), closed head impact (CHI), and blast injuries are all credible and valid models of this non-penetrating, diffuse injury. In mFPI, a fluid-filled pulse is delivered straight at the brain midline without disrupting the dura, causing global brain tissue undulation and diffused axonal injury, as well as transient neurological shortfalls. In rodents, moderate mFPI triggers activated microglia which cause a change in microglial phenotype, including an increase in MHCII activity and expression of CD68. These pathological changes last for seven days to thirty days after injury [53].

Increased CD11b and CD68 microglial expression has been observed in blunt head trauma patients at both short and long-term intervals, up to sixteen years after the injury [54]. Another study discovered densely packed, reactive (CR3/43+ or CD68+) microglia 1–18 years after a single moderate or severe TBI. Microglial activation in the human brain after TBI has been detected *in vivo* using magnetic resonance imaging (MRI) methods. On activated microglia, the PK [11C] (R) is expressed to which the PK11195 ligand binds. In TBI patients, PK binding was found to be higher in the thalamus, occipital lobes, putamen, and posterior limb of the internal capsule. Persistent microglial excitation dra-

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matically increases in cell populations further leading to a focal lesion, with subcortical structures such as the thalamus and putamen playing a prominent role.

After CNS Injury, Microglia Reactivity Increases

Another sign of CNS injury is microglia reactivity to a secondary immune challenge. After an optic nerve (ON) crush injury, CD68 overexpression in resident microglia is gathered. Peripheral LPS administration twenty-eight days after ON crush injury triggers an immune response, resulting in amplified levels of cytokines (IL-1β, TNF-α, and IL-6). The development of primed CD68+ microglia is aided by this inflammatory response. Furthermore, thirty days after CNS injury caused by midline fluid percussion, both MHCII mRNA and protein levels have been increased in microglia [55]. In comparison to controls, secondary LPS causes a detrimental rise of IL-1β, TNF-α, and CCL2 in microglia from TBI (thirty-day post-injury) mice [55]. This harmful microglial activation results in withdrawal and depressive-like behavior, which is not seen in LPS-treated control mice [55]. In addition, the LPS challenge causes memory recall impairment in TBI mice. As a result, CNS injury acts as "priming evident", causing hyperresponsiveness and subsequent immune activation.

Six months after a single and repeated closed-head TBI, morphologically reactive astrocytes and microglia are visible in cortices and hippocampal regions [56]. When inflammation lasts for twelve to eighteen months, it results in spatial learning deficits [56]. The cognitive changes that occur twelve and eighteen months after a CNS injury are linked to white matter damage and elevated Iba1 levels, but not to neurodegenerative conditions. TBI with a shorter interval leads to a higher neuroinflammatory reaction, more axonal degeneration, and lower spatial memory and cognitive efficiency. As a result, numerous injuries can aggravate neuroinflammation and impaired functioning. After a TBI microglia become more reactive to subsequent stressors, which results in affective disorders, cognitive problems, and increased inflammatory cytokines.

Role of Inflammasome

The inflammasome [57] is a multi-protein oligomer that activates inflammatory responses. Proinflammatory cytokines like IL-1β and IL-18 are matured and secreted by the inflammasome [58]. Myeloid cells express inflammasomes. Caspases 1, PYCARD or ASC (Apoptosis-associated speck-like protein containing a CARD), NALP, and occasionally caspase-5 make up the inflammasome complex. Inflammasomes can also be formed by Nod-like receptors (NLRs) and AIM2-like receptors (ALRs).

The inflammasome binds to procaspase-1 through caspase activation and recruitment domain (CARD) of the adaptor protein ASC and then stimulates caspase-1. Proteolytic cleavage of pro-IL-1β into IL-1β [58], pro-IL-18 into IL-18 to induce IFN-γ secretion and natural killer cell activation, cleavage on activation of IL-33 [59,60], DNA fragmentation and cell pore formation, suppression of glycolytic enzymes, activation of lipid biosynthesis, and secretion of tissue repair mediators such as pro-IL-1 [61] are some of the early inflammatory responses. AIM2 also has a HIN200 domain, which binds foreign cytoplasmic dsDNA [62]. This stimulates NF-κB, which causes neuroinflammation, as shown in Fig. 11. Hence, NLRP inflammasome, in particular, has been linked to neurodegeneration.

Conclusion

Microglia are activated by the aging process, pollutants, oxidative aggravation, and infection due to microbes, resulting in the production of pro-inflammatory messengers like cytokines, COX-2, and NOS. Overproduction of these elements by overactivated microglia could be a major risk for neurodegeneration via a diversity of inflammatory routes, counting MAPK, COX, and PI3K/AKT. Microglia activation is among the first signs of any change in neuronal function or physiology. In the treatment of neurodegenerative diseases like multiple sclerosis, Alzheimer's disease, and Parkinson's disease, reducing inflammatory cytokines is why the microglial inflammatory reaction is regarded as a therapeutic strategy. Furthermore, the optimistic and unenthusiastic features of neuroinflammation are highlighted in this article, which may aid us in understanding how to target molecules against specific markers in a precise state of neuroinflammation.

Availability of Data and Materials

Not applicable.

Author Contributions

FSM, VRU and MMG designed the conceptualization. FSM, SK, VRU, MM, NSZ, MIS, and MMG performed the research data curation and drafted and revised the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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