REVIEW

Neuroinflammation: The hidden code through the Brain

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Received: 12 Feb 2025 | Revised: 10 April 2025 | Accepted: 23 April 2025 |Published Online: 08 May 2025

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Abstract

Neuroinflammation is a response reaction of the Central Nervous System (CNS) when triggered by a specific external stimulus. It is a positive and natural process of the body defending the vitals from infections. Excessive neuroinflammation leads to multiple pathological conditions, such as the common Alzheimer's disease (AD) and Parkinson's disease (PD). Neuroinflammation is triggered by Microglial and Astrocyte pathways of inflammation with the blood-brain barrier (BBB) changes, which could result in neuroinvasion, if it goes beyond the limit. Polarization responses influence the changes during neuroinflammation, and inflammatory mediator release disrupts the working of BBB in relation to astrocytes. Neuroinflammation is also triggered by aging when morphological changes in blood capillaries of the BBB arises. This review aims to encapsulate the key changes of microglial as well as astrocyte activation during neuroinflammation that may lead to aging related disease such as AD and PD with an intersection of Age-associated vasculopathy, suggesting the relation between BBB and aging.

Key words: *Astrocytes, Blood-Brain Barrier, Brain Aging, Cytokines, Microglia, Neurodegeneration, Neuroinflammation, Oxidative Stress*

ISSN 2816-8119

Open Access

Citation
Latif M., Noreen S., Fatima H., Ahmad H., & Sheikh N. (2025). Neuroinflammation: The hidden code through the brain. *Albus Scientia*, *2025,* Article ID e250508, 1-9.

DOI
http://doi.org/10.56512/AS.2025.1.e250508

Competing interests
The authors have declared that no competing interests exist.

Introduction

Neuroinflammation is a complex reaction of the central nervous system (CNS) in response to specific stimuli, including infection, trauma, and neurodegenerative diseases. Glial cells are triggered with the onset release of inflammatory mediators, leading to production of reactive oxygen as well as nitrogen species contributing to the cell's immune response. Although neuroinflammation plays an important role in defending the brain from infections, excessive inflammation can lead to pathological conditions like Multiple Sclerosis, Parkinson's disease, Alzheimer's disease, and several other neurological diseases (Adamu et al., 2024). Unlike the peripheral immune system, the CNS has a controlled immune response. Research reveals that a robust inflammatory response in the peripheral system, brought on by systemically being exposed to viral infection or lipopolysaccharides, can lead to movement of immune cells from the periphery to infiltrate the CNS (Sharma et al., 2021). This invasion then causes nerve cell death and neuroinflammation. When microglia are activated, pro-inflammatory messengers are dispersed in the blood-brain barrier (BBB), which weakens and as immune response initiates. As a result, peripheral immune system T-cells and macrophages go into the CNS (Ronaldson et al., 2020).

Neuroinflammation in the CNS is complex, and it has many different pathways that are of great importance, both in regard to the use and in pathology. It is important to understand these pathways to design precise strategies against neurodegenerative disorders. These pathways include the activation of microglia and astrocyte cells.

Microglia utilize phagocytosis and synaptic pruning to regulate neuronal overproduction and maintain homeostasis. Through local microenvironment interactions, they control phenotypes. Although microglia shows neuroprotective effects by removing the cell debris in neurodegenerative disorders, yet it also releases cytokines TNF-α and IFN-γ that enhance inflammation, intensifying neuronal inflammation and redox imbalance. One approach that shows promise for controlling neurodegenerative diseases is the therapeutic targeting of microglia (Maurya et al., 2021).

Astrocytes are cells that promote the proper functioning of neurons and synapses. However,

because of their significant chemokine release, they might exacerbate neuroinflammatory processes as well (Rama Rao et al., 2015). Reactive astrocytes exacerbate microglial inflammation in the glial scar following spinal cord injury by activating the fibronectin/β1 integrin process (Yoshizaki et al., 2021). A sufficient number of reactive astrocytes within the hippocampus cause cognitive decline via modulating synaptic transmission and release of LCN2. The pathophysiology of cognitive abnormalities in brain diseases associated with neuroinflammation may be influenced by this aberrant interaction between glial cells and neurons (Kim et al., 2024).

An immunological reaction in the CNS leading to neuroinflammation is a serious risk to human health. Neuroinflammation has been demonstrated to be significantly influenced by the receptor serine/threonine protein kinase family (RIPK) family. This receptor is well-known in neuroinflammation research. Previous studies focused on the connection between neuroinflammation and RIPK1.

To understand neurodegenerative illnesses, it is important to grasp the narrow path that separates normal neuroinflammation from neuroinvasion. While protective neuroinflammation serves useful purposes, pathogenic inflammatory processes have the potential to exacerbate the harm.

The effects of inflammatory responses on the brain can vary, based on the degree of activation at which they occur throughout different stages of neurodegeneration. When microglia and astrocytes are mildly activated, it typically illustrates neuroprotective effects and reduces the early symptoms of neurodegeneration.

Neuroinflammation depicts a strong part in the CNS, involving astrocytes and microglial cells, contributing to cellular aging contributing to the effects on both the CNS as well as PNS by triggering various neuronal pathways. This review focuses the alternation of neuroinflammatory pathways involved in the process of aging.

Neuroinflammatory Changes during Aging

Aging involves three neuroinflammatory pathways i.e.,

- Microglial Activation
- Astrocyte Function
- Blood Brain Barrier (BBB) Changes

Progressive tissue and organ deterioration is a hallmark of aging, and it is positively correlated with a higher death rate. The brain is one of the most severely impacted organs. Age-related alterations in the brain include aberrant neuronal activity, impaired calcium homeostasis, dysregulated function of mitochondria, and elevated reactive oxygen species (ROS) levels. All of these alterations work together to cause cognitive decline (Fan et al., 2024).

Neurodegenerative disorders are significantly influenced by aging, such as in Parkinson's disease (PD) and Alzheimer's disease (AD). Numerous neurodegenerative disorders exhibit neuroinflammation, and microglia have been recognized in causing and aggravating this condition (Mattson & Arumugam, 2018). The hallmarks of neurodegenerative disorder include gradual and long-term loss of neurons, disturbances in mitochondrial homeostasis, abnormally high quantities of cytotoxic chemicals including extracellular debris, impaired DNA repair, aberrant neuronal network activity, high levels of pro-inflammatory proteins, and ROS generation, which leads to oxidative stress (Guzman-Martinez et al., 2019).

Microglia Activation

Glial cells have a significant impact on aging. In the CNS of a developing embryo, neural stem cells intensify the division of the majority of different kinds of cells that make up the brain. In addition to neurons, these cells comprise of non-neuronal cells including glial cells (microglial cells, oligodendrocytes, ependyma, and astrocytes), which makes up over 90% of all CNS cells (Dos Santos et al., 2020).

Development of Microglia

Erythromyeloid progenitors in the yolk sac (YS) mature into YS macrophages giving rise to microglia. Prior to the blood–brain barrier (BBB) maturation, these are the precursors that populate the CNS parenchyma before differentiating into microglia (Goldmann et al., 2016). Microglia colonize the central nervous system and sustain their number through self-renewal at a rate of 0.5 to 16%. Microglia show regional variability within the CNS, (Mrdjen et al., 2018) they are widespread in certain areas, like the substantia nigra, basal ganglia, and hippocampus region, while they are few in the cerebellum and brain stem cells. When microglia establish in the CNS, they show certain traits that set them apart from tissue-resident macrophages. These traits consist of expression of distinct microglia signature genes like trans-membrane protein 119 (TMEM119), P2Y purinergic receptor 12 (P2RY12), and Sal-like protein (SALL1), as well as the down regulation of specific cell surface proteins like cluster of differentiation 45 (CD45) and MHC class II molecules (MHCII) (Wendimu & Hooks, 2022).

Microglia are mostly ramified microglia at rest. They become activated and change their morphology in response to pathogen or brain injury, misfolded proteins, and cellular debris in neurodegenerative disease (Singh, 2022). When microglial activation occurs, the morphological state changes from ramified to amoeboid, with an expanded cell body, shorter processes, and a significant number of cytoplasmic vacuoles (Wolf et al., 2017). As a result of microglial dystrophy, elderly microglia change from a ramified state to a spheroid-activated phenotype. Additionally, aged microglia, sometimes known as "primed microglia", have an inflammatory hypersensitivity phenotype. Primed microglia generate a lot of pro-inflammatory cytokines, chemokines, and reactive species and are hyperreactive to inflammatory and neurotoxic stressors.

Other microglial morphologies have also been reported including satellite microglia, dark microglia, and rod-shaped bipolar microglia. Microglia express immunological pattern recognition receptors commonly known as Pattern Recognition receptors (PRRs) that identify damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). DAMPs cause sterile inflammation, while PAMPs cause antimicrobial action and inflammation. Microglial PRRs correlate with PAMP/DAMPs, triggering intracellular cascades and the onset of transcription factors (Kumar & Stewart IV, 2024; Mahaling et al., 2022).

Microglia activation, influenced by changes in cell surface receptor expression, polarization responses, and inflammatory

mediator release, can either protect or harm the tissues (Figure 1; Tang & Le, 2016). Microglia activation is characterized by two polarization states: M1-like, linked to pro-inflammatory and neurotoxic reactions, and M2-like, primarily mediating neuroprotective with anti-inflammatory outcomes (Yang et al., 2018).

Neuroprotective M2 phenotypes of microglia are polarized into the neurotoxic M1 phenotypes (Wu et al., 2022). By increasing phagocytosis and producing anti-inflammatory cytokines (like IL-4, IL-10, and IL-13), the M2 phenotype contributes to the inflammatory response to AD pathology and has neuroprotective benefits (Wang et al., 2021). Microglial polarization from M2 to M1 phenotypes takes place in the latter stages of AD (Farhangian et al., 2023). Through generating ROS and pro-inflammatory molecules (like IL-1β, IL-6, TNF-α, and IL-18), the M1 microglia worsens AD pathogenesis (Tang & Le, 2016; Yang et al., 2022).

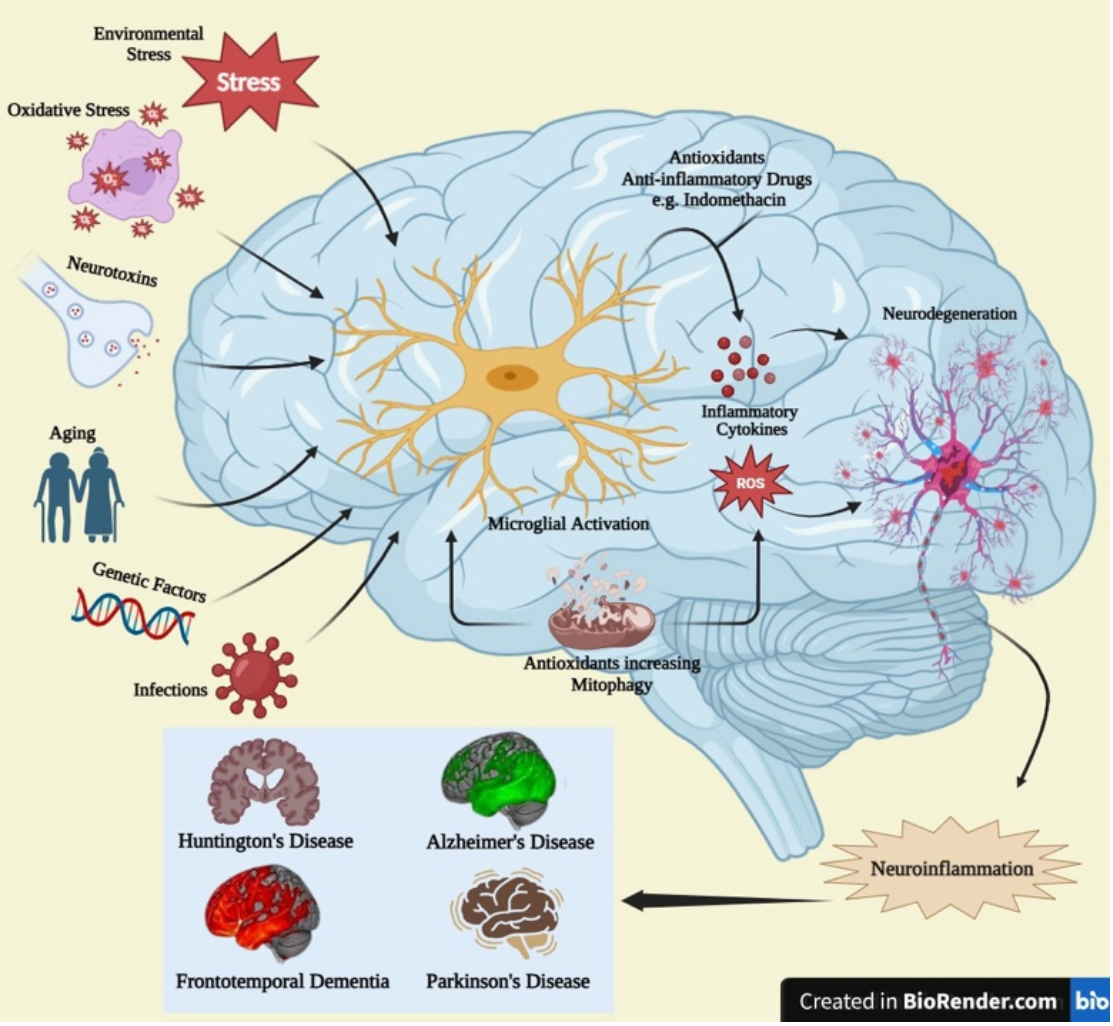

Figure 1: Microglial activation and neuroinflammatory diseases: a connection Age, endogenous or external infection, oxidative stress, and hereditary factors all cause microglia to become activated, which can result in neuroinflammation and neurodegeneration. As people age, activated microglia generate too much ROS, which sets off the nuclear factor (NF)-κB signaling cascade. Neuroinflammation is triggered by activated microglia to encourage cell death and neurological injury. Potential treatment approaches include stopping microglial activation and restoring mitochondrial function.

Oxidative stress and neuroinflammation are closely linked. Reactive nitrogen species (RNS) and ROS are released in excess, which triggers the signaling pathways that cause glial cells, like astrocytes and microglia, to become activated (Wu et al., 2023). Excessively activated glial cells generate inflammatory cytokines that worsen mitochondrial damage and oxidative stress. This procedure sustains the elevated or high release of proinflammatory cytokines and creates vicious loops (Solleiro-Villavicencio & Rivas-Arancibia, 2018).

Astrocytes

Astrocytes, glial, and microglia are crucial for neuronal circuit development and synapse maintenance. They construct brain walls and blood vessels and secrete chemicals like thrombospondins and glypicans (Sparcl1) (Allen & Eroglu, 2017). Microglia phagocytic capacity was directly enhanced by the cytokine interleukin (IL)-33, which is generated by growing astrocytes.

Adult brain microglia and astrocytes maintain homeostatic neuronal activity by expressing glutamate, GABA, and adrenergic receptors, allowing them to perceive neurotransmitters and respond to intracellular Ca^{+2} changes (Adamsky et al., 2018). To control neuronal excitability and perhaps react to other neurotransmitters, astrocytes also ingrain glutamate (Poskanzer & Molofsky, 2018).

Polymerization of Astrocytes

Similar to microglia, astrocytes have distinct phenotypes and roles depending on the stage of neurodegenerative diseases (Wu et al., 2023; Yang et al., 2022). The astrocytes are dormant during physiological situations protecting synaptic function, neuroimmune response, brain homeostasis, and neurotransmitter regulation (Preman et al., 2021). Astrocytes, activated in response to brain trauma or neurodegenerative disorders, exhibit distinct roles, predominantly polarizing into the neuroprotective A2 phenotype in early stages of AD and PD (Fan & Huo, 2021). Oxidative stress, neuroinflammation, mitochondria fragmentation, and excessive Aβ buildup cause A2 astrocytes to polarize to the A1 phenotype, producing pro-inflammatory cytokines that worsen Alzheimer's disease pathology (Habib et al., 2020; Leng & Edison, 2021). Astrocytes contribute to neuroinflammation by altering the BBB and producing inflammatory cytokines (Vainchtein & Molofsky, 2020).

Synchronized actions of astrocytes and microglia maintain the normal functioning of the BBB, neuroinflammation, and other cellular processes in both healthy and pathological conditions (Yang et al., 2020). Research shows astrocyte derived cytokines, including chemokines and inflammatory cytokines, control microglial activity, increase pro-inflammatory cytokine production, encourage microglial polarization, and worsen neuronal damage after intracerebral hemorrhage .(Shi et al., 2020) With IL-33 astrocytes regulate microglial migration, phagocytosis, microglial-mediated synaptic pruning, and neural circuit development (Vainchtein et al., 2018). By increasing blood-brain barrier permeability, astrocyte-derived cytokines facilitate microglial migration, phagocytosis, and recruitment of immune cells (Yang et al., 2020) Meanwhile, microglia also control astrocyte activity and intensify neurotoxicity and neuroinflammation in brain trauma and neurodegenerative disorders (Rothhammer et al., 2018). Co-cultures of astrocytes and microglia dramatically increase the production of neurotoxic cytokines from astrocytes induced by lipopolysaccharide (LPS), indicating that microglia amplify the neurotoxic impact of astrocytes after excessive activation (Luchena et al., 2022).The fragmented mitochondria generated by the microglia in AD and normal aging help astrocytes polarize toward the neurotoxic A1 phenotype (Clarke et al., 2018).

Table 1: Role of Chemokines and risk of neurodegeneration.

Chemokine / Cytokine	Role	Risks of Neurodegeneration	References
IL-1β (Cytokine)	Stimulates the synthesis of more inflammatory mediators and the activation of microglia.	A worsening of neurodegenerative disorders, persistent inflammation, and neuronal damage.	(Adamu et al., 2024; Kiguchi et al., 2012)
TNF-α (Cytokine)	Overexpression of this inflammatory response-related protein can cause neurons to undergo apoptosis.	Neurotoxicity, elevated neuronal death, and involvement in diseases such as Alzheimer's.	(Adamu et al., 2024; Hamilton, 2020; Ramesh et al., 2013)
IL-6 (Cytokine)	Controls immunological responses and has dual roles as a pro- and anti-inflammatory cytokine.	Irregular levels can contribute to persistent inflammation and are linked to multiple sclerosis along with different neurological disorders.	(Brown et al., 2010; Ma et al., 2023)
IL-23 (Cytokine)	Contributes to maintaining inflammatory responses and stimulates pathogenic activity by activating T cells.	A greater prevalence of autoimmune diseases, such as multiple sclerosis, and persistent inflammation that damages the brain.	(Ma et al., 2023)
CCL2 (MCP-1) (Chemokine)	Contributes to the mobilization of immune cells by attracting monocytes to areas of inflammation.	Neuropathic pain aggravation, persistent neuroinflammation, and possible neurodegenerative involvement.	(Adamu et al., 2024)
CXCL10 (IP-10) (Chemokine)	Boosts T-helper 1 (Th1) responses and aids in attracting triggered T cells to inflammatory areas.	In conditions like Alzheimer's, chronic neuroinflammation can result in neuronal damage and cognitive impairment.	(Adamu et al., 2024)
Fractalkine (CX3CL1) (Chemokine)	It possesses both pro-inflammatory and with neuroprotective effects; and controls microglial activation & neuronal survival.	Excessive microglial activation brought on by dysregulation may result in neurodegeneration and compromised neuronal function.	(Fornari Laurindo et al., 2024)

Blood-Brain Barrier (BBB) Changes

The BBB is a crucial barrier that maintains CNS function and homeostasis, preventing invasion and neuronal death (Iadecola, 2017). The BBB's health relies on proper functioning of astrocytes, pericytes, basement membrane, and intricate junctions between brain endothelial cells to create a continuous barrier (Dong, 2018). Perivascular components maintain and control the characteristics of the blood-brain barrier, including cerebral blood flow, neuroinflammation, neurovascular coupling, angiogenesis, and vasculogenesis (Joost et al., 2019). Perivascular macrophages and microglia play crucial roles in angiogenesis and BBB recovery, regulating inflammation, BBB stability, integrity, and vasoconstriction (Hartmann et al., 2022).

Aging and BBB changes

Age-associated vasculopathy in people results in morphological changes in brain capillaries, including irregular branching patterns, uneven diameter, thickening of basement membrane,

increased vascular tortuosity, and clusters resembling raspberries (Ek Olofsson & Englund, 2019). Capillary vascular abnormalities manifest as metabolic changes, decrease in Glut-1 expression, increase in pinocytotic vesicles, and lessen mitochondria and BBB hyperpermeability owing to junction structural changes (Dickie et al., 2021; Parodi-Rullán et al., 2021). NVU remodeling is significant, involving recruitment of macrophages, microglia, leukocytes, astrocytic end-feet enlargement basement membrane thickening, loss of vessel-matrix connections and pericyte engagement (Figure 2; Ceafalan et al., 2019; Ding et al., 2020; Li et al., 2023). Age impacts cerebrovascular and BBB function, contributing to neurodegenerative disorders, with capillaries being particularly vulnerable due to zonation effects rather than brain region (Zhao et al., 2020).Aging leads to vascular-guided damage in the brain's blood vessels, with a diminished representative expression of key tight junction (TJ) proteins like occluding, ZO-1, and claudin-5 linked to BBB leakage (Stamatovic et al., 2019). Claudin-5 down regulation is a key indicator of aging BBB, but TJ remodeling also involves non-typical TJ proteins of claudin-1, found in aging leaking blood vessels (Bony et al., 2021).

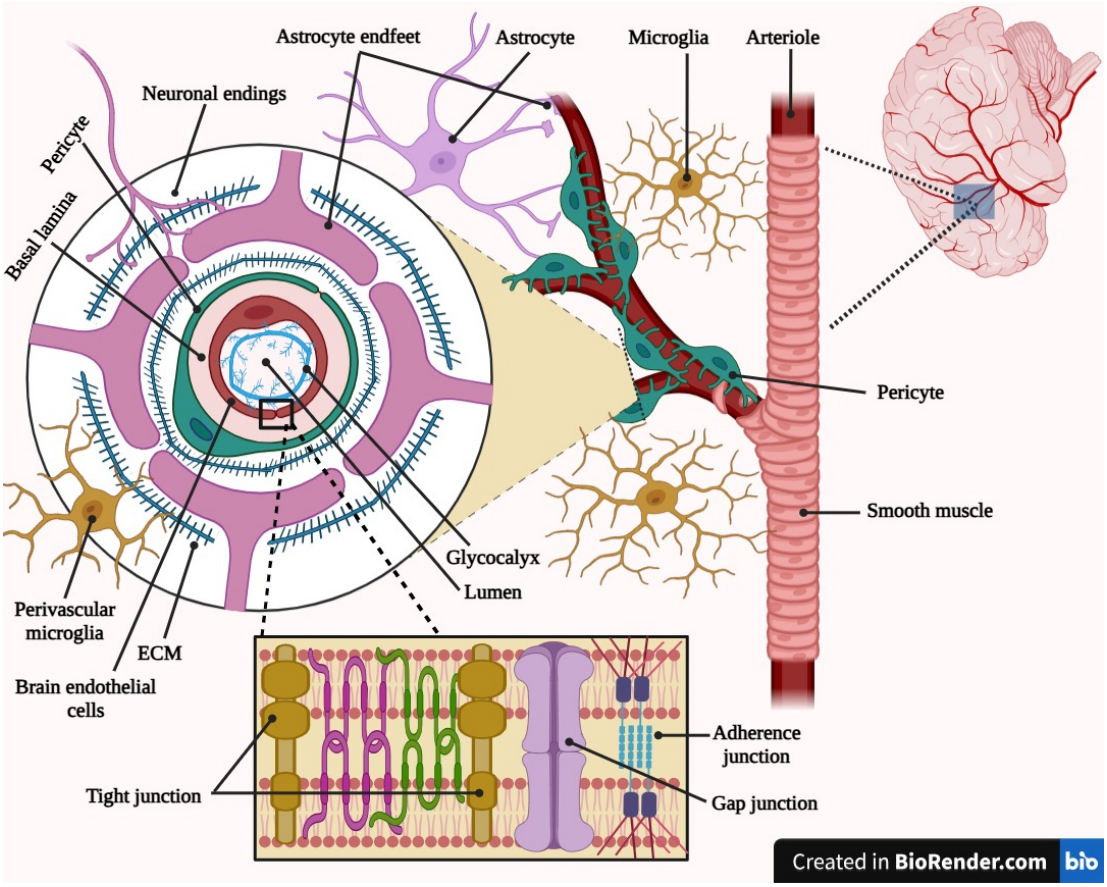

Figure 2: Diagrammatic illustration of the BBB/ Neurovascular Unit (NVU) cellular structure. The junctional complex (box) that limits paracellular mobility is a characteristic of brain endothelial cells that are BBB-endowed. Tight junctions, adherens junctions, and gap junctions make up the junctional complex.

Cell and barrier damage is likely caused by endothelial-based processes like inflammation, mitochondrial damage, epigenetic modification, and noncoding RNA (Chen et al., 2020; Lu et al., 2021). NVU remodeling may exacerbate endothelial and barrier aging processes, involving reduced pericytes, brain endothelial cells (BEC) pericyte contact loss, reactive astrocytes, as well as altered neurovascular coupling (Kalaria & Hase, 2019).

Aging affects the basement membrane, interstitial extracellular matrix (ECM), and BEC glycocalyx, leading to changes in glycocalyx content, basement membrane thickness, collagen IV buildup, and interstitial ECM expression, potentially causing capillary disease and decreased BBB function (Nikolakopoulou et al., 2020; Reed et al., 2019).

Conclusion

Neuroinflammation is a natural process of the body in which microglial cells, as well as astrocytes, have a significant role, with the interference of the BBB, but excessive neuroinflammation could lead to negative impacts on the body, leading to neuroinvasion. This usually happens due to an immunological reaction in the CNS. Neuroinflammation could lead to neurological disorders as well as aging disorders. By proper therapeutic targeting of microglia, neuroinflammation could be cured. Proper therapeutic targeting of microglial cells, as well as deciphering the role of aging with the BBB, could lead to significant outcomes on the process of understanding and improving how neuroinflammation could be altered during neurodegenerative diseases.

Authors Contribution

ML, SN, HF did literature review, curated data and prepared the initial draft. SN and ML drew the visual illustrations. HA reviewed and edited the initial draft. The study was conceptualized, designed supervised, and validated by NS.

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