IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

The Impact of Neuroinflammation on the advancement of Neurodegenerative Disorders

[1]J. Ramganesh, [2] S. Anu jeya, [3] V. Abirami

[1]M. pharm, [2] M. pharm, [3]M. pharm

[1] Department of Pharmacology,

[1]Arulmigu kalasalingam college of pharmacy, Srivilliputhur, Tamil Nadu, India

Abstract: Neuroinflammation is a significant pathological mechanism that plays a crucial role in the onset and advancement of neurodegenerative condition including Amyotrophic Lateral Sclerosis, Parkinson's disease, and Alzheimer's disease. Prolonged stimulation of microglia along with astrocytes, triggered due to external toxins, microbial infections, and genetic predisposition, leads to excessive secretion of proinflammatory cytokines, oxidative stress, along with the generation of neurotoxic mediators. These processes result in progressive neuronal damage and synaptic dysfunction. Commonly used anti-inflammatory agents such as NSAIDs and minocycline provide limited clinical benefit. Due to the restricted effectiveness of conventional therapies, researchers are exploring new and more effective treatment strategies. Advanced approaches under development include stem cell–based therapies, GLP-1 receptor agonists, and RNA-based therapeutics targeting inflammatory pathways through mechanisms involving microRNAs and aptamers. These strategies aim to promote neuroprotection, immunomodulation, reduction of oxidative stress, and suppression of proinflammatory signalling. This review highlights the underlying causes and cellular processes of neuroinflammation and examines emerging therapeutic strategies that may slow or modify disease progression rather than merely providing symptomatic relief.

Keywords:
Neuroinflammation, Neurodegenerative diseases, Microglial activation, GLP-1 receptor agonists, RNA-based therapeutics (microRNAs and aptamers)

I. INTRODUCTION

Amyotrophic lateral sclerosis (ALS), Parkinson's disease, and Alzheimer's disease are largely associated with long-term neuroinflammation. This occurs due to the presence of inflammatory cytokines including TNF-α, IL-1β, and IL-6, which are released via activation of microglia and astrocytes within the brain. Normally, microglia and astrocytes play a protective role in the brain. However, excessive secretion of inflammatory cytokines damages neurons, impairs synaptic function, and reduces neurogenesis. NSAIDs, glucocorticoids, and minocycline are the current treatments used to reduce inflammation. However, they show only mixed efficacy and do not provide complete recovery, indicating the need for novel therapeutic approaches. Emerging and future therapies such as probiotics, fecal microbiota transplantation (FMT), and stem cell therapies (mesenchymal and neural stem cells) may help reduce neuroinflammation and slow down disease progression.(1)In normal conditions, neuroinflammation protects the brain from injury or infection through an immune response. However, when it is prolonged, it contributes to condition including Alzheimer's disease and multiple sclerosis. Excessive release of pro-

inflammatory cytokines damages neurons, impairs synaptic function, and reduces neurogenesis. This leads to cognitive decline and worsens protein pathologies such as amyloid-β and tau, which are responsible for cognitive decline observed in Alzheimer's disease.Targeted anti-inflammatory therapies may help control neuroinflammation and slow down disease progression.(2)

Neuroinflammation is an immune response within the brain linked to disorder like Alzheimer's disease, Parkinson's disease, and depression. Initially, it protects the brain from injury or infection. However, long-term inflammation causes neuronal damage and impairs brain function. It is influenced by factors such as aging, infection, and sex hormones. Neuroinflammation can be reduced through regular exercise and anti-inflammatory treatments(3)

Causes of Neuroinflammation

Air Pollution – Shannon Levesque Study

In this research, investigators examined the impact of sub-chronic diesel exhaust (DE) exposure on the brain. During the experiment, male Fischer 344 rats were subjected to varying concentrations of diesel exhaust for a period of six months to assess the development of neuroinflammation and early neuropathological markers. The findings revealed elevated TNF-α levels in most brain regions, while no significant changes were detected in the cerebellum. These results suggest that prolonged exposure to diesel exhaust can trigger inflammatory responses within the brain. The researchers therefore concluded that chronic exposure to diesel exhaust, a major component of air pollution, may increase the risk of neurodegenerative disorders and emphasized the importance of further studies to understand the long-term consequences of such exposure.(4)Another investigation evaluated the influence of air pollution on brain inflammation and pathology resembling Alzheimer's disease in humans. The researchers analyzed post-mortem brain samples from individuals who had lived their entire lives in highly polluted cities, including Mexico City and Monterrey, and compared them with samples from residents of less polluted regions. The results demonstrated that individuals from polluted urban areas had significantly higher concentrations of cyclooxygenase-2 (COX-2), an inflammatory marker, as well as β-amyloid (Aβ42), a protein linked with Alzheimer's disease. These alterations were primarily observed within the frontal cortex, hippocampus, and olfactory bulb. Such findings indicate neuronal dysfunction and early Alzheimer's-like pathological changes. The study concluded that long-term exposure to air pollution contributes to brain inflammation and may accelerate neurodegenerative progression.(5)Further research assessed the effects of prolonged air pollution exposure in Mexico City on both the body and the brain, with observations reported in canines and children. The study focused mainly on systemic inflammation, which resulted in elevated levels of COX-2 and IL-1β, increased pro-inflammatory cytokines, inflammation of the respiratory tract, and disruption of the nasal and olfactory barriers. Additionally, the researchers reported greater oxidative stress in the brain along with the accumulation of β-amyloid (Aβ42) in the frontal cortex and olfactory bulb. These alterations represent early indicators of Alzheimer's disease. Variations in heart rate and endothelial dysfunction were also observed as cardiovascular effects. Overall, the study concluded that chronic exposure to air pollution, particularly particulate matter, can damage the brain and increase the likelihood of cardiovascular disease among residents of heavily polluted regions.(6)

Another investigation described the important role of microglia. Microglia function as the primary immune cells of the brain and are essential for immune defense and protection in neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, Multiple sclerosis, and HIV-associated dementia. Under normal physiological conditions, microglia protect neural tissue when their activity is well regulated. However, excessive activation may lead to neuronal damage. Various stimuli, including lipopolysaccharide (LPS), amyloid-β, interferon-γ, thrombin, and pathogens, can stimulate microglial activation, leading to the secretion of pro-inflammatory cytokines (TNF-α, IL-1β), nitric oxide (NO), and reactive oxygen species (ROS). Excessive release of these mediators causes neuronal damage and neurotoxicity. Reactive microgliosis refers to the chronic activation of microglia that maintains continuous inflammation, neuronal injury, and faster disease progression. The article suggests that suppression of microglial activation may protect the brain by using agents such as minocycline, dexamethasone, retinoic acid, endocannabinoids, and TGF-β1. Further research is needed to better understand resting microglial physiology and to develop safer therapies for inflammation control(7)This study states that chronic microglial activation is a major reason for progressive neuron loss in neurodegenerative diseases. Brain exposure to toxins, infection, or injury activates microglia. Initially, they play a protective role by removing pathogens and damaged cells. However, chronic activation causes microglia to release harmful molecules including TNF-α, ROS, and additional inflammatory mediators.

NADPH oxidase plays a major role in excessive ROS production, increasing oxidative stress and damaging neurons. This sustained response is referred to as reactive microgliosis, which creates a self-sustaining inflammatory cycle that particularly damages dopaminergic neurons in Parkinson's disease.[8]This study investigated how long-term air pollution exposure in Mexico City causes neuroinflammatory responses and neurodegenerative changes in children and young adults. The study analysed high levels of air pollutants, especially extremely fine particulate pollutants (UFPM), which are capable of directly entering brain tissue and cause neuro-inflammatory reactions and impairment of the blood–brain barrier. These are early neurodegenerative markers. The study observed these changes even in young and healthy individuals and showed an increased likelihood of developing Alzheimer's disease and Parkinson's disease. Individuals among genetic vulnerability, particularly those individuals possessing the APOE ε4 allele showed a higher risk of inflammation, increased oxidative stress, and faster neurodegeneration. The study concluded that both environmental exposure and genetics together increase the risk of neuroinflammation and neurodegeneration.[9]

Microbial Infection

This review paper explores how persistent microbial infections are related to neurodegenerative disorders such as Multiple sclerosis, Parkinson's disease, and Alzheimer's disease. It describes three primary pathways the gut–brain route, lung–brain route, and nasal–brain route, through which bacteria, viruses, and fungi may penetrate the central nervous system and trigger neuroinflammatory and neurodegenerative processes.The study explains how microbial components such as LPS and viral particles activate microglia and astrocytes within brain tissue, resulting in persistent inflammation. This chronic inflammation causes injury to neuronal cells and promotes neurodegeneration. The review also discusses the potential use of certain antibiotics and therapies targeting specific neuropathogenesis as treatment strategies. However, more clinical research is needed. The study concluded that infection-induced inflammation gradually contributes to neurodegeneration.[10]

Diabetics

In this experiment, rats with streptozotocin-induced diabetes were used. Streptozotocin damages the pancreatic β-cells responsible for insulin production. Because of this, levels of glucose in the bloodstream increase (hyperglycemia), which is similar to human diabetes. The extract of Borreria hispida markedly lowers blood glucose concentration and enhances glucose tolerance. The plant's phenolics along with flavonoid compounds have anti-inflammatory as well as antioxidant properties that lower levels of cytokines including IL-1β and TNF-α, which consequently decreases inflammatory activity.

The study concluded that hyperglycemia and together with oxidative stress represent major contributors to neuroinflammation. Therefore, the Borreria hispida extract may help reduce the risk of diabetes-associated neurodegeneration.[11] In this experiment, rats with STZ-induced diabetes were used. STZ damages insulin-producing pancreatic β-cells. As a result, insulin production decreases while blood glucose concentration increase (hyperglycemia). The methanol-derivative extract obtained from Pavetta indica significantly reduces blood glucose levels and controls diabetes.This plant contains abundant phytochemical components including flavonoids constituents. These compounds are strong antioxidant compounds that reduce oxidative stress, prevent free radical formation, protect brain cells, and reduce inflammation.The study concluded that the methanolic extract of Pavetta indica Linn reduces oxidative stress and inflammation, thereby preventing diabetes-associated neurodegeneration.[12]

In this study, rats with isoproterenol-induced myocardial infarction were examined. Isoproterenol causes oxidative stress and damages heart muscle. The plant Merremia emarginata extract was evaluated for its cardioprotective effect. The study discovered that the extract prevents lipid peroxidation, which produces oxidative stress and damages heart muscle. The plant extract maintains the normal histological structure of heart tissue and reduces myocardial damage. It also reduces elevated levels of cardiac enzyme markers such as LDH, CPK, CRP, and SGOT.The study confirmed that the extract reduces oxidative stress and prevents heart muscle injury. The extract has anti-ischemic potential.[13]

Emerging Therapeutics

Rahimi Darehbagh stated that stem cell–based therapy represents a promising approach for treating neurological conditions. Through cell replacement, damaged neurons are replaced with new functional cells. Through paracrine signaling, stem cells release growth factors and cytokines that repair surrounding damaged cells. Through immunomodulation, stem cells reduce overactivation of microglia and decrease neuroinflammation. They also activate endogenous repair mechanisms in the brain to improve neurogenesis and tissue repair.[14]Mesenchymal stem cells (MSCs) are among the stem cell types most frequently applied, which can be readily obtained from bone marrow and adipose tissue sources. These Stem cell–based therapies mainly involve neural stem cells (NSCs) and induced pluripotent stem cells

(iPSCs), for managing neurological diseases. NSCs are present in the brain and help in brain repair and regeneration. Induced pluripotent stem cells originate from mature somatic cells that are reprogrammed back to a pluripotent condition, which can generate patient-specific neural cells.Stem cell therapies are studied for targeting neurological conditions including Alzheimer's disease, Parkinson's disease, Multiple sclerosis and Stroke. They act through mechanisms such as reducing neuroinflammation and enhancing synaptic connectivity. In stem cell therapy, current challenges include tumorigenicity, immune rejection, delivery limitations, and long-term safety issues. Ongoing research is advancing toward improving safety and effectiveness through gene editing technologies and patient-specific therapeutic strategies.(15)

Joshi Study: Stem Cell Therapy for Neuropathic Pain

The study mainly used neural stem cells (NSCs) and mesenchymal stem cells (MSCs) as therapeutic strategies for neuropathic pain and modulation of neuroinflammatory responses. Stem cells supress activation of glial cells and produce anti-inflammatory cytokines that control pain-related inflammation. They secrete neurotrophic factors that release growth factors and repair damaged neurons. They also suppress excitotoxic pathways, including NMDA receptor signaling, and reduce central sensitization and pain response. MSC-derived extracellular vehicles (EVs) release vesicles that provide additional healing effects.

Even though the results are encouraging, there are still issues regarding therapeutic dose, administration route, and long-term safety confirmation. Further research is necessary.(16)

MSCs and their extracellular vesicles have potential for stroke treatment by reducing neuroinflammation. After stroke, ischemic injury disrupts the blood–brain barrier (BBB), activates microglia, and triggers the release of inflammatory cytokines, which worsen neuronal damage. The main role of MSCs is to reduce inflammation, provide neuroprotection, stimulate neurogenesis, improve angiogenesis, and enhance brain repair processes. MSC-derived EVs are a cell-free therapy option that can penetrate the BBB and have a low risk of immune rejection. They are safer compared to whole stem cells. This study demonstrated that MSCs are safe and show certain functional improvements in clinical trials. EVs are still in the preclinical stage. Early research shows better improvement and suggests that they may become a strong and effective therapy in the future, but further research is needed for final approval.(17)

Therapeutic Potential of GLP-1 Receptor Agonists in Alzheimer's Disease (Du et al., 2022)

GLP-1 receptor agonists were initially developed for the treatment of Type 2 diabetes. These agents lower circulating blood glucose levels by improving insulin secretion. Recent studies suggest that these drugs may also be useful in treating Alzheimer's disease (AD).GLP-1 receptor agonists are being studied as possible disease-modifying therapies for AD. They have neuroprotective, anti-inflammatory, as well as antioxidant effects. These medications help safeguard the brain against neuroinflammatory damage and reduce neuronal damage, thereby delaying the progression of Alzheimer's disease. They also improve cognitive performance by enhancing memory as well as learning ability through the promotion of synaptic plasticity. In addition, they reduce accumulation of amyloid-beta (Aβ) plaques and excessive phosphorylation of tau proteins, which decreases AD pathology. Some GLP-1 receptor agonists including Liraglutide, Exenatide, and Semaglutide are capable of penetrating the blood–brain barrier (BBB). These agents stimulate neuroprotective signaling cascades including the cAMP/PKA and PI3K/Akt pathways, which support cell survival and reduce apoptosis. Overall, GLP-1 receptor agonists are considered potential therapeutic agents for Alzheimer's disease, but further clinical trials are required for confirmation.(18)

Exenatide in Neuroinflammation

Exenatide is a GLP-1 receptor agonist mainly primarily prescribed for Type 2 diabetes to regulate blood glucose levels. A study was conducted in obese mice produced through a high-fat diet, as obesity increases metabolic inflammation and neuroinflammation. Exenatide significantly reduced brain inflammation and anxiety-like behaviour in obese mice. This effect was as a result of decreased levels of inflammatory cytokines including TNF-α and IL-1β, which normally increase inflammation. Exenatide also reduced glial cell activation, including glial cells such as astrocytes and microglial cells. Overactivation of these neuroglial cells contributes to brain damage. The drug increased anti-inflammatory microglial M2 polarization, which helps in tissue repair and reduces inflammation. The expression of SR-A4 (scavenger receptor A4), which was elevated in obese mice and linked to neuroinflammation, was reduced by Exenatide. The the neuroprotective action was linked to stimulation of the ERK signaling pathway, whereas the Akt pathway was not significantly involved. The study concluded that GLP-1 receptor agonists not only reduce blood sugar but may also help treat neurodegenerative symptoms caused by metabolic inflammation.(19)

Neuroprotective Effect of GLP-1 in Neuroinflammation (Based on Song J, Kim YK, and Yoon G)

Glucagon-like peptide-1 (GLP-1) is an incretin hormone widely recognized for its glucose-lowering effects. This study examined the the protective effects of GLP-1 on the nervous system during neuroinflammatory states. The focus was on how GLP-1 protects the brain during inflammation. The study showed that GLP-1 decreases the generation of inflammatory cytokines, which helps decrease brain inflammation. It also decreases the activation of glial cells including microglia and astrocytes. Overactivation of these glial cells contributes to neuronal damage.GLP-1 treatment improved the structural stability of brain tissue, suggesting a protective effect on neurons. The effects were related to the regulation of inflammatory signaling pathways, especially NF-κB, which plays an important role in inflammation and oxidative stress regulation. The finding suggest that GLP-1 and its analogs may act as therapeutic agents and could be useful in treating neurodegenerative disorders and neuroinflammatory conditions.[20]

Role of non-coding RNAs (miRNAs) in Neuroinflammation (Based on Chen)

Non-coding RNAs (ncRNAs) are RNA molecules that lack protein – coding capacity. They control gene expression at the molecular level. An important type of ncRNA is microRNA (miRNA). miRNAs play an important role in regulating neuroinflammatory processes because they regulate immune and inflammatory responses in neurological diseases. They influence inflammation by acting on Toll-like receptors (TLRs), cytokines, and the NF-κB pathway. They also modify neuronal signaling and influence microglial polarization, which helps maintain immune balance in the brain. Abnormal miRNA expression is linked with neurological disorder such as epilepsy, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Specific miRNAs such as miR-155, miR-124, and miR-146a are closely associated with the regulation of neuroinflammatory responses. These miRNAs regulate oxidative stress, cytokine production, and inflammasome activation.[21]Aptamers and microRNAs (miRNAs) were identified as emerging RNA-based therapeutic agents with potential therapeutic uses in neurodegenerative disease including Alzheimer's disease, Parkinson's disease, and ALS. These molecules were reported to reduce disease progression by lowering neuroinflammation. MicroRNAs regulated gene expression through post-transcriptional regulation and controlled major inflammatory pathways by altering the activity of microglia and astrocytic cells. Certain microRNAs, including miR-155, were associated with inflammatory responses, while miR-124, miR-146a, and miR-21 exhibited anti-inflammatory effects. Aptamers, often described as chemical antibodies, bound selectively to specific molecular targets, including abnormally folded proteins including Tau protein, Alpha-synuclein, and Amyloid-beta. Aptamers were considered useful for both diagnostic and therapeutic purposes. Together, these RNA-based strategies were viewed as promising, targeted, and non-immunogenic approaches for managing neuroinflammation in neurodegenerative disease conditions.[22]

Aptamers

In this study by Brugada, the CD200R1-targeting aptamer, also known as M52, was evaluated in glial cultures. The results showed that low quantities (25–50 nM) of PAGE-purified M52 decreased nitric oxide generation. However, higher doses resulted in possible morphological changes in glial cells, which may be caused by cellular toxicity or stress. This study showed only a few effects on inflammatory gene expression, and the researchers did not clearly confirm CD200R1-mediated signaling.[23]Aptamers were reviewed as useful diagnostic and therapeutic tools for neuroinflammation as well as neurodegenerative condition including Parkinson's disease and Alzheimer's diseases. Aptamers are defined as short nucleic acid, strands composed of a single chain. Aptamers have the ability to target misfolded proteins, such as tau, α-synuclein, and Aβ. They modulate inflammatory mediators and penetrate the blood–brain barrier (BBB) through delivery carriers including carrier like exosomes and nanoparticles systems. They have several benefits over antibodies, including high specificity, chemical stability, and minimal immunogenicity. However, they still have issues with distribution, uniformity, and stability. The study emphasized the strong potential of aptamers for real-time biomarker detection and targeted brain therapy.[24]Khan reviewed the functions of aptamers and microRNAs as RNA-based treatments for neurodegenerative diseases. MicroRNAs including miR-124, miR-146a, and miR-155 controlled neuroinflammation by altering signalling pathways like TLR and NF-κB, microglial activation, and cytokine production, while aptamers acted as chemical antibodies by binding disease-related proteins including tau, α-synuclein, and Aβ, showing therapeutic potential despite specificity issues in neurological disorder including Parkinson's disease, Alzheimer's disease, and releated conditions.[25]The increasing therapeutic promise of aptamers, short synthetic DNA/RNA molecules, was highlighted by Hernández-Jiménez in the treatment of neuroinflammation and neurodegenerative illnesses. The article focused on ApTOLL, a TLR4-binding aptamer, which improved multiple sclerosis models and reduced

inflammation, infarct volume, and disability in stroke patients. Compared to antibodies, aptamers showed minimal low immunogenic response, strong target specificity, and simple chemical modification. However, the study reported limitations related to clinical translation, regulatory classification, and pharmacokinetics.[26]Wang et al. (2021) reviewed aptamers as short, single-stranded nucleic acids selected by SELEX and highlighted their potential for the detection and management of neurodegenerative disorders. Aptamers showed strong specificity and high binding affinity toward targets such as tau, α-synuclein, amyloid-β, and TDP-43, making them promising therapeutic tools for for the detection and management of neurodegenerative disorders. They showed advantages including low immunogenicity, chemical stability, and the capacity to penetrate the Blood–brain barrier by targeting transferrin receptors. The review also described advanced strategies, such as modified aptamers (SOMAmers and LNA) and aptamer-conjugated nanoparticles, which improved therapeutic efficacy and distribution. Although challenges such as off-target effects and in vivo degradation remained, the review concluded that aptamers are promising alternatives to antibodies in neuromedicine.[27]Qu reviewed the expanding use of aptamers, which consist of short single-chain nucleic acid molecules peptides, as diagnostic and therapeutic agents for neurodegenerative neurological conditions including Multiple sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, and Prion disease. The study reported that aptamers selectively bound pathological proteins, such as amyloid-β (Aβ), α-synuclein, and mutant huntingtin protein, thereby preventing aggregation and neurotoxicity.Aptamers were considered suitable for targeting misfolded proteins within the central nervous system because of their small size, low immunogenicity, and high chemical stability compared to antibodies. The study also highlighted SELEX-based selection, chemical modifications for stability, and nanoparticle delivery systems.[28]Rhinehardt designed and analyzed aptamers targeting major traumatic brain injury (TBI) biomarkers such as GFAP, S100β, and IL-6 using molecular dynamics simulations. The study used surface plasmon resonance imaging (SPRi) to validate aptamer–protein binding interactions and to evaluate binding strength and specificity. Both peptide and nucleic acid aptamers were assessed for their stability and selectivity. This research showed that computational modelling may be used to pre-screen aptamers before experimental testing, supporting an effective and cost-efficient method for designing biosensors and diagnostic methods for neuroinflammation.[29]

Choi developed a 3D neurovascular unit-on-a-chip model, which more accurately simulated the human brain than conventional animal models. The chip combined neurons, astrocytes, along with endothelial cells to mimic the blood–brain barrier structure. Neuroinflammation was induced using LPS, which led to cytokine release, a reduction in TEER, and disruption of the barrier. The device successfully detected inflammatory biomarkers including TNF-α and IL-6 in real time through graphene oxide–linked fluorescent aptamers, enabling non-invasive monitoring. This human-relevant platform was reported as a useful tool for studying neuroinflammatory mechanisms and for drug screening applications.[30]Fan reported that TNF-α triggered necroptosis within bone microvascular endothelial cells (BMECs) by activating the RIP1/RIP3/MLKL signaling cascade, which contributed to the development of femoral head osteonecrosis. The study demonstrated that TNF-α could be efficiently inhibited by an aptamer (ApTNF-α), which improved BMEC viability and reduced necroptotic cell death. These findings suggested that TNF-α-targeting aptamers have potential as a potential targeted treatment approach for ONFH[31]Chowdhury et al and colleagues. (2023) examined the design and validation of biosensors based on aptamers for identifying blood biomarkers associated with neurodegenerative diseases (NDDs). The study mainly focused on identifying brain-derived neurotrophic factor (BDNF) through an assay linked with aptamer (ALISA) together with a unique DNA aptamer. In addition, the study evaluated other biomarkers such as NFL, p-tau181, neurogranin, and NSE in a tauopathy mouse model (rTg4510) to understand their relationship with brain pathology and treatment response. These findings supported the use of aptamers as effective alternatives to antibodies in diagnostic applications and highlighted the value of blood-based biomarkers useful for early diagnosis and monitoring of NDDs.[32]

Minocycline:

Cheng et al. used a Dicer conditional knockout (cKO) mouse experimental model used to investigate the effects of minocycline on neuroinflammation. The study showed that minocycline significantly reduced neuroinflammatory markers such as GFAP, Iba1, and IL-6, indicating suppression of microglial and astrocyte activation. However, the treatment did not prevent tau hyperphosphorylation, neuronal apoptosis, synaptic damage, or neuronal loss. These observations suggested that although minocycline exhibited clear anti-inflammatory activity, it was not sufficient on its own to halt the progression of neurodegeneration.[33]Kielian reported findings from a a murine model of brain abscess caused by Staphylococcus aureus, showing that minocycline reduced neuroinflammation independent of its

antibacterial action. The study demonstrated that even when a minocycline-resistant bacterial strain was used, the drug reduced inflammatory mediators including IL-1β, TNF-α, and CCL2, reduced the size of brain abscess lesion,while helped preserve tissue viability, without changing bacterial load. These anti-inflammatory effects were also observed when minocycline was administered after infection onset. In addition, the drug reduced glial TLR2 expression and suppressed astrocyte and microglial activation, suggesting its potential as an adjuvant immunotherapy for CNS infections accompanied by severe inflammation.[34]This study reported that minocycline, a tetracycline - class antibiotic known for its anti-inflammatory activity, effectively reduced lipopolysaccharide neuroinflammation caused by LPS along with related behavioral alterations. By employing BV-2 microglial cell cultures and BALB/c mice, the study showed that minocycline suppressed inflammatory cytokine secretion, reduced TLR2 expression, and lowered expression levels of IL-1β, IL-6, and IDO mRNA in the cortex and hippocampus. Behavioral assessments indicated that minocycline improved recovery from body weight reduction while social withdrawal and prevented anhedonia in LPS-treated mice. Notably, similar protective effects were observed in aged mice, where the drug attenuated exaggerated neuroinflammatory responses. Overall, the findings suggested that minocycline limited microglia-driven cytokine production and related behaveioral disturbances, supporting its potential use in conditions characterized by excessive neuroinflammation and mood or cognitive impairment.[35]Yang (2020) investigated the effects of minocycline in mice exposed to chronic unpredictable mild stress (CUMS) and reported that long-term treatment reduced depressive-like behaviors. The study showed that prolonged medication restored gut microbiota balance, improved metabolic profiles, and maintained intestinal barrier integrity. It also attenuated hippocampal neuroinflammation through reduction of inflammatory cytokines including IL-1β, IL-6, and TNF-α. In contrast, acute treatment did not produce significant effects. This result indicated that the antidepressant effect of minocycline was linked to combined regulation of gut microbiota and neuroinflammation, rather than its antibacterial properties alone.[36]Cai (2010) investigated the effects of minocycline in rats with vascular cognitive impairment caused by chronic cerebral hypoperfusion. The study reported that minocycline treatment markedly reduced astrocytic activation and overall neuroinflammation. It was shown that minocycline suppressed astroglial reactivity and inflammatory cytokine release by downregulating the level of GFAP, COX-2, NF-κB, IL-1β, and TNF-α expression. These findings supported the view that minocycline exerted neuroprotective effects by controlling astrocyte-mediated inflammatory responses.[37]Hisken's accessed the neuroprotective activity of minocycline using a murine model of repetitive mild traumatic brain injury (mTBI). The study reported that, at chronic time points, minocycline treatment reduced biomarkers of neurodegeneration (MAPT, TARDBP, NEFL), decreased neuroinflammation (e.g., TNF, AIF1, GFAP), and reduced glutamate excitotoxicity (GRIA1). Behavioral analysis showed that minocycline improved cognitive performance in the Morris Water Maze test. Additionally, the treatment reduced tau and TDP-43 pathological changes and reduced long-term microglial and astrocytic activation. These findings suggested that minocycline may help limit persistent neurotoxicity following repeated sub-concussive brain injuries.[38]Petrakis conducted a randomized, placebo-controlled study to examine whether minocycline could reduce ethanol-induced neuroinflammation in heavy alcohol users. Participants received placebo or minocycline doses of 100 mg or 200 mg administered for 10 days, followed by an intravenous ethanol infusion. The study reported that minocycline was well tolerated, but it did not produced significant changes serum cytokine concentration, alcohol craving, subjective responses to ethanol, or cognitive performance. However, the sedative effects of ethanol were associated with baseline cytokine levels. Overall, the findings indicated that short-term minocycline treatment was ineffective in reducing alcohol-related inflammation, highlighting the need for alternative neuroimmune-targeted therapies in alcohol use disorder.[39]

Future Directions:

Microglia act as memory cells and show a dual role in diseases. They act as protective cells in the early stages by removing protein aggregates such as tau and Aβ. In later stages, they contribute to neuroinflammation and neurodegeneration. Harmful microglial states are due to continuous activation. This persistent activation depends upon aging, TREM2 or APOE4 polymorphisms, and peripheral immune system signals. Current findings support therapeutic strategies that enhance microglial phagocytosis, regulate inflammatory signaling routes including NF-κB and NLRP3 mechanisms, and promote protective microglial phenotypes, including disease-associated microglia. Such strategies help to maintain and re-established microglial homeostasis.[40]Neuroinflammation plays an important role in neurodegenerative conditions including ALS, Parkinson's disorder, and Alzheimer's disorder. Protein aggregation and other cellular stress cause microglia and astrocytes to remain chronically activated.

Sustained inflammation due to chronic activation leads to increased neuronal damage. External influences like infections, advancing age, and traumatic brain injury (TBI) further intensify this response. Genetic risk factors, including APOE4 and TREM2, also influence disease progression. Inflammatory signalling pathways such as TLRs and NLRP3 contribute significantly to disease development. Targeting neuroinflammation shows therapeutic potential, especially when intervention occurs at early stages of disease.[41]The bibliometric analysis examines research trends related to neuroinflammation-induced mild cognitive impairment (MCI) over the past eleven years. The authors evaluate research themes, active authors, institutions, and publication patterns using established bibliometric tools. Since 2018, the volume of published studies increases markedly, with the United States leading globally in both research output and influence. Current evidence shows that inflammatory processes enhance the activation of microglia and astrocytes, which thereby leading to cognitive decline. This activation is influenced by genetic and metabolic variables such as APOE4 and TREM2. Research also focuses on the gut–brain axis, neuroimmune interactions, and biomarkers including tau and TREM2. Recent therapeutic strategies aim to modify microglial phenotypes, regulate the gut microbiome, and apply anti-inflammatory agents such as IFN-β1a, IL-33, and tanshinone IIA. This analysis highlights the need for improved collaboration between institutions, deeper understanding of glial phenotypes, and further exploration of gender differences and metabolic factors in future studies.[42]

CONCULSION:

Neuroinflammation represents a central pathological feature of neurodegenerative disorder, such as ALS, Parkinson's disease, and Alzheimer's disease. Regulation of inflammatory signalling by non-coding RNAs, particularly microRNAs, has a crucial influence on the progression of the disease. MicroRNAs including miR-124, miR-146a, and miR-155 function as major regulators of neuroimmune balance by controlling microglial activation and cytokine production. In parallel, aptamers, which are short single-stranded nucleic acid molecules, demonstrate high specificity toward pathogenic target proteins including tau, α-synuclein, and amyloid-β, which supports this molecules diagnostic and therapeutic potential. Together, microRNA-based approaches and aptamer technologies form a promising group of RNA-based strategies for managing neurodegeneration and neuroinflammation. Although preclinical findings show encouraging outcomes, further research remains necessary to overcome limitation associated with molecular stability, effective delivery and unintended off-target impacts before clinical application becomes feasible.

REFERANCE

1. Bonsack B, Corey S, Shear A, Heyck M, Cozene B, Sadanandan N, et al. Mesenchymal stem cell therapy alleviates the neuroinflammation associated with acquired brain injury. CNS Neurosci Ther. 2020;26(6):603–15. doi:10.1111/cns.13378
2. Calderón-Garcidueñas L, Franco-Lira M, Torres-Jardón R, Henriquez-Roldán C, Barragán-Mejía G, Valencia-Salazar G, et al. Pediatric Respiratory and Systemic Effects of Chronic Air Pollution Exposure: Nose, Lung, Heart, and Brain Pathology. Toxicol Pathol. 2007 Jan 1;35(1):154–62. doi:10.1080/01926230601059985
3. Calderón-Garcidueñas L, Reed W, Maronpot RR, Henriquez-Roldán C, Delgado-Chavez R, Calderón-Garcidueñas A, et al. Brain Inflammation and Alzheimer's-Like Pathology in Individuals Exposed to Severe Air Pollution. Toxicol Pathol. 2004 Oct 1;32(6):650–8. doi:10.1080/01926230490520232
4. Chen Y, Mateski J, Gerace L, Wheeler J, Burl J, Prakash B, et al. Non-coding RNAs and neuroinflammation: implications for neurological disorders. Exp Biol Med. 2024 Feb 28;249:10120. doi:10.3389/ebm.2024.10120 PubMed PMID: 38463392; PubMed Central PMCID: PMC10911137.
5. Cheng S, Hou J, Zhang C, Xu C, Wang L, Zou X, et al. Minocycline reduces neuroinflammation but does not ameliorate neuron loss in a mouse model of neurodegeneration. Sci Rep. 2015 May 22;5(1):10535. doi:10.1038/srep10535
6. Chowdhury MA. Developing the potential of blood-based biomarkers for neurodegenerative disease [thesis] [Internet]. University of Tasmania; 2024 [cited 2026 Apr 17]. Available from: https://figshare.utas.edu.au/articles/thesis/Developing_the_potential_of_blood-based_biomarkers_for_neurodegenerative_disease/25793919/1 doi:10.25959/25793919.v1
7. Computational modeling of nucleic and peptide aptamer interactions – IL6,S100β and GFAP protein biomarkers for traumatic brain injury - ProQuest [Internet]. [cited 2026 Apr 17]. Available from: https://www.proquest.com/openview/7e5ea54bac7bb299edf8bbef6b482671/1?pq-origsite=gscholar&cbl=18750

8. Dabrowska S, Andrzejewska A, Lukomska B, Janowski M. Neuroinflammation as a target for treatment of stroke using mesenchymal stem cells and extracellular vesicles. J Neuroinflammation. 2019 Sep 12;16(1):178. doi:10.1186/s12974-019-1571-8
9. Dheen ST, Kaur C, Ling EA. Microglial Activation and its Implications in the Brain Diseases. Curr Med Chem. 2007 May 1;14(11):1189–97. doi:10.2174/092986707780597961
10. Du H, Meng X, Yao Y, Xu J. The mechanism and efficacy of GLP-1 receptor agonists in the treatment of Alzheimer's disease. Front Endocrinol. 2022 Nov 17;13. doi:10.3389/fendo.2022.1033479
11. Fan X, Xu X, Wu X, Xia R, Gao F, Zhang Q, et al. The protective effect of DNA aptamer on osteonecrosis of the femoral head by alleviating TNF-α-mediated necroptosis via RIP1/RIP3/MLKL pathway. J Orthop Transl. 2022 Sep 1;36:44–51. doi:10.1016/j.jot.2022.07.001
12. Ferigle Burgada L. Evaluation of the anti-inflammatory potential of an agonistic CD200R1 aptamer on activated glial cultures [Internet]. 2018 Jun 11 [cited 2026 Apr 17]. Available from: https://digital.csic.es/handle/10261/177862
13. Ferretti MT, Allard S, Partridge V, Ducatenzeiler A, Cuello AC. Minocycline corrects early, pre-plaque neuroinflammation and inhibits BACE-1 in a transgenic model of Alzheimer's disease-like amyloid pathology. J Neuroinflammation. 2012 Apr 2;9(1):62. doi:10.1186/1742-2094-9-62
14. Frontiers | The past, present, and future of research on neuroinflammation-induced mild cognitive impairment: A bibliometric analysis. (n.d.). Retrieved June 3, 2025, from https://www.frontiersin.org/journals/aging-neuroscience/articles/10.3389/fnagi.2022.968444/full?utm_source=chatgpt.com
15. Gao C, Jiang J, Tan Y, Chen S. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. Signal Transduct Target Ther. 2023 Sep 22;8(1):359. doi:10.1038/s41392-023-01588-0
16. Heneka MT, Carson MJ, Khoury JE, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015 Apr 1;14(4):388–405. doi:10.1016/S1474-4422(15)70016-5 PubMed PMID: 25792098.
17. Hernández-Jiménez M, de Castro F. Aptamers as new promising entities for therapeutics: our experience from the neurological diseases. Neural Regen Res. 2025 Dec 1;20(12):3523–4. doi:10.4103/NRR.NRR-D-24-00667 PubMed PMID: 40095658; PubMed Central PMCID: PMC11974658.
18. Hiskens MI, Vella RK, Schneiders AG, Fenning AS. Minocycline improves cognition and molecular measures of inflammation and neurodegeneration following repetitive mTBI. Brain Inj. 2021 Jun 7;35(7):831–41. doi:10.1080/02699052.2021.1909139 PubMed PMID: 33818227.
19. Choi JH, Choi HK, Lee KB. In Situ Detection of Neuroinflammation Using Multicellular 3D Neurovascular-Unit-on-a-Chip. Adv Funct Mater. 2023;33(46):2304382. doi:10.1002/adfm.202304382
20. Joshi HP, Jo HJ, Kim YH, An SB, Park CK, Han I. Stem Cell Therapy for Modulating Neuroinflammation in Neuropathic Pain. Int J Mol Sci. 2021 May 3;22(9). doi:10.3390/ijms22094853
21. Khan I, Preeti K, Fernandes V, Khatri DK, Singh SB. Role of MicroRNAs, Aptamers in Neuroinflammation and Neurodegenerative Disorders. Cell Mol Neurobiol. 2022 Oct 1;42(7):2075–95. doi:10.1007/s10571-021-01093-4
22. Role of MicroRNAs, Aptamers in Neuroinflammation and Neurodegenerative Disorders | Cellular and Molecular Neurobiology | Springer Nature Link [Internet]. [cited 2026 Apr 17]. Available from: https://link.springer.com/article/10.1007/s10571-021-01093-4
23. Kielian T, Esen N, Liu S, Phulwani NK, Syed MM, Phillips N, et al. Minocycline Modulates Neuroinflammation Independently of Its Antimicrobial Activity in Staphylococcus aureus-Induced Brain Abscess. Am J Pathol. 2007 Oct 1;171(4):1199–214. doi:10.2353/ajpath.2007.070231
24. Kong AHY, Wu AJ, Ho OKY, Leung MMK, Huang AS, Yu Y, et al. Exploring the Potential of Aptamers in Targeting Neuroinflammation and Neurodegenerative Disorders: Opportunities and Challenges. Int J Mol Sci. 2023 Jul 22;24(14). doi:10.3390/ijms241411780
25. Levesque S, Surace MJ, McDonald J, Block ML. Air pollution & the brain: Subchronic diesel exhaust exposure causes neuroinflammation and elevates early markers of neurodegenerative disease. J Neuroinflammation. 2011 Aug 24;8(1):105. doi:10.1186/1742-2094-8-105
26. Lin MH, Cheng PC, Hsiao PJ, Chen SC, Hung CH, Kuo CH, et al. The GLP-1 receptor agonist exenatide ameliorates neuroinflammation, locomotor activity, and anxiety-like behavior in mice with diet-induced obesity through the modulation of microglial M2 polarization and downregulation of SR-A4. Int Immunopharmacol. 2023 Feb 1;115:109653. doi:10.1016/j.intimp.2022.109653

27. Lull ME, Block ML. Microglial Activation and Chronic Neurodegeneration. Neurotherapeutics. 2010 Oct 1;Glial-Based Neurotherapeutics7(4):354–65. doi:10.1016/j.nurt.2010.05.014
28. Lyman M, Lloyd DG, Ji X, Vizcaychipi MP, Ma D. Neuroinflammation: The role and consequences. Neurosci Res. 2014 Feb 1;79:1–12. doi:10.1016/j.neures.2013.10.004
29. Menaa F, Shahrokhi S, Prasad Shastri V. Impact and Challenges of Mesenchymal Stem Cells in Medicine: An Overview of the Current Knowledge. Stem Cells Int. 2018 Dec 17;2018:5023925. doi:10.1155/2018/5023925 PubMed PMID: 30662468; PubMed Central PMCID: PMC6312597.
30. Henry CJ, Huang Y, Wynne A, Hanke M, Himler J, Bailey MT, et al. Minocycline attenuates lipopolysaccharide (LPS)-induced neuroinflammation, sickness behavior, and anhedonia. J Neuroinflammation. 2008 May 13;5(1):15. doi:10.1186/1742-2094-5-15
31. Ferretti MT, Allard S, Partridge V, Ducatenzeiler A, Cuello AC. Minocycline corrects early, pre-plaque neuroinflammation and inhibits BACE-1 in a transgenic model of Alzheimer's disease-like amyloid pathology. J Neuroinflammation. 2012 Apr 2;9(1):62. doi:10.1186/1742-2094-9-62
32. Neuroinflammation. In: Handbook of Clinical Neurology [Internet]. Elsevier; 2020 [cited 2026 Apr 17]. p. 235–59. Available from: https://www.sciencedirect.com/science/chapter/handbook/abs/pii/B9780444641236000175 doi:10.1016/B978-0-444-64123-6.00017-5
33. Roy D, Brar S, Bhatia R, Rangra NK. An insight into the ethnopharmacological importance of Indian subcontinent medicinal plant species of Rubiaceae family. Adv Tradit Med. 2024 Dec 1;24(4):947–69. doi:10.1007/s13596-023-00714-1
34. Preliminary study of antidiabetic activity of Methanolic extract of Pavetta indica Linn in diabetic rats | Request PDF. (2025). ResearchGate. https://www.researchgate.net/publication/287065881_Preliminary_study_of_antidiabetic_activity_of_Methanolic_extract_of_Pavetta_indica_Linn_in_diabetic_rats
35. Qu J, Yu S, Zheng Y, Zheng Y, Yang H, Zhang J. Aptamer and its applications in neurodegenerative diseases. Cell Mol Life Sci. 2017 Feb 1;74(4):683–95. doi:10.1007/s00018-016-2345-4
36. Rahimi Darehbagh R, Seyedoshohadaei SA, Ramezani R, Rezaei N. Stem cell therapies for neurological disorders: current progress, challenges, and future perspectives. Eur J Med Res. 2024 Jul 25;29(1):386. doi:10.1186/s40001-024-01987-1
37. Role of neuroinflammation in neurodegeneration development | Signal Transduction and Targeted Therapy. (n.d.). Retrieved June 3, 2025, from https://www.nature.com/articles/s41392-023-01486-5?utm_source=chatgpt.com
38. Tran VTA, Lee LP, Cho H. Neuroinflammation in neurodegeneration via microbial infections. Front Immunol. 2022 Jul 28;13. doi:10.3389/fimmu.2022.907804
39. Vaughan MB, Ramirez RD, Wright WE, Minna JD, Shay JW. A three-dimensional model of differentiation of immortalized human bronchial epithelial cells. Differentiation. 2006 Apr 1;74(4):141–8. doi:10.1111/j.1432-0436.2006.00069.x
40. Wang B, Kobeissy F, Golpich M, Cai G, Li X, Abedi R, et al. Aptamer Technologies in Neuroscience, Neuro-Diagnostics and Neuro-Medicine Development. Molecules. 2024 Mar 2;29(5). doi:10.3390/molecules29051124
41. Yang Q, Luo L, Sun T, Yang L, Cheng LF, Wang Y, et al. Chronic minocycline treatment exerts antidepressant effect, inhibits neuroinflammation, and modulates gut microbiota in mice. Psychopharmacology (Berl). 2020 Oct 1;237(10):3201–13. doi:10.1007/s00213-020-05604-x
42. Yoon G, Kim YK, Song J. Glucagon-like peptide-1 suppresses neuroinflammation and improves neural structure. Pharmacol Res. 2020 Feb 1;152:104615. doi:10.1016/j.phrs.2019.104615