WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 17, 1127-1142. Review Article ISSN 2277–7105

INVESTIGATING THE IMPACT OF NEUROINFLAMMATION ON NEURODEGENERATIVE DISEASES

Bipin Singh*, Md. Sayam Sheikh, Md. Shamim Ahmad, Shikha Kalyan, Md. Tanvir, Shadab and Atul Kumar Prasad

College of Pharmacy, RIMT University, Mandi Gobindgarh, Punjab, India.

School of Pharmacy, RIMT University, Mandi Gobindgarh, Punjab, India.

Article Received on
17 July 2024,

Revised on 06 August 2024,
Accepted on 27 August 2024

DOI: 10.20959/wjpr202417-33797

***Corresponding Author**
Bipin Singh
College of Pharmacy, RIMT University, Mandi Gobindgarh, Punjab, India.

ABSTRACT

Neuroinflammation stands as a pivotal contributor to the pathogenesis of Parkinson's Disease (PD), significantly impacting disease progression and neuronal health. Toll-like receptors (TLRs), integral components of the innate immune system, play a central role in orchestrating neuroinflammatory responses in PD. This review elucidates the multifaceted involvement of TLRs in PD pathophysiology, highlighting their upregulated expression and contribution to dopaminergic neuronal loss. Elevated levels of TLR2, TLR4, and TLR9 in PD brains underscore their significance in exacerbating neuroinflammation and driving disease pathology. Modulating TLR activation emerges as a promising therapeutic strategy for mitigating neurodegenerative processes and preserving dopaminergic neurons in PD. However, the complex interplay between TLR-mediated neuroinflammation and neuronal survival presents challenges in translating these insights into effective clinical interventions. Further research is imperative to unravel the specific mechanisms by which TLRs influence PD pathogenesis and to identify novel therapeutic targets for neuroprotection and disease modification. By elucidating the intricate roles of TLRs in PD-associated neuroinflammation, this review aims to contribute to the development of targeted therapies aimed at halting disease progression and improving clinical outcomes for individuals affected by PD.

KEYWORDS: Neuroinflammation, Parkinson's Disease, Toll-Like Receptors, Dopaminergic Neurons, Neurodegeneration, Therapeutic Intervention, Disease Modification.

INTRODUCTION

One of the most prevalent neurodegenerative diseases, Parkinson's disease (PD) is characterized by a wide range of symptoms, including impaired motor function, psychological issues like anxiety and depression, and non-motor symptoms like autonomic neuropathy, sleep disturbances, and cognitive dysfunction. These non-motor symptoms are highlighted by T. Maruo, who also emphasizes the holistic aspect of Parkinson's disease and their effect on patients' quality of life.[1] Furthermore, as Shanmughavel, Piramanayagam, and Suganya Selvaraj noted, James Parkinson originally defined Parkinson's disease (PD) in 1817. He stated that the disease began with gradual, progressive involuntary tremors and progressed to swallowing, walking, and speaking difficulties.[2] According to T. Chow and J. Cummings, the prevalence of Parkinson's disease is approximately 100 per 100,000 people in the general population, with a considerably higher prevalence rate among those 65 years of age and older.[3] According to M. Takeda.[4] this frequency places Parkinson's disease (PD) as the second most common neurological disease among the elderly, after Alzheimer's disease. The fact that Parkinson's disease (PD) primarily affects those over 65 is another point made by A. Gitler and J. Shorter to emphasize the impact of this disease on the aging population.[5] Bradykinesia, resting tremor, rigidity, and postural instability are among the clinical features of Parkinson's disease (PD), as outlined by A. Kouli, K. Torsney, and Wei-Li Kuan. These features are essential for the diagnosis and distinguishing PD from other causes of parkinsonism.[6] The diagnosis makes use of these symptoms in addition to non-motor symptoms such as cognitive impairment and sleep disturbance, as elucidated by J. Greenland and R. Barker.[7] Neuroinflammation is an essential physiological process that protects the body from pathogens, toxins, and neurodegenerative factors while preserving neuroplasticity via the coordinated actions of neuronal, glial, and endothelial cells.[8] Despite its advantageous functions, neuroinflammation cannot be cured or prevented by medicine; present therapies only manage symptoms momentarily.[9] Because it is involved in the pathophysiology of many diseases, neuroinflammation has a dual function in neurological disorders by both contributing to neurodegeneration and, in certain cases, promoting recovery.[10,11] Neuroinflammation is relevant to a range of neurological and cognitive illnesses other than multiple sclerosis, and it has been shown to have both positive and negative effects on human health.[12] In neurodegenerative illnesses, it is proposed as a primary target for therapeutic intervention.[13] The intricate mechanisms behind neuroinflammation, which are impacted by things like viral infections and inflammation in peripheral organs, highlight the varied functions neuroinflammation plays in a range of

neurological and psychiatric conditions.[14] The contrast between damaging chronic neuroinflammation and beneficial low-level neuroinflammation is highlighted by the role played by the innate immune system, which includes macrophages and the complement system, in maintaining CNS homeostasis after damage and infection.[15] The intricate interaction between neuroinflammation and neurodegenerative illnesses highlights the need of regulating neuroinflammation as a therapeutic approach, as well as its potential role as a supporting factor in neuronal recovery.[16, 17] Given its importance in the pathophysiology of both acute and chronic neurological disorders, including multiple sclerosis and Alzheimer's disease, neuroinflammation is an important target for neuroprotective interventions.[18] Furthermore, glia-mediated inflammation is a critical area for the development of pharmacological and immunosuppressive treatments due to its role in the evolution of brain disorders, specifically through reactive gliosis and cellular reactivity.[19] The development of novel treatment strategies for neurodegenerative illnesses such as Parkinson's disease requires a thorough understanding of the immunological mechanisms underlying neuroinflammation.[20] Because neuroinflammation is involved in a wide range of illnesses, from neurodegenerative diseases to chronic pain syndromes, it displays a complicated interplay between inflammatory processes and immune dysregulation that is essential for the development of effective treatments.[21] The pathophysiology of Parkinson's disease (PD) is closely associated with neuroinflammation, which is important in both aggravating and maybe reducing the illness's course. Due to the activation of microglia and the production of reactive oxygen species, which cause dopaminergic neuronal death, neuroinflammation is recognized as a pathologic characteristic of Parkinson's disease (PD).[22] It has a role in the destruction of dopaminergic neurons in the substantia nigra pars compacta, which results in the disease's characteristic motor symptoms and cognitive deficits.[23] Nimesulide and levodopa's effects on LPS-induced neuroinflammation point to a complicated interplay between inflammatory processes and therapeutic agents in Parkinson's disease (PD).[24] According to research, neuroinflammation plays a role in the progression of Parkinsonism by causing mitochondrial malfunction and nigral dopamine neurons to degenerate via processes such S-nitrosylation/nitration of mitochondrial complex I.[25] One such mechanism that may be involved in the gradual degeneration of dopaminergic neurons and exacerbate existing neurodegeneration is microglial cell-mediated neuroinflammation.[26] The involvement of neuroinflammation in PD pathogenesis involves glial activation and inflammatory processes leading to disease initiation or progression, with unresolved arguments on whether these events are neuroprotective or neurotoxic.[27] Neuroinflammation strongly effects PD

pathogenesis, leading to oxidative stress, excitotoxicity, energy failure, and disruption of the neuronal membrane by α-synuclein proteins, which are essential contributors in the neurodegenerative process.[28]

Neuroinflammation in PD

Studies on the pathophysiology of Parkinson's disease (PD) have consistently indicated the important roles that neuroinflammation plays, as evidenced by a variety of biomarkers and mechanisms: Increased Proinflammatory Cytokines: Research has shown that people with Parkinson's disease (PD) have higher blood and cerebrospinal fluid (CSF) levels of proinflammatory cytokines, which suggests both localized and systemic inflammatory responses within the central nervous system (CNS). This increase raises the possibility that an immunological reaction is accelerating neurodegeneration.[29] Activation of Microglia in the Substantia Nigra: A plethora of data indicates heightened activation of CNS's central innate immune cells, or microglial cells, especially in the substantia nigra region, a crucial location linked to Parkinson's disease. The release of inflammatory and neurotoxic substances is linked to microglial activation, which exacerbates the death of dopaminergic neurons.[30,31] Peripheral inflammatory cells' infiltration into the brain and their participation in neuroinflammatory processes point to a possible break in the blood-brain barrier (BBB), which exacerbates neuroinflammation and the death of neurons.[32] Modified Immunity: Studies show that Parkinson's disease (PD) is associated with a modification of immune cell functions, including T-cell populations. These alterations may hasten the course of the disease by reflecting systemic immune dysregulation and its effects on CNS pathology.[33]

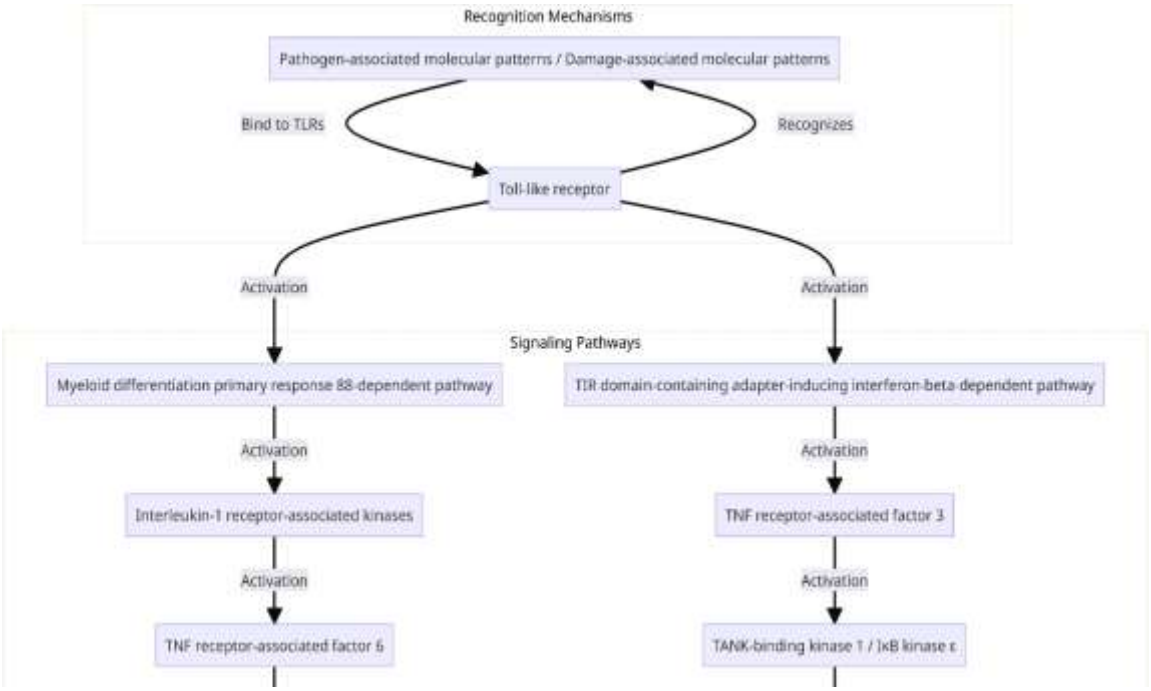
The primary active immune defense mechanism in the brain and spinal cord is provided by microglia, which are resident immune cells in the central nervous system (CNS). They are essential for participating in neuroinflammatory processes, restoring homeostasis, and reacting to damage. Microglia have the ability to become activated in response to pathogenic signals or damage, which results in changes to their shape, function, and gene expression.[34] The functional states of M1 (classically activated) and M2 (alternatively active) are commonly used to simplify the description of microglia activation. It's crucial to recognize that this classification is oversimplified, and that more sophisticated and nuanced responses to diverse stimuli may be reflected in a spectrum of activation states that extends beyond the M1/M2 classifications.

Microglial Activation States: M1 vs. M2

Activation State	Characteristics	Impacton Neuroinflammation	Reference
M1: An anti-inflammatory	Contributes toinflammation andneurodegeneration by producingcytokines that are pro-inflammatory.	Frequently linked to harm and the advancement of neurodegenerative illnesses	[35]
M2 (Anti-inflammatory)	Encourages tissue healing and releases substances that reduce inflammation	Protective; linked to reducing inflammation andpromoting CNS healing	[36]

Toll-like Receptors (TLRs)

The innate immune system relies heavily on toll-like receptors (TLRs), which help recognize damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). TLRs are essential for preserving physiological homeostasis and fighting infections because of their critical function in triggering immunological responses.[37] They are widely expressed in a variety of cell types, including non-immune cells like epithelial cells and immune cells like dendritic cells and macrophages. The resident immune cells of the brain and spinal cord, known as microglia, are the primary target of TLR expression in the context of the central nervous system (CNS), making them important participants in both neuroinflammation and CNS immunity.[38] A wide variety of TLRs (1 through 9) are expressed by microglia, allowing them to react to various microbial ligands and innate danger signals. Their broad pattern of expression makes it easier for them to monitor the neuronal environment and regulate inflammatory reactions in the brain.[39] A different type of glial cell found in the central nervous system called astrocytes also expresses some TLRs, though not as many as microglia. They contribute to the brain's innate immune response, particularly in reaction to viral infections, by expressing TLR3 and having reduced amounts of TLR1, 4,5, and 9.[40] Human choroidal melanocytes, which are cells found in the vascular layer of the eye, have been demonstrated to express TLR1 through TLR9, further illustrating the diversity of TLR expression. Their possible involvement in modulating innate immune responses against ocular infections is suggested by this expression pattern.[41] The complex networkof innate immunity within the brain and its role in maintaining CNS homeostasis and pathology are further demonstrated by the unique pattern of expression of TLRs in other CNS-resident cells, such as oligodendrocytes.[42]



Flowchart illustrating Toll-like Receptor Recognition and Signaling Pathways.

TLRs and Neuroinflammation in PD, Upregulation of TLRs

There has been a lot of interest in the relationship between Parkinson's disease (PD) and the expression of the toll-like receptor (TLR). TLRs, particularly TLR2, TLR4, and TLR9, have been shown to be overexpressed in the brains and peripheral blood cells of Parkinson's disease patients in recent research, indicating a major role for TLRs in the pathophysiology of the disease. TLR4 is increased in Parkinson's disease brains and co-localizes with pSer129αSyn, according to a study by Conte et al. (2023)[37], suggesting a possible connection between neuroinflammation and Parkinson's disease pathology.[37] This is consistent with the research conducted by Dabi et al. (2023), which highlighted the importance of TLR2, TLR4, and TLR9 in relation to Parkinson's disease.[38] Interestingly, Trudler et al. (2010) also observed elevated expression of these TLRs in the illness, highlighting their importance in the pathophysiology of the sickness.[39] Studies have demonstrated that TLRs, including TLR2 and TLR4, are expressed in cerebral cortical neurons and contribute to brain injury caused by ischemic stroke, indicating that they are involved in inflammatory processes associated with neurological disorders.[40] The importance of TLRs in the neuroimmune mechanisms underlying Parkinson's disease and maybe other neurodegenerative diseases is highlighted by this body of research. All of the aforementioned research show that there is growing agreement about the critical role that TLRs—particularly TLR2, TLR4, and TLR9—play in the neuroimmunological context of

Parkinson's disease. According to the research, these receptors might have a role in the development of the disease by means of immunological responses and neuroinflammation in the brain and peripheral blood cells.

Impact on Neuronal Health

The complex relationship that exists between the survival of dopaminergic neurons and the activation of proinflammatory pathways by TLRs is essential to comprehending the etiology of neurodegenerative illnesses like Parkinson's disease (PD). Studies have clarified the critical function of proinflammatory pathways, which involve the activation of transcription factors such as nuclear factor κB and YY1, in causing neuroinflammation, oxidative stress, and ultimately, dopaminergic neuronal death in Parkinson's disease (PD).[41] This implies that there may be therapeutic potential in focusing on these pathways.

According to research, mice with TLR3 deficiency develop resistance to MPTP-induced neurotoxicity, preserving the integrity of dopamine neurons.[42] This demonstrates TLR3's potential role in dopaminergic neuronal survival and provides information about potential PD treatment approaches. Numerous studies have exhibited the therapeutic advantages of anti-inflammatory drugs like celecoxib and pioglitazone. These medications may protect mitochondrial bioenergetics and enhance nigral dopaminergic neuron survival by diminishing the inflammatory response triggered by lipopolysaccharides (LPS).[43] The consequences of neuroinflammation for dopaminergic neuronal survival have been further clarified in animal models, with a particular emphasis on the inflammatory processes-induced degeneration of nigrostriatal dopaminergic neurons.[44] This emphasizes how crucial it is to fight neuroinflammation in order to safeguard dopaminergic neurons. Toll-like receptors (TLRs) on neurons have been extensively studied in relation to ischemia brain injury and functional impairments. Elevated TLR2 and TLR4 levels in neurons have been found to contribute to proapoptotic signaling cascades, which in turn increase the vulnerability of neurons to ischemic death.[45] Dopaminergic neuronal survival is further complicated by the neurotoxic effects of levodopa and the oxidative stress caused by exogenous toxins; yet, there is some optimism due to the potential protective effects of dopamine agonists and Coenzyme Q10.[46] Immunomodulatory drugs have demonstrated their critical role in preventing the degeneration of dopaminergic neurons in animal models of Parkinson's disease by alleviating motor impairments, inhibiting proinflammatory pathways, and decreasing oxidative stress.[47] This suggests that these drugs may be used in PD treatment. All of the studies point

to the complex relationship between TLR-mediated proinflammatory system activation and dopaminergic neuronal survival. In addition to aiding in the development of Parkinson's disease (PD), the pathways involved in this process provide opportunities for therapeutic intervention that aims to reduce neuroinflammation and oxidative stress in order to shield dopaminergic neurons and eventually maintain neuronal health.

Balancing Inflammation Acute vs. Chronic Inflammation

A complex and important process in both acute and chronic neurological disorders is neuroinflammation. In the context of chronic traumatic brain injury (TBI), liver disease, the transition from acute to chronic pain, cognitive and motor functions, and injury and repair mechanisms in the nervous system are just a few of the ways it performs a dual role. Acute to Chronic Pain Transition**: Early peripheral inflammation triggers neuroinflammation, which sets off signaling pathways that alter sensory neuron function over time and maintain persistent sensitization.[48] Liver Disease and Cognitive Functions: Both acute and chronic liver diseases are associated with neuroinflammation, which activates microglial cells and secretes pro-inflammatory cytokines that impair motor and cognitive function. This process is greatly influenced by changes in the gut microbiota, which implies that treating the gut microbiota could be a successful treatment approach.[49]

Traumatic Brain Injury (TBI) that is chronic: When acute colitis is generated in mice with chronic traumatic brain injury, neuroinflammation intensifies neurological impairments and results in persistent extraintestinal, systemic, and central nervous system inflammatory.[50]

Axonal Degeneration and Virus-Induced Demyelination: The CD40/CD40 ligand system interacts between CD4+ T cells and microglia/macrophages to influence both acute-adaptive and chronic-adaptive immune responses.[51]

Function of IL-1β produced by NLRP3: This is important because it helps sepsis go from acute to chronic neuroinflammation, which emphasizes how important it is for the development of neurodegenerative illnesses like Parkinson's.[52]

Reducing Neuroinflammation in Alzheimer's: A mouse model of Alzheimer's disease has shown that IL-37 expression can repair cognitive impairment by drastically reducing both acute and chronic neuroinflammation.[52]

Therapeutic Implications Targeting TLRs

Toll-like receptors (TLRs) are targets for therapeutic targeting with substantial implications for a variety of medical applications, such as immunotherapy, cancer treatment, and autoimmune and inflammatory disease management. As the main sensors for identifying infections and starting subsequent immunological reactions, TLRs are essential to the body's immune response. Their potential as targets for therapeutic therapies stems from their participation in a variety of clinical diseases. TLR agonists and antagonists have been investigated as preventative and therapeutic medicines, among other TLR-targeting techniques. Adjuvant vaccination immunotherapy, cancer treatment, allergy disease management, persistent viral infections, and the creation of TLR-specific antagonists for long-term non-infectious inflammatory and autoimmune disorders are only a few of these uses.[53] TLR-targeted approaches have demonstrated potential in oncology for changing the tumor microenvironment to tumoricidal phenotypes. This involves incorporating certain TLR-targeting medications, supported by pre-clinical research and continuing clinical trials, into routine treatment.[54] These tactics make use of the immune system's built-in defences against cancer, underscoring the potential therapeutic uses for TLR agonists and antagonists beyond the management of infectious diseases.[55]

Furthermore, there are encouraging prospects for the use of TLRs or their downstream signals in the treatment of inflammatory illnesses like rheumatoid arthritis in the future.[56] Developments in TLR antagonists, such as antibodies against TLRs, peptides derived from TLRs, and small compounds that efficiently block or lessen TLR signaling, provide additional evidence for this.[57]

Hematology experts have discovered that Toll-like receptors may be used as therapeutic targets in hematologic malignancies. These receptors have the ability to enhance antigen presentation and stimulate the production of target molecules, which is essential for creating therapeutic alternatives that work.[58]

TLR ligands are a novel family of drugs that modulate cytokine production and activate lymphocytes to prevent or cure allergic diseases.[59] This highlights the range of applications for TLR targeting, including immunological disorders, inflammation, and cancer treatment, and emphasizes the need for more study to fully realize their therapeutic potential.

Challenges and Future Directions

Neural Connectivity and Brain Function: Neurite outgrowth is adversely modulated and synapse formation is altered when nucleic acids activate neuronal Toll-like receptors. This affects brain function and neural connections and may be a factor in deficiencies linked to neuropsychiatric diseases.[63] Alcohol-Induced Neuroinflammation: TLR4 and TNF receptors are involved in intricate interactions that cause neuroinflammation. By focusing on this route, new treatment options for reducing neuroinflammation may be available.[64] Neuroimmune Dysregulation: As Receptors, in particular TLR4, shows An important aspect of the pathophysiology of many neurodegenerative illnesses is neuroinflammation, and Toll-like receptors (TLRs) are becoming more and more understood in this regard. Recognizing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), TLRs are essential parts of the demonstrated in models such as BTBR T+ Itpr3tf/J mice, inhibition of neuronal Toll-like innate immune system that trigger immunological responses. Their involvement in neuroinflammation and neuronal complications is complex; they affect neurite outgrowth and synapse formation, modulate astrocytic pathways, cause dopaminergic neural loss in Parkinson's disease (PD), and synucleinopathy in neurodegeneration, among other things.

Synucleinopathy and Neurodegeneration: During neuroinflammation, TLRs—especially TLR2 and TLR4—are elevated in the brain. This leads to synucleinopathy in Parkinson's disease by interfering with autophagy. This suggests that mechanistic-based treatments for neurodegenerative illnesses should target the neuronal TLR2/4 pathways.[60] Alterations in Astrocytic Routes: By influencing astrocytic Toll-like Receptor 4, blocking the A1 astrocytic pathway, and fostering the A2 pathways, which produce neurotrophic factors, dopamine mediates neuroprotection. Cognitive impairments and neuroinflammatory diseases are influenced by this regulation.[61] Parkinson's disease-related loss of dopaminergic neurons: In Parkinson's disease, the overexpression of TLRs is associated with increased neuroinflammation, which exacerbates the death of dopaminergic neurons. This emphasizes how essential TLRs are for the recognition of both endogenous and external stimuli, which set off inflammatory reactions in the central nervous system.[62]

promise in alleviating neuroimmune dysregulation and opening the door for therapeutics that target neuroinflammation in neuropsychiatric illnesses.[65] Alzheimer's disease: TLR4 has been identified as a viable therapeutic target for the disease, emphasizing its function in

controlling neuroinflammation and the possibility of creating novel treatment approaches that center on this receptor.[66]

CONCLUSION

Neuroinflammation, driven in part by Toll-like receptor (TLR) activation, emerges as a central player in the pathogenesis of Parkinson's Disease (PD), influencing disease progression and neuronal health. The upregulated expression of TLRs, notably TLR2, TLR4, and TLR9, exacerbates neuroinflammation and contributes to dopaminergic neuronal loss, a hallmark of PD pathology. Targeting TLR-mediated neuroinflammatory processes presents a promising therapeutic avenue for preserving dopaminergic neurons and mitigating neurodegeneration in PD. However, the complexity of TLR signaling and its interplay with neuronal survival mechanisms pose challenges in translating these insights into effective clinical interventions. Further research is essential to elucidate the specific mechanisms by which TLRs influence PD pathogenesis and to identify novel therapeutic targets for neuroprotection and disease modification. By unraveling the intricate roles of TLRs in PD-associated neuroinflammation, future endeavors aim to develop targeted therapies that halt disease progression and improve clinical outcomes for individuals affected by PD.

REFERENCE

1. Maruo T. The Diagnosis and Indication for Surgical Treatment in Parkinson's Disease.No Shinkei geka. Neurological Surgery, 2021 Jul 1; 49(4): 750-9.
2. Selvaraj S, Piramanayagam S. A review on factors causing Parkinson’s syndrome. MOJ Proteomics Bioinf, 2018; 7(4): 257-61.
3. Chow TW, Cummings JL. Treatment of depression in the patient with Parkinson's disease. Clinical geriatrics, 1998 Oct; 6(11): 34.
4. Takeda M. Neural transplantation to neurodegenerative disorders. Psychogeriatrics, 2003 Jun 1; 3(2).
5. Gitler AD, Shorter J. Prime time for α-synuclein. Journal of Neuroscience, 2007 Mar 7; 27(10): 2433-4.
6. Kouli A, Torsney KM, Kuan WL. Parkinson’s disease: etiology, neuropathology, and pathogenesis. Exon Publications, 2018 Dec 21: 3-26.
7. Greenland JC, Barker RA. The differential diagnosis of Parkinson’s disease. Exon Publications, 2018 Dec 21: 109-28.
8. Tohidpour A, Morgun AV, Boitsova EB, Malinovskaya NA, Martynova GP, Khilazheva

ED, Kopylevich NV, Gertsog GE, Salmina AB. Neuroinflammation and infection: molecular mechanisms associated with dysfunction of neurovascular unit. Frontiers in cellular and infection microbiology, 2017 Jun 20; 7: 276.

9. Luo B. Insights into the advances in therapeutic drugs for neuroinflammation-related diseases. International Journal of Neuroscience, 2023 Sep 15: 1-26.
10. Gorji A. Neuroinflammation: the pathogenic mechanism of neurological disorders. International Journal of Molecular Sciences, 2022 May 20; 23(10): 5744.
11. Wee Yong V. Inflammation in neurological disorders: a help or a hindrance?. The Neuroscientist, 2010 Aug; 16(4): 408-20.
12. Andereggen L, Trakhtenberg EF, Yin Y, Benowitz LI. Inflammation and optic nerve regeneration. Neuroinflammation: New Insights into Beneficial and Detrimental Functions, 2015 May 4: 189-204.
13. Nabizadeh F, Fallahi MS, Zafari R, KamaliZonouzi S, Khodkam M, Alilou S, Aarabi MH. Neuroimaging findings of covid-19: a systematic review on longitudinal studies. Neurology Letters, 2024 Jan 1; 3(1): 27-36.
14. Sun Y, Koyama Y, Shimada S. Inflammation from peripheral organs to the brain: how does systemic inflammation cause neuroinflammation?. Frontiers in aging neuroscience, 2022 Jun 16; 14: 903455.
15. Shastri A, Bonifati DM, Kishore U. Innate immunity and neuroinflammation. Mediators of inflammation, 2013; 2013(1): 342931.
16. Liu Z, Qiu AW, Huang Y, Yang Y, Chen JN, Gu TT, Cao BB, Qiu YH, Peng YP. IL-17A exacerbates neuroinflammation and neurodegeneration by activating microglia in rodent models of Parkinson's disease. Brain, behavior, and immunity, 2019 Oct 1; 81: 630-45.
17. David S. Neuroinflammation: new insights into beneficial and detrimental functions. John Wiley & Sons, 2015 May 26.
18. Sentürk E, Esen F. Neuroprotection in Sepsis by Complement Inhibition and Immunoglobulin Therapy. Turkish Journal of Anaesthesiology & Reanimation, 2012 Jul 1; 40(4): 184.
19. Kumar Jha M, Suk K. Management of glia-mediated neuroinflammation and related patents. Recent Patents on Inflammation & Allergy Drug Discovery, 2014 May 1; 8(2): 118-24.
20. de Sousa AA, Braga SA, da Rocha Sobrinho HM. Neuroinflamação na doença de Parkinson. Revista EVS-Revista de Ciências Ambientais e Saúde, 2016 Nov 8; 43:

79- 89.

21. Arias C, Sepúlveda P, Castillo RL, Salazar LA. Relationship between hypoxic and immune pathways activation in the progression of neuroinflammation: role of HIF-1α and Th17 cells. International journal of molecular sciences, 2023 Feb 4; 24(4): 3073.
22. Prasad EM, Hung SY. Behavioral tests in neurotoxin-induced animal models of Parkinson's disease. Antioxidants, 2020 Oct 16; 9(10): 1007.
23. Affia BS. Neurodegeneration-Disease And Dementia. J Biomed Allied Res, 2021; 2(2): 1-5.
24. FLORES PC. Reflexão sobre o câncer ginecológico e suas políticas públicas. Atena.
25. Choi DY, Hunter R, Liu M, Cass W, Pandya J, Sullivan P, Shin EJ, Kim HC, Gash D, Bing G. Striatal neuroinflammation promotes parkinsonism in rats. Nature Precedings, 2008 Jun 16: 1-.
26. Yao L, Wu J, Koc S, Lu G. Genetic imaging of neuroinflammation in Parkinson's disease: Recent advancements. Frontiers in Cell and Developmental Biology, 2021 Jul15; 9: 655819.
27. Chung YC, Ko HW, Bok EG, Park ES, Huh SH, Nam JH, Jin BK. The role of neuroinflammation on the pathogenesis of Parkinson's disease. BMB reports, 2010; 43(4): 225-32.
28. Amato A, Mulè F. Protective potential of glucagon like peptide 2 (GLP-2) against the neurodegeneration. Neural Regeneration Research, 2019 Nov 1; 14(11): 1901-2.
29. Ouchi Y, Yagi S, Yokokura M, Sakamoto M. Neuroinflammation in the living brain of Parkinson's disease. Parkinsonism & related disorders, 2009 Dec 1; 15: S200-4.
30. Choi DY, Liu M, Hunter RL, Cass WA, Pandya JD, Sullivan PG, Shin EJ, Kim HC, Gash DM, Bing G. Striatal neuroinflammation promotes Parkinsonism in rats. PLoS One, 2009 May 8; 4(5): e5482.
31. Yao L, Wu J, Koc S, Lu G. Genetic imaging of neuroinflammation in Parkinson's disease: Recent advancements. Frontiers in Cell and Developmental Biology, 2021 Jul 15; 9: 655819.
32. Lee JK, Tran T, Tansey MG. Neuroinflammation in Parkinson's disease. Journal of Neuroimmune Pharmacology, 2009 Dec; 4: 419-29.
33. Sita G, Graziosi A, Hrelia P, Morroni F. NLRP3 and Infections: β-Amyloid in Inflammasome beyond Neurodegeneration. International Journal of Molecular Sciences, 2021 Jun 29; 22(13): 6984.
34. Liu LR, Liu JC, Bao JS, Bai QQ, Wang GQ. Interaction of microglia and astrocytes inthe

neurovascular unit. Frontiers in immunology, 2020 Jul 8; 11: 1024.

35. Liu L, Tang J, Liang X, Li Y, Zhu P, Zhou M, Qin L, Deng Y, Li J, Wang Y, Jiang L. Running exercise alleviates hippocampal neuroinflammation and shifts the balance of microglial M1/M2 polarization through adiponectin/AdipoR1 pathway activation in mice exposed to chronic unpredictable stress. Molecular Psychiatry, 2024 Feb 15: 1-2.
36. Xu S, Zhu W, Shao M, Zhang F, Guo J, Xu H, Jiang J, Ma X, Xia X, Zhi X, Zhou P. Ecto-5′-nucleotidase (CD73) attenuates inflammation after spinal cord injury by promoting macrophages/microglia M2 polarization in mice. Journal of neuroinflammation, 2018 Dec; 15: 1-4.
37. Conte C, Ingrassia A, Breve J, Bol JJ, Timmermans-Huisman E, van Dam AM, Beccari T, van de Berg WD. Toll-like receptor 4 is upregulated in Parkinson's Diseasepatients and co-localizes with pSer129αSyn: A possible link with the pathology. Cells, 2023 May 11; 12(10): 1368.
38. Dabi YT, Ajagbe AO, Degechisa ST. Toll-like receptors in pathogenesis of neurodegenerative diseases and their therapeutic potential. Immunity, Inflammation and Disease, 2023 Apr; 11(4): e839.
39. Trudler D, Farfara D, Frenkel D. Toll-like receptors expression and signaling in glia cells in neuro-amyloidogenic diseases: towards future therapeutic application. Mediators of inflammation, 2010; 2010(1): 497987.
40. Güner A. *Lamium Purpureum Bitkisinin Prostat Kanseri Hücre Hattında Antikanser Etkisinin Incelenmesi* (Master's thesis, Marmara Universitesi (Turkey)).
41. Tiwari PC, Pal R. The potential role of neuroinflammation and transcription factors in Parkinson disease. Dialogues in clinical neuroscience, 2017 Mar 31; 19(1): 71-80.
42. Chung YC, Jeong J, Jin BK. TLR3 contributes to degeneration of dopamine neurons in an MPTP mouse model of parkinson's disease. The Journal of Immunology, 2018 May 1; 200(1_Supplement): 166-55.
43. Garrido-Gil P, Rodriguez-Perez AI, Fernandez-Rodriguez P, Lanciego JL, Labandeira-Garcia JL. Expression of angiotensinogen and receptors for angiotensin and prorenin in the rat and monkey striatal neurons and glial cells. Brain Structure and Function, 2017 Aug; 222(6): 2559-71.
44. Machado A, Herrera AJ, Venero JL, Santiago M, De Pablos RM, Villaran RF, Espinosa-Oliva AM, Argüelles S, Sarmiento M, Delgado-Cortes MJ, Maurino R. Peripheral inflammation increases the damage in animal models of nigrostriatal dopaminergic

neurodegeneration: possible implication in parkinson′ s disease incidence. Parkinson's disease, 2011; 2011(1): 393769.

45. Tang SC, Arumugam TV, Xu X, Cheng A, Mughal MR, Jo DG, Lathia JD, Siler DA, Chigurupati S, Ouyang X, Magnus T. Pivotal role for neuronal Toll-like receptors in ischemic brain injury and functional deficits. Proceedings of the National Academy of Sciences, 2007 Aug 21; 104(34): 13798-803.
46. Gille G, HUNG ST, Reichmann H, RAUSCH WD. Oxidative stress to dopaminergic neurons as models of Parkinson's disease. Annals of the New York Academy of Sciences, 2004 Jun; 1018(1): 533-40.
47. Martinez B, Peplow PV. 免疫调节剂在帕金森病动物模型中的神经保护作用. 中国神经再生研究 (英文版), 2018 Sep 15; 13(9): 1493.
48. Schumacher MA. Peripheral Neuroinflammation and Pain: How Acute Pain Becomes Chronic. Current Neuropharmacology, 2024 Jan 1; 22(1): 6-14.
49. Hanscom M, Loane DJ, Aubretch T, Leser J, Molesworth K, Hedgekar N, Ritzel RM, Abulwerdi G, Shea-Donohue T, Faden AI. Acute colitis during chronic experimental traumatic brain injury in mice induces dysautonomia and persistent extraintestinal, systemic, and CNS inflammation with exacerbated neurological deficits. Journal of neuroinflammation, 2021 Dec; 18: 1-31.
50. Zhao Z, Wang Y, Zhou R, Li Y, Gao Y, Tu D, Wilson B, Song S, Feng J, Hong JS, Yakel JL. A novel role of NLRP3-generated IL-1β in the acute-chronic transition of peripheral lipopolysaccharide-elicited neuroinflammation: implications for sepsis- associated neurodegeneration. Journal of neuroinflammation, 2020 Dec; 17: 1-9.
51. Sarma JD, Saadi F, Chakravarty D, Kamble M, Kumar S, Shindler KS. The CD40/CD40 ligand system in linking acute neuroinflammation with chronicprogressive demyelination. The Journal of Immunology, 2022 May 1; 208(1_Supplement): 53-12.
52. Lonnemann N, Hosseini S, Ohm M, Geffers R, Hiller K, Dinarello CA, Korte M. IL- 37 expression reduces acute and chronic neuroinflammation and rescues cognitive impairment in an Alzheimer's disease mouse model. Elife, 2022 Aug 30; 11: e75889.
53. Hedayat M, Takeda K, Rezaei N. Prophylactic and therapeutic implications of toll-like receptor ligands. Medicinal research reviews, 2012 Mar; 32(2): 294-325.
54. Yang Y, Li H, Fotopoulou C, Cunnea P, Zhao X. Toll-like receptor-targeted anti-tumor therapies: Advances and challenges. Frontiers in Immunology, 2022 Nov 21; 13: 1049340.

55. Quesniaux VF, Ryffel B. Toll-like receptors: emerging targets of immunomodulation. Expert Opinion on Therapeutic Patents, 2004 Jan 1; 14(1): 85-100.
56. Lu Z. Potential therapeutic interventions on toll like receptors for clinical applications. Res Pharm Biotechnol, 2010; 2(1): 7-13.
57. Patra MC, Choi S. Recent progress in the development of Toll-like receptor (TLR) antagonists. Expert opinion on therapeutic patents, 2016 Jun 2; 26(6): 719-30.
58. Wolska A, Lech-Maranda E, Robak T. Toll-like receptors and their role in hematologic malignancies. Current molecular medicine, 2009 Apr 1; 9(3): 324-35.
59. Goldman M. Translational mini-review series on Toll-like receptors: Toll-like receptor ligands as novel pharmaceuticals for allergic disorders. Clinical & Experimental Immunology, 2007 Feb; 147(2): 208-16.
60. Chung LY, Lin YT, Liu C, Tai YC, Lin HY, Lin CH, Chen CC. Neuroinflammation upregulated neuronal toll-like receptors 2 and 4 to drive synucleinopathy in neurodegeneration. Frontiers in Pharmacology, 2022 Mar 24; 13: 845930.
61. Gurram PC, Manandhar S, Satarker S, Mudgal J, Arora D, Nampoothiri M. Dopaminergic signaling as a plausible modulator of astrocytic toll-like receptor 4: a crosstalk between neuroinflammation and cognition. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders), 2023 May 1; 22(4): 539-57.
62. Chen CY, Shih YC, Hung YF, Hsueh YP. Beyond defense: regulation of neuronal morphogenesis and brain functions via Toll-like receptors. Journal of biomedical science, 2019 Nov 4; 26(1): 90.
63. Flores-Bastías O, Karahanian E. Neuroinflammation produced by heavy alcohol intake is due to loops of interactions between Toll-like 4 and TNF receptors, peroxisome proliferator-activated receptors and the central melanocortin system: A novel hypothesis and new therapeutic avenues. Neuropharmacology, 2018 Jan 1; 128: 401-7.
64. Ahmad SF, Ansari MA, Nadeem A, Alzahrani MZ, Bakheet SA, Attia SM. Resveratrol Improves Neuroimmune Dysregulation Through the Inhibition of Neuronal Toll-Like Receptors and COX-2 Signaling in BTBR T+ Itpr3 tf/J Mice. Neuromolecular Medicine, 2018 Mar; 20: 133-46.
65. Wu L, Xian X, Xu G, Tan Z, Dong F, Zhang M, Zhang F. Toll-Like Receptor 4: A Promising Therapeutic Target for Alzheimer's Disease. Mediators of inflammation, 2022; 2022(1): 7924199.