The Role of Systemic Chronic Inflammation and Shared Neuroinflammatory Loops in Neurodegeneration

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Abstract

This study analyzed the role of chronic inflammation in neurodegeneration with special consideration for external variables like alcohol intake, gut inflammation, and the immune system. The goal was to examine the impact of systemic inflammation on neurodegeneration and its contribution to cognitive disorders, neuronal damage, and Alzheimer's and Parkinson's diseases. The literature analysis method was applied to study scientific articles published in academic databases. The outcomes revealed that inflammation is an important factor in causing and accelerating neurodegeneration due to its development in external locations like the gut and immune system and subsequent spread to the brain via blood-brain barrier damage, microglia activation, cytokines, and reactive oxygen species. Lifestyle aspects like alcohol abuse and excessive high-fat diet were associated with the exacerbation of inflammation, oxidative stress, and neuronal damage manifested in protein changes such as tau tangles and amyloid plaques. A cycle of inflammation and neuronal damage was identified, although specific links and interactions between risk factors require further exploration. Future research should examine the cumulative impact of alcohol consumption, dietary habits, and gut microbial dysbiosis. More human-based clinical studies are needed, and potential treatments, including anti-inflammatory drugs, antioxidants, and neuroprotectants like melatonin, should be explored further.

Keywords

Cellular and Molecular Biology, Neuroinflammation, Neurodegeneration, Gut-brain Axis, Blood-brain Barrier

Introduction

In neurodegenerative diseases, the brain and the nervous system experience slow damage over time. As time progresses, individuals frequently experience significant memory impairment and the capacity for clear thought is lost. Scientists believed that proteins that fold in an incorrect manner cause these diseases.[1] It was also commonly believed that genes played the primary role, but current research demonstrates that chronic inflammation is a significant factor.[2] Among the factors that cause neurodegenerative diseases, approximately 10% of cases are inherited genetically.[15] Although the contribution of many individual factors to neurodegeneration still remains unknown, research indicates that individuals with neurodegenerative diseases have elevated neuroinflammation levels.[14] A multitude of factors contribute to neurodegenerative diseases such as environmental factors such as smoking, alcohol consumption, prolonged exposure to pesticides, mutations in the genome, aging, and inherited predisposition. [1]

Inflammation is the body's natural response to infection. When inflammation becomes chronic, it begins to destroy healthy cells. For example, prolonged inflammation can cause harm to brain cells. Microglia and astrocytes are present in the brain during inflammation. The gut and the brain are very closely linked by a system that scientists refer to as the gut-brain axis. Disruptions in the gut biome in the digestive system can lead to chronic inflammation throughout the body.[3] Alcohol weakens the gut lining, allowing damaging substances, particularly lipopolysaccharide, to enter the bloodstream. This increases inflammation and may also harm the blood-brain barrier, the protective covering of the brain. When that brain barrier is damaged, it becomes easier for inflammatory substances to get into the brain and create neuroinflammation. Research indicates that diet plays a very important role. The kind of high-fat, high-sugar diet typical in Western diets can cause a mild but consistent level of inflammation, damage the blood-brain barrier, and encourage the formation of amyloid plaques.[4] Along the same lines, high-fat diets increase indicators of inflammation and activate immune cells within the brain.[5]

Currently, alcohol, disorders in the digestive system, and damage to tau are examined in many studies as separate entities, not how they influence each other. Researchers do not yet have a complete picture of

what occurs when inflammation in the gastrointestinal tract affects the blood-brain barrier, subsequently triggers inflammation in the brain, and eventually causes brain cells to die. Some treatments appear promising but require further investigation. In fact, there is still a need to better understand how long-term inflammation contributes to neurodegeneration. This paper explores alcohol's effect on the gut-brain axis, alterations in the blood-brain barrier, and how microglial cells become activated leading to neuroinflammation arising in the hippocampus, cortex, and other brain regions. It also examines damage to neurons, alterations in tau, and amyloid plaques, all in relation to inflammation however, many questions remain unanswered.

Understanding the mechanisms of inflammation in the development of neurodegenerative disease is critically important. This research could show how lifestyle factors such as alcohol and high fat diets increase the risk of neurodegenerative diseases, help identify early warning signs of cognitive decline, discover new treatments that focus on reducing inflammation, and encourage healthier lifestyle choices to protect brain health. While there are many other factors that contribute to neuroinflammation causing neurodegenerative diseases, this paper primarily focuses on alcohol and Western diets since they directly influence gut health. Pesticides and other factors are excluded from this research paper since they do not disrupt the gut biome and the gut-brain axis directly.

Methods

In this study, the articles used for research include both studies conducted on humans and animals, as well as molecular/cellular experiments. Examining various types of literature will enable researchers to get a clearer picture of the role played by inflammation in promoting neurodegeneration. The literature cited in this paper is taken from peer-reviewed scientific journals and academic databases. The review focuses on studies published from 2014 to 2026 to ensure the inclusion of current and relevant research on the topic. Main sources of data include databases such as PubMed and journals including Frontiers in Immunology, Neurobiology of Disease, and Nature.com.

To obtain useful sources for this research, a number of key terms were used. These include keywords such as "neuroinflammation", "neurodegeneration", "gut-brain axis", "blood-brain barrier", "inflammation", "oxidative stress", "cognitive decline", and "alcohol induced neuroinflammation". Only articles written in English that provided a clear explanation of the impact of inflammation on neurodegeneration were considered appropriate. Studies were excluded if they focused primarily on acute traumatic brain injury, non-neurological inflammatory conditions, or non-English publications. Those which explored issues related to diet, gut microbiota, immune response, and cell signaling processes were most relevant to this work. A total of 92 sources were initially acquired, and 14 studies were found suitable for this research. Once all the sources were acquired, the data obtained were compared.

Within the framework of the study, no experiments involving participants or any testing on humans or animals were carried out, since all the information was gathered from previous publications and resources containing scientific data. Therefore, this study did not require any ethical approval, as all information was obtained through the analysis of the previous works.

Results and Discussion

Microglial Activation and Chronic Neurodegenerative Cascades

Researchers found in their study that inflammation begins in the body, rather than within the brain itself, and can significantly alter brain function and lead to neurodegenerative disease.[16] Additionally, there is evidence linking environmental factors to brain decline due to inflammation.

Microglia are the resident immune cells (macrophages) of the central nervous system (CNS). They continuously survey the brain, remove dead cells and debris through phagocytosis, regulate synaptic pruning, and coordinate immune and inflammatory responses. They also play important roles in brain development, homeostasis, injury repair, and neurodegenerative diseases.[21,22,23]

Alcohol consumption activates microglia in the CNS.[6] Microglia are activated upon the release of inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[1] These substances serve an important role in protecting the body, but excessive levels can injure brain cells.

Prolonged alcohol consumption causes oxidative stress, issues with mitochondria, and ultimately cell death.[17] Alcohol impacts neural stem cells in the hippocampus (the brain's memory center); the hippocampus is critical for learning and memory. Damage to these cells affects the brain's ability to produce new neurons, causing both loss of memory and a worsening of cognitive skills. This persistent inflammation may raise the risk of developing neurodegenerative diseases over time.[1,2,11,14]

Inflammation is also associated with tau, a protein that causes Alzheimer's disease. Tau develops into tau tangles in neurons, a process that is abnormal, and can destroy brain cells. Inflammation can in fact intensify tau-related damage.[7] Their experiments on animals showed that lowering tau levels safeguarded neurons from damage caused by inflammation. This suggests that inflammation might begin prior to and make tau abnormalities more severe, rather than being a result of them. And because of inflammation's significant impact, scientists are now investigating therapies to reduce it.[8] An example is melatonin. Melatonin is a hormone produced by the pineal gland and is a regulator of sleep.[18] Since melatonin can cross the blood-brain barrier, it may be useful in protecting brain cells from inflammation-related damage.[19]

Lots of research has linked inflammation to neurodegenerative diseases, but there is still much to learn. This study discovered how chronic inflammation contributes to neurodegenerative diseases, especially in relation to alcohol consumption, gut health, and brain function. The analysis from multiple scientific studies found that clear patterns were identified, showing that chronic inflammation plays a central role in damaging neurons and affecting brain health. The results also show that inflammation does not act alone but instead works through interconnected systems such as the gut-brain axis and immune responses.

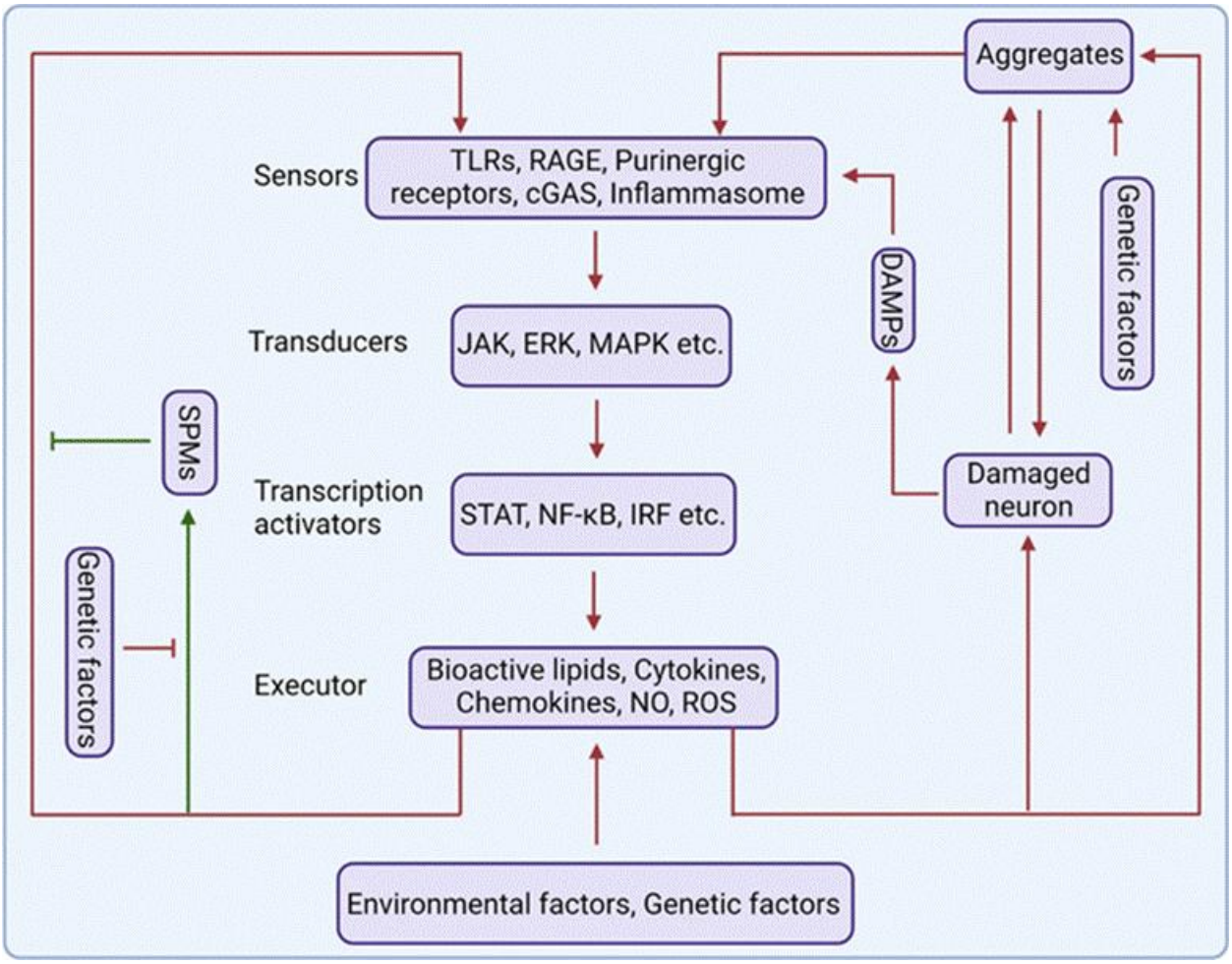

Figure 1 Signaling Pathways & Inflammation Loop. This figure illustrates the self-perpetuating cycle of chronic neuroinflammation, a process believed to contribute to neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and ALS. Source: 10.1038/s41392-023-01486-5

This figure shows how environmental and genetic factors initiate inflammatory signaling pathways that cause neuronal injury. Damage-associated molecular patterns (DAMPs) are released from injured neurons. These DAMPs activate additional inflammatory pathways. This causes a self-reinforcing cycle of neuroinflammation.[14]

The pathways shown in Figure 1 show how chronic neuroinflammation becomes self-sustaining. Neuronal injury occurs and causes the release of DAMPs. This activates the microglia and immune signaling pathways resulting in more neuronal damage. This continuous loop answers the question of why neurodegenerative diseases continue to progress long after the initial trigger has been removed. This has led researchers to believe that reducing chronic inflammation by therapeutic means interrupts the cycle before it becomes self-reinforcing. This could lead to slowing down disease progression.[14] As part of this review, alcohol induced inflammation and gut-derived signals represent the events that initiate neuroinflammatory cascades. Alcohol exposure or dietary factors begin the process, but evidence suggests that chronic microglial activation can eventually cause sustained neuronal damage. This finding directly addresses the primary question of this review why does neuroinflammation persist and worsen even when the original trigger is removed? The literature suggests that once the inflammatory loops become established the disease may continue to progress through self-amplifying immune and neuronal signaling mechanisms.[14]

Neuroinflammatory Feedback Loops in Alzheimer's Disease

Alzheimer’s disease was first identified as a distinct medical disease by Alois Alzheimer, a German psychiatrist and neurologist, in 1901. There are two abnormal features in a patient with Alzheimer’s disease, the presence of Amyloid plaques and Neurofibrillary tangles.[20] In modern medicine, Alzheimer’s disease is considered both a neurodegenerative and neuroinflammatory disorder. Even though the defining features of the disease are the presence of amyloid-β (Aβ) plaques and tau tangles, evidence from research shows that chronic inflammation plays a major role in accelerating their formation and toxicity. Many studies have shown that activated microglia release inflammatory mediators such as IL-1β, TNF-α, and reactive oxygen species, contributing to neuronal injury and cognitive decline.[6,8,14]

Persistent neuroinflammation also reduces the brain’s ability to clear Aβ aggregates and simultaneously promotes tau hyperphosphorylation, this links inflammation directly to the pathological characteristics of Alzheimer's disease.[8,11,14]

These findings point out that neuroinflammation is not merely a consequence of Alzheimer's disease but is one of the main drivers of disease progression. Evidence collected from animal and cellular studies also shows that injured neurons release DAMPs which further activate microglia and amplify inflammatory signaling. Neuronal damage then accumulates interactions between Aβ plaques, tau abnormalities, and chronic immune activation creating self-sustaining feedback loops that cause neurodegeneration over time. These relationships are summarized in Figure 2.

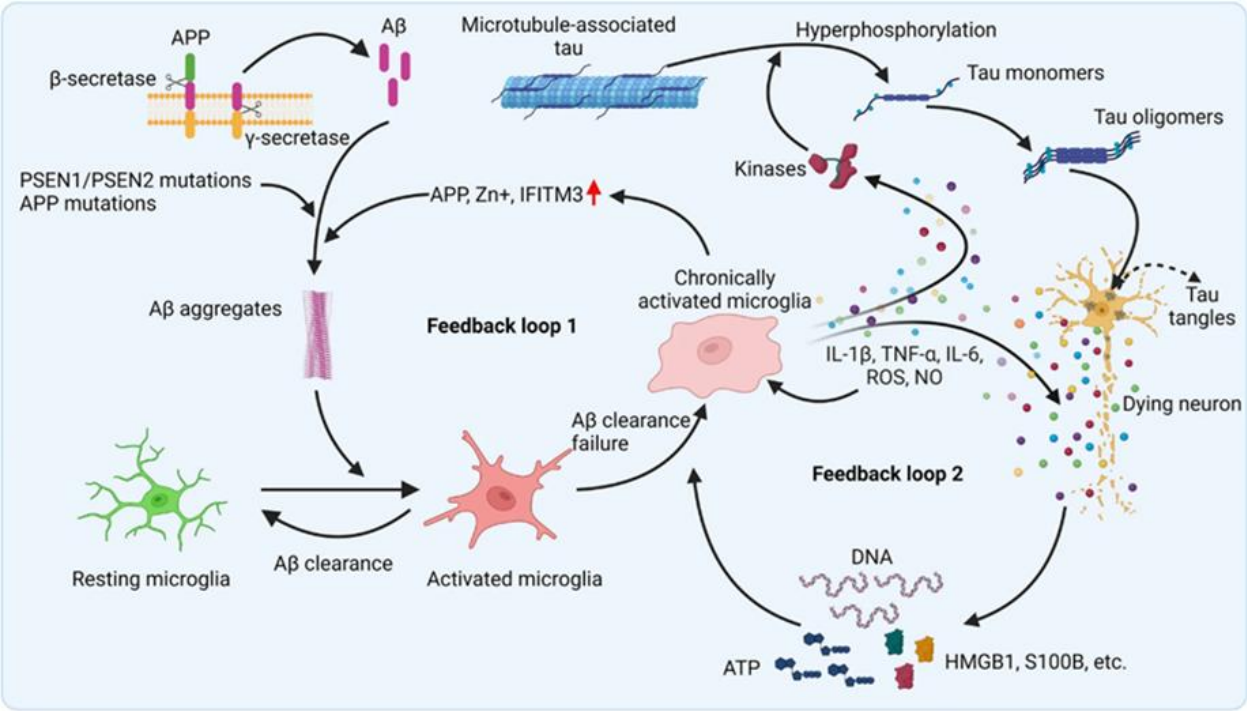

Figure 2 How Chronic Inflammation Connects to Alzheimer's. Inflammatory mediators promote further neuronal injury, impair Aβ clearance, and accelerate tau pathology, creating self-perpetuating cycles that contribute to progressive neurodegeneration. Source: 10.1038/s41392-023-01486-5

This figure illustrates the interconnected feedback loops linking amyloid-β accumulation, tau pathology, microglial activation, and chronic neuroinflammation. Inflammatory mediators cause further neuronal injury and impair Aβ clearance. They also accelerate tau pathology and reinforce progressive neurodegeneration.[14]

The pathways shown in Figure 2 demonstrate how inflammation, amyloid accumulation and tau pathology become reinforcing mechanisms. Microglia are activated and remain in an activated state. The inflammatory mediators damage the neurons and reduce the brain's ability to clear Aβ. This leads to additional plaque accumulation. The inflammatory signaling also promotes tau abnormalities and further impairs neuronal function. This self-perpetuating cycle helps explain why Alzheimer's disease progression continues despite therapies that focus on amyloid plaque removal. The findings also suggest that in order for treatment to be effective, the treatment must target both protein pathology and chronic neuroinflammation together and not in isolation.

In this review, these findings help answer the research question as to why inflammation contributes to cognitive dysfunction and neuronal destruction. The evidence also shows that inflammation is not simply a result of Alzheimer's disease but is one of the main causes of neuronal loss and cognitive decline. Chronic inflammation signals are capable of amplifying the damaging effects of Aβ plaques and tau tangles. This continuous feedback mechanism accelerates disease progression. However, there are still knowledge gaps regarding the exact sequence of events linking protein aggregation and immune activation. Future research should focus on whether early anti-inflammatory intervention can interrupt these feedback loops and stop the neuronal damage and arrest the disease progression.

Neuroinflammatory Mechanisms Driving Parkinson's Disease Progression

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized primarily by the loss of dopamine-producing neurons in the substantia nigra pars compacta and the accumulation of misfolded α-synuclein protein aggregates known as Lewy bodies. These changes lead to motor symptoms such as tremors, rigidity, bradykinesia (slowness of movement), postural instability, and non-motor symptoms including cognitive impairment, sleep disorders, and autonomic dysfunction.[24]

Studies in the past identified α-synuclein aggregation as the main driver of the disease. Growing evidence suggests that chronic neuroinflammation plays a critical role in the acceleration of neuronal damage and disease progression. Recent studies have identified inflammation as a key contributor to neurodegeneration by demonstrating that activated microglia release pro-inflammatory cytokines, reactive oxygen species and other mediators capable of damaging neurons.[1] Similar studies also emphasize that neuroinflammation can exacerbate nerve dysfunction through sustained immune activation and oxidative stress.[2] Studies also show how chronic activation of microglia contributes to neurodegenerative disease progression including Parkinson's disease, by causing neuroinflammation in the brain.[14] As part of this research paper, these findings put together show that neuroinflammation acts as a major accelerator of neuronal injury and is not just a response to existing damage.

Evidence also indicates that inflammation and α-synuclein pathology together cause interconnected feedback mechanisms. It is also reported that damaged neurons release danger-associated molecular patterns (DAMPs), including ATP, mitochondrial DNA, and other inflammatory signals that activate microglia. [14] Once the microglia get activated, they release cytokines such as TNF-α, IL-1β, and IL-6. These join with reactive oxygen species and create an environment that promotes additional neuronal dysfunction and α-synuclein accumulation. [14] Further studies also found that inflammatory signaling pathways amplify oxidative stress and neuronal vulnerability causing accelerated neurodegeneration and disease progression.[1] Collectively, these findings support the concept that inflammation and protein aggregation become mutually reinforcing processes that drive continuous disease progression. These mechanisms are summarized in Figure 3.

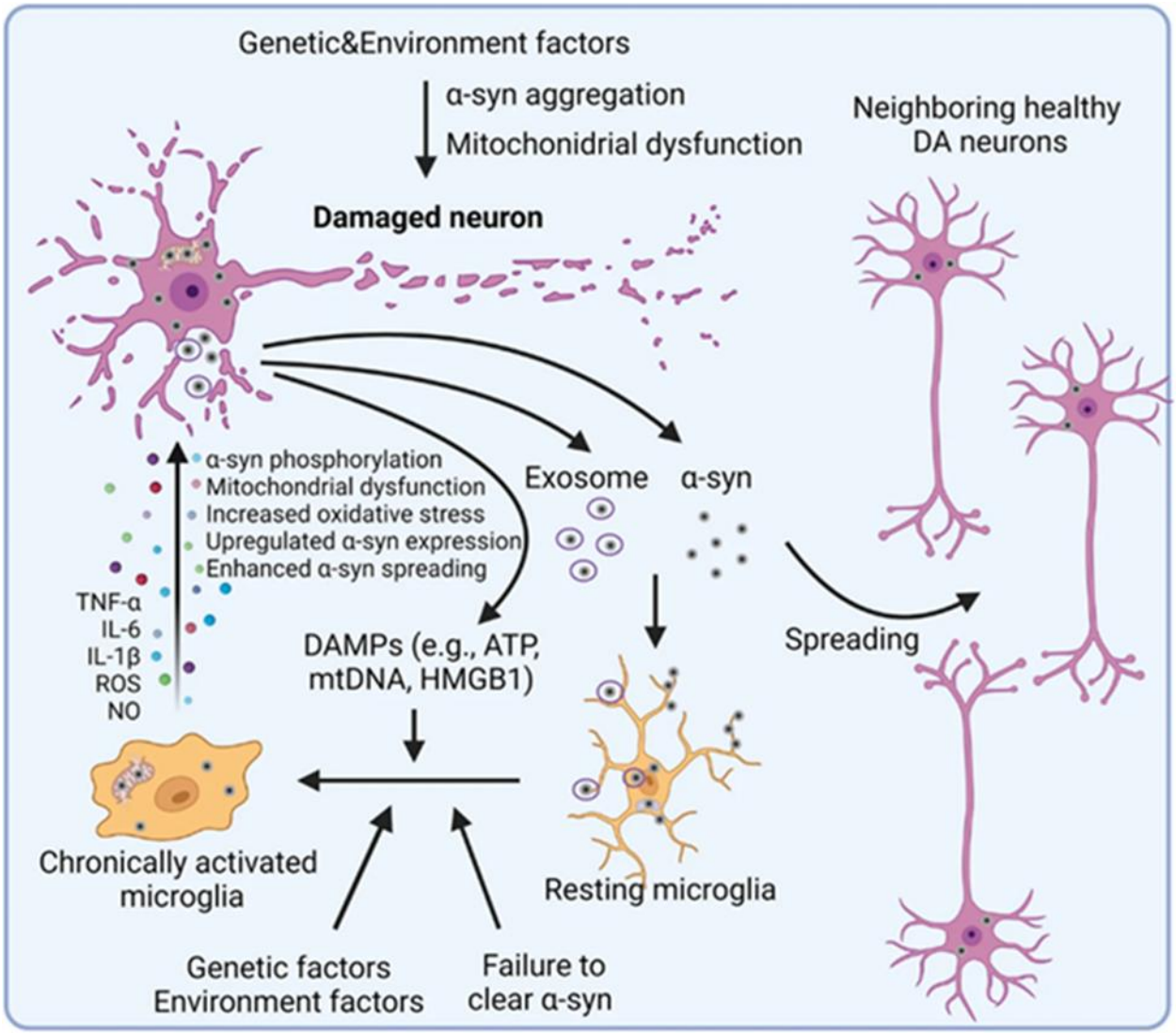

Figure 3 How Chronic Inflammation Connects to Parkinson's. α-synuclein accumulation and chronic microglial activation cause ongoing neuronal damage in Parkinson's disease. Neuroinflammation creates feedback loops that worsen disease progression and promote the spread throughout the brain. Source: 10.1038/s41392-023-01486-5

The pathways summarized in Figure 3 show that inflammation continuously amplifies neuronal injury. Damaged neurons release inflammatory signals this in turn, activates the microglia which produces mediators that increase oxidative stress and cause cellular dysfunction. At the same time α-synuclein aggregates spread to neighboring neurons causing the neurodegeneration to spread from damaged neurons to healthy neurons. It is proposed that these interactions create a self-perpetuating cycle the inflammation accelerates neuronal loss while neuronal damage further strengthens inflammatory signaling. [14] This feedback mechanism explains why Parkinson's disease steadily progresses over time even after the original trigger is no longer present.

In this review, these findings put together help answer the research question of how inflammation accelerates neurodegeneration. The collective evidence from Glass et al., Hurley and Tizabi, and Leng and Edison suggests that inflammation does not merely accompany Parkinson's disease but actively promotes its progression.[1,2,14] The chronic activation of microglia increases oxidative stress that enhances α-synuclein pathology and facilitates the spread of neuronal damage throughout the brain. These observations show that reducing neuroinflammation protects vulnerable neurons and slows disease progression by disrupting the feedback loops that cause sustained neurodegeneration. Future research is

also needed to determine whether therapies targeting inflammatory pathways can stop neuronal loss and the spread of α-synuclein pathology.

Microglial Activation and Neuroinflammatory Feedback Loops in ALS

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by the degeneration and loss of upper and lower motor neurons. This leads to muscle weakness, paralysis, and eventually respiratory failure. The disease was first described in detail by French neurologist Jean-Martin Charcot in 1869, who identified the characteristic degeneration of motor pathways in the spinal cord.[25]

Although ALS has traditionally been associated with genetic mutations and protein aggregation, new evidence shows that chronic neuroinflammation is a major factor in the progression of the disease. Studies show that inflammation is a major contributor to neurodegenerative disorders. Activated microglia promote neuronal injury by the release of cytokines, reactive oxygen species and other neurotoxic mediators.[1] Similarly, other studies also observed that neurodegeneration caused by inflammation is also evidenced by the presence of iron and ferritin within microglia and neurons. This shows the link between immune activation and neuronal damage.[11] In another study it is shown that chronic neuroinflammation is the central mechanism where the underlying neurodegeneration is sustained by the connection between signaling pathways.[14] Put together these findings show that microglial activation is one of the main factors causing the progression of ALS rather than it being a consequence of neuronal damage.

Research also shows that damaged motor neurons amplify the inflammatory responses through self-reinforcing feedback mechanisms. These mechanisms are shown in Figure 4.

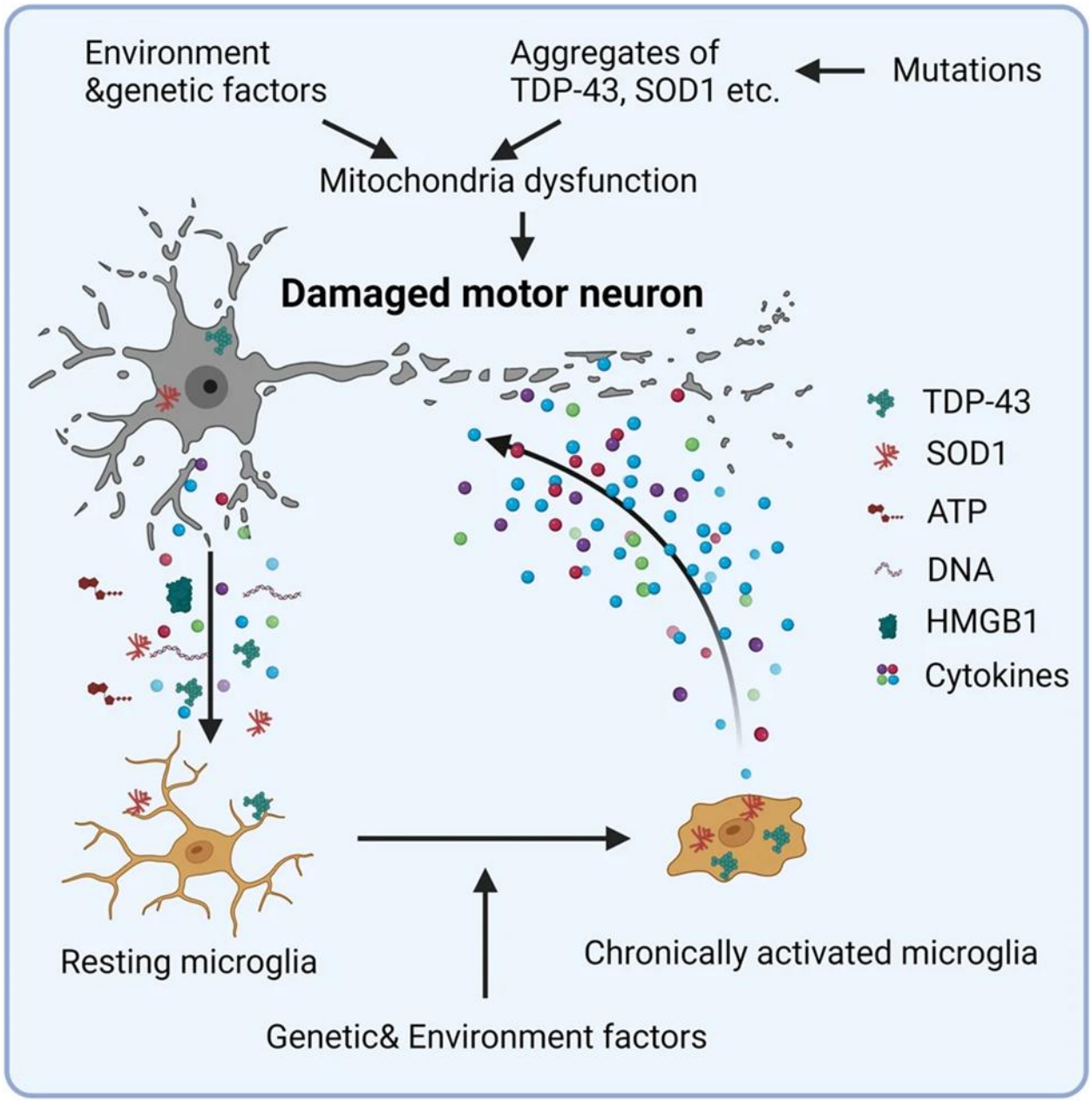

Figure 4 Environmental & Genetic Factors. ALS neuroinflammatory cascade showing protein aggregation, motor neuron damage, microglial activation, and chronic inflammatory feedback. Source: 10.1038/s41392-023-01486-5

This figure shows that genetic susceptibilities, protein aggregation, motor neuron injury and microglial activation cause chronic inflammatory feedback loops. These in turn contribute to progressive neuronal loss in ALS.[14]

The pathways shown in Figure 4 show that neuronal injury and inflammation continuously reinforce each other. Damaged motor neurons release inflammatory signals that activate microglia. The activated microglia generate cytokines and oxidative molecules which in turn increase neuronal stress and degeneration. This self-perpetuating cycle of inflammation and cellular damage continues long after the initiating trigger is no longer present. In studies, the feedback mechanisms are very similar to the inflammatory processes observed in Alzheimer's and Parkinson's disease. This shows that chronic neuroinflammation may show a common pattern across multiple neurodegenerative diseases.[14]

Within the context of this review, these findings from the different studies help address the question of whether inflammation serves as a common pathway connecting different neurodegenerative diseases. The evidence shown from the various studies suggest that chronic microglial activation, oxidative stress, and inflammatory signaling are recurring features of Alzheimer's disease, Parkinson's disease, and ALS.[1,11,14] This leads us to believe that therapies targeting shared inflammatory pathways such as chronic microglial activation, NF-κB signaling and oxidative stress have benefits across multiple neurodegenerative diseases and are not just limited to a single disease. However, further research is needed to understand why some individuals develop ALS, but others develop different neurodegenerative diseases when the inflammatory mechanisms are similar.

Gut Dysbiosis, Blood-Brain Barrier Disruption, and Neuroinflammatory Cascades in Alzheimer's Disease

Problems in the gut can lead to inflammation in the brain. Damage to the gut lining allows harmful substances to enter the bloodstream. This causes brain inflammation that may lead to nerve cell damage and neurodegenerative diseases. The disruption in the gut microbiota commonly known as gut dysbiosis has been linked to chronic systemic inflammation and neurodegeneration. Goyal et al. showed that alterations in the gut microbiome cause inflammatory signaling through the gut-brain axis. This affects both immune function and neurological health. [7] Tan and Norhaizan reported that Western diets with high fatty content cause oxidative stress. This in turn increases the inflammatory signaling which causes impaired cognitive function. This further supports the relationship between systemic inflammation and neurodegeneration.[10]

Multiple studies show that the blood-brain barrier (BBB) is a critical link between systemic inflammation and neurodegeneration. Anand et al. reported that alcohol induced inflammation caused damage to the BBB by increasing the permeability of protective barriers. This allows inflammatory mediators to enter the CNS. 3 Similarly, Więckowska-Gacek et al. reported that high fat Western diets have a direct correlation with increased systemic inflammation, blood-brain barrier dysfunction, neuroinflammation, and neurodegeneration.[13] Evans et al. similarly observed that high-fat diets cause elevated inflammatory markers and accelerated cognitive impairments.[5] When we put these findings together, they show that gut dysbiosis, alcohol consumption, and unhealthy high-fat diets may cause an inflammation cycle that reaches the brain due to damage to the BBB. These interconnected mechanisms are summarized in Figure 5.

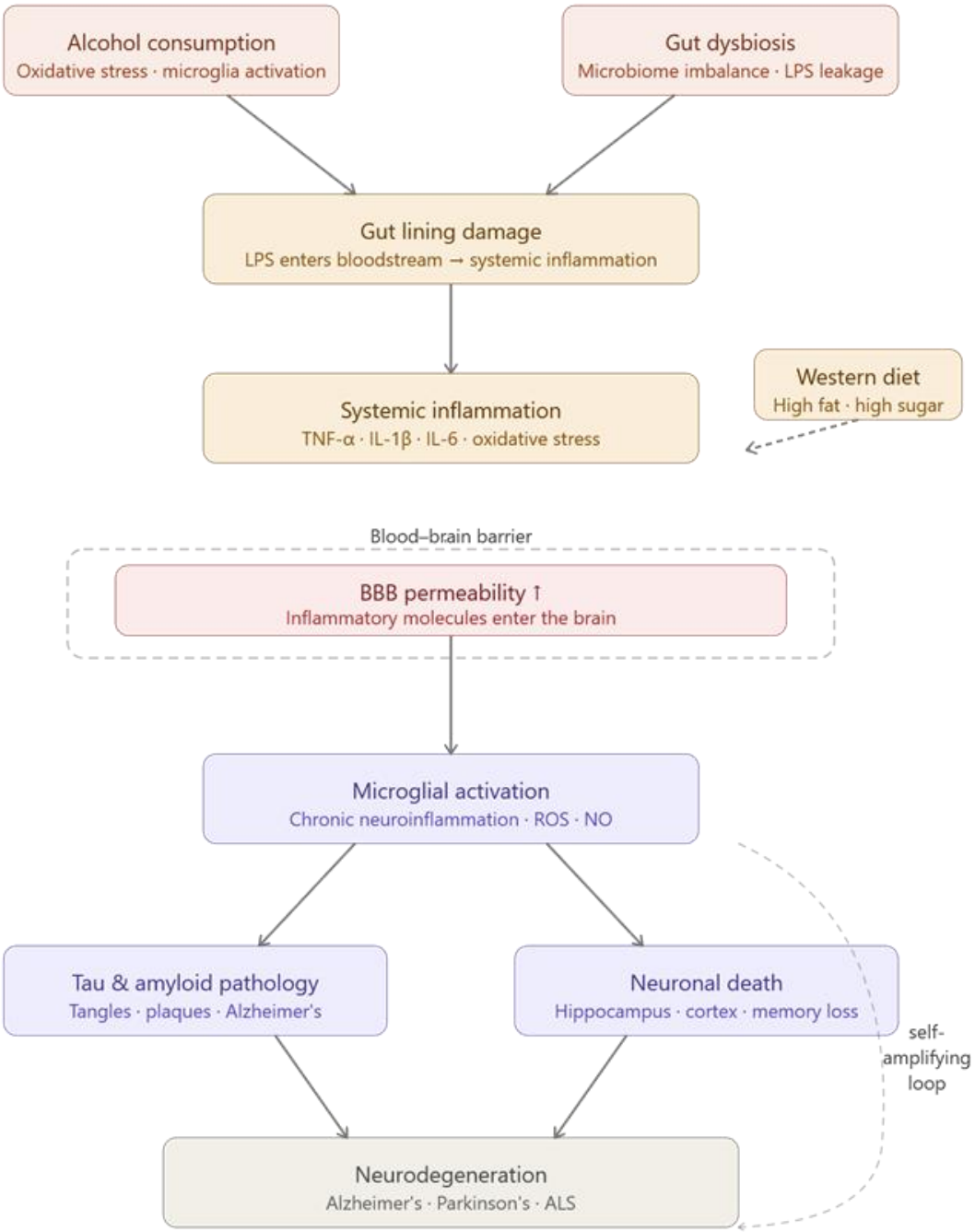

Figure 5 Inflammatory cascade from gut dysfunction to neurodegeneration. Alcohol consumption, gut dysbiosis, and Western dietary patterns contribute to gut lining damage and systemic inflammation. Source: Author-created figure based on references 3, 5, 7, 9, and 13.

Figure 5 illustrates how alcohol causes microglial activation and oxidative stress, while gut dysbiosis causes a microbiome imbalance, both of which lead to the weakening of the gut lining causing LPS and other bacterial products to leak into the bloodstream, triggering cytokine release (TNF-α, IL-1β, IL-6) throughout the body.[9]

This causes systematic inflammation, with a Western diet acting as a secondary driver of systemic inflammation. The systemic inflammation causes the blood-brain barrier to weaken, allowing inflammatory molecules to enter the brain. This causes the immune system to react causing microglia to become chronically activated, releasing ROS and neuroinflammatory mediators in a self-reinforcing feedback loop (shown by the dashed arrow on the right). Microglial activation causes tau tangles and amyloid plaques (Alzheimer's pathway), while also directly causing hippocampal and cortical neuron death, both converging on end-stage neurodegeneration.

Within the context of this review, these findings from the different studies help address the research question, “How do alcohol and a high fat western diet contribute to neurodegeneration”? The evidence collected from the studies quoted by Anand et al., Goyal et al., Mou et al., Evans et al., and Więckowska-Gacek et al. shows that alcohol abuse, gut dysbiosis and high-fat western diets may act as initiating events that trigger systemic inflammation and cause cascading cycles of neuroinflammation.[3,5,7,9,13] Unlike the previous sections which looked at neurodegenerative disease, this evidence suggests that neurodegeneration may begin with disruptions to gut health. This finding is important since it identifies risk factors that are avoidable and how lifestyle changes can prevent the progression of the disease. Future researchers should focus on the impact of lifestyle changes and other interventionary cures and the impact on reducing systemic inflammation. This will allow researchers to find possible ways to decrease the risk of neurodegeneration before irreversible neuronal damage occurs.

Conclusion

This research paper underscores the importance of chronic inflammation as an interconnected process between various lifestyle-related conditions and neurodegenerative diseases. These findings show that neurodegenerative diseases such as Parkinson’s, Alzheimer’s and ALS are influenced by the interaction between the gut-brain axis, blood-brain barrier, microglial activation, oxidative stress, and protein abnormalities. This is important because inflammation may not simply happen after neurodegeneration begins; it may also help start the disease and speed up its progression.

More importantly, this review highlights a major gap in current research. Alcohol consumption, gut dysbiosis, blood-brain barrier disruption, and abnormal protein accumulation are often studied independently instead of being studied as parts of the same biological network. As a result, scientists still lack a complete understanding of how these interconnected factors interact over time to cause neuronal damage. Another important issue related to previous investigations of the phenomenon under discussion is the use of animal studies, which makes the findings less generalizable to humans.

Future research will likely consider several factors simultaneously, such as alcohol consumption, dietary habits, and the gut microbiome. Moreover, there is a need to examine the effectiveness of some interventions to mitigate the inflammatory response, e.g., antioxidant agents or melatonin administration. Additionally, future research involving more clinical trials on humans would be appropriate to confirm these results. Clinical trials need to be conducted to test whether early anti-inflammatory intervention before neurological symptoms appear can meaningfully reduce the risk and rate of neurodegeneration.

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