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Microplastic Neurotoxicity: Pathways, Mechanisms, and Implications for Neurodegenerative Diseases

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ABSTRACT

This review synthesizes and elaborates on current studies examining the neurotoxic effects of microplastics, emphasizing their mechanisms of entry into the central nervous system and their possible involvement in the development of neurodegenerative disorders. The pervasive presence of microplastics in the environment has heightened concerns about their accumulation in biological systems, particularly their capacity to traverse biological boundaries and engage with neuronal tissues. This article seeks to synthesize and critically evaluate the existing scientific literature on microplastic neuroinvasion, concentrating on the mechanisms through which these particles penetrate the blood-brain barrier (BBB) specifically via transcellular, paracellular, or Trojan horse pathways—and their ensuing effects on neuronal homeostasis.

We investigate the physiological and molecular reactions triggered by microplastics, encompassing oxidative stress induction, mitochondrial failure, neuroinflammation, and synaptic disruption. These pathogenic processes may facilitate the onset and advancement of several neurodegenerative disorders, including Alzheimer's disease, by intensifying amyloid-beta aggregation, tau phosphorylation, and neuroimmune activation. Additionally, we examine the burgeoning epidemiological and experimental evidence associating microplastic exposure with cognitive deterioration and neuronal impairment.

This review offers a thorough analysis of microplastic neurotoxicity by evaluating both in vitro and in vivo studies, with the objective of elucidating the potential neurological hazards associated with these environmental contaminants. We emphasize significant deficiencies in existing research and propose future avenues, encompassing enhanced detection techniques, public health initiatives, and efforts to reduce human exposure to microplastics.

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INTRODUCTION

Microplastics, defined as plastic particles less than 5 millimetres in diameter, originate from diverse sources. Primary microplastics are intentionally manufactured, such as microbeads in personal care products or plastic pellets used in industrial processes (1). Secondary microplastics, however, result from the breakdown of larger plastic debris through environmental weathering, including UV radiation, wave action, and abrasion. These fragmentation processes yield progressively smaller particles, contributing significantly to environmental contamination. Additionally, the washing of synthetic textiles releases microfibers, a prevalent form of secondary microplastic (2).

Quantifying annual microplastic production is complex due to the varied sources and ongoing fragmentation. Nevertheless, it is known that the global production of plastics is massive, and a portion of that plastic ends up breaking down into microplastics (3). Recent studies indicate that millions of tons of plastic waste enter aquatic environments annually, with a significant portion degrading into microplastics (4).

Factors contributing to the amount of microplastics produced yearly include the amount of plastic produced globally, the amount of plastic waste that is mismanaged, and the rate which plastic degrades in the environment. Therefore, the estimated amounts of microplastics entering the environment vary, but all evidence points to a massive and growing problem (5).

The pervasive nature of microplastics raises significant concerns about their potential harm to human health. Entry into the human body occurs through various pathways, including ingestion via contaminated food and water, inhalation of airborne particles, and dermal absorption (6). Once inside, these minute plastic fragments can trigger inflammatory responses and oxidative stress, potentially damaging tissues and organs. Furthermore, microplastics can act as vectors, carrying harmful chemicals and pathogens that can leach into the body, further exacerbating health risks. Research is actively investigating the long-term effects of microplastic accumulation, with studies exploring links to disruptions in the endocrine system, immune responses, and potential carcinogenic effects (7).

The distribution of microplastics throughout the human body is becoming increasingly understood. They have been detected in various tissues and organs, including the lungs, liver, kidneys, and even the brain, indicating their ability to traverse biological barriers. Nanoplastics, even smaller particles, pose a heightened risk due to their capacity to penetrate cells and potentially interact with cellular components (8). The implications of this widespread presence are still being explored, but the potential for chronic exposure to lead to a range of adverse health outcomes is a growing concern. The ability of micro and nano plastics to carry other harmful chemicals also increases the likelihood of negative health impacts (9).

The nervous system, a complex network of neurons and supporting cells orchestrates communication throughout the body, including the brain and spinal cord (10). Nerve fibers of this system originate in the fascia, muscles, joints, and skin and include heat, mechanical, chemical, itching, and pain Receptors (11). Its delicate structure is protected by the blood-brain barrier (BBB), a highly selective membrane that restricts the passage of many substances (12). However, recent research suggests that microplastics, particularly nanoplastics, can breach this barrier (13). Several mechanisms facilitate this entry: direct translocation through the BBB via endocytosis, a process where cells engulf particles; indirect transport by acting as carriers for other neurotoxic substances; and inflammatory responses triggered by microplastic presence, which can compromise BBB integrity (14). Once inside, these particles can accumulate in neural tissues, potentially disrupting synaptic function and triggering neuroinflammation. The potential link between microplastic exposure and neurodegenerative diseases is an emerging area of concern (15). Neuroinflammation, a hallmark of many neurodegenerative conditions like Alzheimer's and Parkinson's disease, can be exacerbated by the presence of microplastics. These particles can activate microglia, the brain's resident immune cells, leading to the release of inflammatory cytokines and oxidative stress, which can damage neurons (16, 17). Furthermore, the ability of microplastics to adsorb and transport neurotoxic chemicals, such as heavy metals and persistent organic pollutants, could further contribute to neuronal dysfunction and accelerate the progression of neurodegenerative processes (18). While direct causal links are still being investigated, the potential for microplastics to contribute to neurotoxicity is significant. The small size of nanoplastics allows for intracellular uptake, potentially interfering with cellular processes like protein folding and mitochondrial function, both critical for neuronal health (13, 19). The accumulation of these particles could lead to chronic neuroinflammation and neuronal damage over time. Further research is needed to fully understand the long-term effects of microplastic exposure on the nervous system and to establish definitive links between these particles and the development or progression of neurodegenerative diseases (19). This article aims to review the neurotoxicity of microplastics, detailing how these particles break down into the nervous system and their potential role in neurodegenerative processes. It seeks to integrate the understanding of the mechanisms by which microplastics affect neurological health.

A History of Microplastic Origins and Production

The emergence of microplastics as a pervasive environmental contaminant is intrinsically linked to the rise of synthetic polymers in the mid-20th century. While large plastic debris was recognized as a pollution problem earlier, the insidious nature of microscopic plastic fragments became increasingly apparent in the late 20th and early 21st centuries (20). Initially, primary microplastics were intentionally manufactured for industrial and consumer applications. Examples include microbeads in personal care products, designed for exfoliation, and plastic powders used in cleaning and blasting. These intentionally produced microplastics were released directly into the environment through wastewater systems (21).

However, the vast majority of microplastics originate from the breakdown of larger plastic items. Secondary microplastics are formed through the fragmentation of plastic litter due to environmental weathering. Factors such as ultraviolet radiation, wave action, abrasion, and temperature fluctuations contribute to the gradual degradation of plastic waste into smaller and smaller

particles (22). This process occurs in both terrestrial and aquatic environments, with oceans acting as significant sinks for plastic debris. The widespread use of synthetic textiles, particularly those made from polyester, nylon, and acrylic, has also emerged as a significant source of microfibers (22). These microfibers are released during washing and are transported through wastewater systems into rivers and oceans. The production of plastics has increased exponentially since the 1950s, leading to a corresponding rise in microplastic pollution (23). The sheer volume of plastic waste generated globally, coupled with inadequate waste management practices, has resulted in the widespread dissemination of microplastics throughout the environment. As our understanding of the environmental and health implications of microplastics grows, efforts are being made to reduce plastic production, improve waste management, and develop alternative materials (24).

Microplastic Entry and Mechanisms of Human Health Impact

Microplastics, ubiquitous in modern environments, enter the human body through multiple pathways. Ingestion is a primary route, occurring via contaminated food and beverages, including seafood, drinking water, and even honey. Inhalation of airborne microplastics, particularly fibres released from textiles, also contributes to internal exposure (25). Dermal absorption, while less understood, may also play a role, especially with prolonged contact with contaminated surfaces or personal care products. Once inside the body, these particles can translocate across biological barriers, reaching various tissues and organs. The mechanisms by which microplastics exert adverse health effects are multifaceted (26). Their small size, especially in the nanometer range, allows them to penetrate cell membranes and interact with intracellular components. This can disrupt cellular processes, induce oxidative stress, and trigger inflammatory responses. Furthermore, microplastics can act as vectors for other harmful substances (27). They can adsorb and concentrate toxic chemicals, such as heavy metals and persistent organic pollutants, releasing them into the body upon ingestion or cellular uptake. This co-exposure to microplastics and other contaminants can amplify the overall toxicity (28). The immune system plays a crucial role in responding to microplastic exposure. Macrophages, immune cells that engulf foreign particles, attempt to clear microplastics from tissues. However, chronic exposure can lead to persistent inflammation and tissue damage. The body's inability to fully eliminate these particles can result in their accumulation, potentially leading to long-term health consequences (29). Chronic inflammation can also disrupt normal immune function, which could lead to increased susceptibility to other illnesses. Research is ongoing to fully elucidate the long-term health impacts of microplastic exposure. Studies are investigating potential links to endocrine disruption, respiratory diseases, reproductive disorders, and even cancer (30). The ability of microplastics to cross the blood-brain barrier raises concerns about neurotoxicity and potential contributions to neurodegenerative diseases. The growing body of evidence underscores the need for further research to assess the full scope of microplastic toxicity and to develop strategies to mitigate their impact on human health (31).

Microplastic Neuroinvasion and Neurological Impact

The blood-brain barrier (BBB), a highly selective physiological barrier, meticulously regulates the passage of substances from the bloodstream into the central nervous system (CNS), safeguarding the delicate neural environment. However, increasing evidence suggests that microplastics, particularly nanoplastics, can circumvent this formidable defense (32). Several mechanisms facilitate this neuroinvasion. Firstly, direct translocation across the BBB can occur via endocytosis, a process where cells engulf particles, allowing nanoplastics to be internalized and transported. Secondly, microplastics can serve as Trojan horses, adsorbing and carrying neurotoxic substances like heavy metals or persistent organic pollutants, effectively delivering these harmful agents into the brain parenchyma (33). Thirdly, the presence of microplastics can trigger localized inflammation, disrupting the tight junctions that maintain BBB integrity, thereby increasing permeability and facilitating particle entry. This compromise of the BBB is particularly concerning, as it allows for the potential accumulation of microplastics and associated toxins within the CNS (19).

Once within the nervous system, microplastics can interact with various neural components, disrupting normal neuronal function. They can accumulate in different brain regions, including the hippocampus, cortex, and cerebellum, potentially interfering with synaptic transmission and neuronal signaling (14). Microplastics can induce oxidative stress by generating reactive oxygen species, which can damage cellular components like lipids, proteins, and DNA, leading to neuronal dysfunction and even cell death (34). Furthermore, they can activate microglia, the brain's resident immune cells, triggering the release of pro-inflammatory cytokines, and contributing to chronic neuroinflammation. This neuroinflammation, a hallmark of many neurodegenerative diseases, can exacerbate neuronal damage and accelerate disease progression (35). The ability of nanoplastics to enter cells also means they can potentially disrupt intracellular processes, like protein folding, and mitochondrial function, which are essential for

neuronal viability (36).

The potential link between microplastic exposure and neurodegenerative diseases is a growing area of concern. The chronic neuroinflammation induced by microplastics can contribute to the pathogenesis of diseases like Alzheimer's and Parkinson's. The ability of these particles to carry neurotoxic substances can further exacerbate neuronal damage and accelerate disease progression (33). For example, some studies suggest that microplastics may facilitate the accumulation of amyloid-beta plaques, a hallmark of Alzheimer's disease. Moreover, the disruption of synaptic function and neuronal signaling caused by microplastics can contribute to cognitive decline and behavioral changes (37). The long-term effects of chronic microplastic exposure on brain health are still being investigated, but the potential for these particles to contribute to neurotoxicity and neurodegenerative diseases is significant. The implications of microplastic neuroinvasion extend beyond direct neuronal damage (38). The disruption of the BBB can also compromise the brain's ability to clear metabolic waste and maintain ionic homeostasis, further contributing to neuronal dysfunction. The interaction of microplastics with neurotransmitter systems can also lead to alterations in mood, behavior, and cognitive function (39). Furthermore, the potential for microplastics to interact with neural stem cells raises concerns about developmental neurotoxicity and the potential for long-term neurological consequences (39). Further research is crucial to fully understand the mechanisms by which microplastics affect the nervous system and to assess the long-term health risks associated with chronic exposure.

Mitigating the Microplastic Burden: Detection and Reduction Strategies

Detecting microplastics within the human body, particularly the nervous system, presents significant challenges. Current methods primarily rely on analyzing tissue and fluid samples using techniques like Raman spectroscopy, Fourier-transform infrared spectroscopy (FTIR), and mass spectrometry (40). These techniques allow for the identification and quantification of microplastic particles, but they are often invasive and limited in their ability to provide real-time or in vivo assessments. Developing non-invasive imaging techniques, such as advanced microscopy or nanoparticle-based sensors, is crucial for understanding the distribution and dynamics of microplastics within the body (41). Additionally, improving analytical techniques to detect and quantify nanoplastics, which pose a greater challenge due to their smaller size, is essential for a comprehensive assessment of internal exposure. Research is also being conducted into the use of biological markers to assess exposure and potential harm (42).

Reducing microplastic exposure requires a multi-faceted approach, targeting both environmental and individual behaviors. At the environmental level, reducing plastic production and improving waste management are paramount. Implementing stricter regulations on single-use plastics, promoting the use of biodegradable alternatives, and investing in advanced recycling technologies can significantly decrease the amount of plastic entering the environment (43). Wastewater treatment plants can be upgraded to more effectively filter microplastics. Additionally, addressing microfiber pollution from textiles by promoting the use of natural fibers, developing washing machine filters, and improving textile manufacturing processes is crucial. Individual behavioral changes, such as reducing plastic consumption, choosing products with minimal plastic packaging, and properly disposing of plastic waste, can also contribute to reducing environmental contamination (44). Within the human body, strategies for reducing microplastic burden are still in their early stages. Research is exploring the potential of chelating agents or other compounds that can bind to and remove microplastics from tissues. However, these approaches require careful consideration of potential side effects and the long-term safety of these interventions (45). Lifestyle modifications, such as consuming filtered water and avoiding processed foods with plastic packaging, can minimize further exposure. Supporting research into methods that promote the body's natural clearance mechanisms, such as enhancing macrophage activity or improving lymphatic drainage, may also prove beneficial. Further studies on the human microbiome may also provide insights into how to improve the body's natural ability to degrade or eliminate microplastics (46).

The Role of Microplastics in Causing Alzheimer's Disease

The potential link between microplastic exposure and Alzheimer's disease is an emerging area of scientific inquiry. While direct causation remains to be established, several lines of evidence suggest a plausible connection (47). Alzheimer's disease is characterized by the accumulation of amyloid-beta plaques and tau protein tangles in the brain, leading to neuronal dysfunction and cognitive decline (48). Microplastics, particularly nanoplastics, can potentially contribute to these pathological processes. Firstly, their ability to breach the blood-brain barrier allows them to directly interact with brain tissue (49). Secondly, they can act as vectors for neurotoxic substances, such as heavy metals and persistent organic pollutants, which are known risk factors for Alzheimer's. Thirdly, microplastics can induce chronic

neuroinflammation, a key factor in the progression of the disease (37).

The mechanisms by which microplastics might contribute to Alzheimer's pathology are multifaceted. Chronic neuroinflammation, triggered by the presence of microplastics, can activate microglia, the brain's immune cells, leading to the release of pro-inflammatory cytokines (50). These cytokines can promote the formation of amyloid-beta plaques and tau tangles, exacerbating the pathological hallmarks of Alzheimer's. Furthermore, microplastics can disrupt calcium homeostasis in neurons, a process crucial for synaptic function and neuronal survival. Dysregulation of calcium signaling can contribute to neuronal damage and promote the aggregation of amyloid-beta (51). The oxidative stress induced by microplastics can also damage cellular components, including proteins and lipids, further contributing to neuronal dysfunction and the accumulation of pathological aggregates. The ability of nanoplastics to enter cells means they can also potentially interfere with protein folding, which is relevant to both amyloid beta and tau protein aggregation (52).

The role of microplastics as carriers of neurotoxic substances is particularly concerning. Heavy metals like aluminum, lead, and mercury, which are known neurotoxins, can adsorb onto microplastic particles and be transported into the brain. These metals can contribute to oxidative stress, neuroinflammation, and the formation of amyloid-beta plaques and tau tangles (53). Similarly, persistent organic pollutants, such as pesticides and flame retardants, can also be carried by microplastics and contribute to neurotoxicity. These substances can disrupt neuronal signaling, promote neuroinflammation, and increase the risk of Alzheimer's disease (32). The synergistic effect of microplastics and these neurotoxic substances may amplify the overall neurotoxicity and accelerate the progression of Alzheimer's. Further research is needed to fully elucidate the connection between microplastic exposure and Alzheimer's disease (38). Longitudinal studies that track microplastic exposure and cognitive function over time are essential. In vitro and in vivo studies are also needed to investigate the specific mechanisms by which microplastics contribute to Alzheimer's pathology. Understanding the potential role of microplastics in Alzheimer's disease is crucial for developing strategies to mitigate their impact on brain health and to prevent or delay the onset of this debilitating disease (54).

DISCUSSION AND CONCLUSION

The burgeoning field of microplastic research has illuminated the pervasive nature of these pollutants and their potential to inflict significant harm on human health, particularly within the delicate confines of the nervous system. The ability of microplastics, especially nanoplastics, to breach the blood-brain barrier and induce neuroinflammation, oxidative stress, and neuronal dysfunction raises serious concerns about their contribution to neurodegenerative diseases like Alzheimer's (55). While direct causal links are still under investigation, the accumulating evidence strongly suggests that chronic exposure to microplastics can exacerbate existing neuropathologies and potentially accelerate disease progression. The role of microplastics as vectors for neurotoxic substances further amplifies these concerns, highlighting the complex interplay between environmental pollutants and human health (56).

The challenges associated with detecting and quantifying microplastics within the human body, particularly the nervous system, necessitate the development of advanced analytical and imaging techniques. Current research efforts are focused on refining existing methods and exploring novel approaches to assess internal exposure and track the distribution of microplastics in vivo (57). Simultaneously, mitigating microplastic exposure requires a multi-pronged strategy encompassing environmental remediation, individual behavioral changes, and the development of interventions to reduce the internal microplastic burden (58). Reducing plastic production, improving waste management, and promoting the use of sustainable alternatives are crucial for minimizing environmental contamination. Research into chelating agents and other compounds that can remove microplastics from tissues, as well as strategies to enhance the body's natural clearance mechanisms, holds promise for mitigating internal exposure (59).

The potential connection between microplastics and Alzheimer's disease underscores the urgency of addressing this global health issue. The ability of microplastics to induce neuroinflammation, disrupt calcium homeostasis, and act as carriers for neurotoxic substances suggests a plausible mechanism by which they can contribute to the pathological hallmarks of Alzheimer's (60). Further research is needed to fully elucidate the complex interplay between microplastic exposure and neurodegenerative processes. Longitudinal studies, in vitro and in vivo experiments, and epidemiological analyses are essential for establishing definitive links and identifying potential therapeutic targets (60).

In conclusion, microplastics represent a significant and growing threat to human health, particularly the nervous system. The ability of these particles to penetrate biological barriers and induce a cascade of adverse effects necessitates a concerted effort to mitigate their impact. Addressing this challenge requires a holistic approach, encompassing

environmental protection, technological innovation, and individual responsibility. Continued research is crucial for deepening our understanding of microplastic toxicity and developing effective strategies to protect human health from these ubiquitous pollutants.

Authors's Contribution

Shabnam Radbakhsh and Rezvan Norouzzadeh: Conceptualization and writing. The authors read and confirmed the final manuscript.

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