Microplastic Exposure and the Onset of Parkinson's Disease

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ABSTRACT

Microplastics (MPs) are small particles or fragments of plastic that have leaked into the environment and ecosystems in recent decades. Numerous animal studies have suggested that an organism's exposure to microplastics may evoke responses from the body that are similar to the pathogenesis of human diseases. In particular, a collection of evidence has suggested that microplastics exposure may mimic Parkinson's disease pathology (decreased dopaminergic neurons and interrupted motor function). Parkinson's disease is an often progressive and fatal neurodegenerative disease that is defined by the degeneration of dopaminergic neurons in the brain; this degeneration leads to decreased motor function and abnormal motor movements. Studies have indicated that, upon entering the body, microplastics may trigger oxidative stress, organ inflammation, neurotoxicity, and transgenerational effects. Parkinson's disease diagnoses are predicted to greatly increase in upcoming generations while microplastics continue to enter the environment at growing rates, inciting a point of concern for the human population and other organisms. In this review, the possible effects of organisms' exposure to microplastics are explored through the review of animal studies and the comparison of these findings to the pathogenesis of Parkinson's disease. By understanding the ways in which MPs affect the body and contribute to PD and other neurodegenerative disorders, the danger that MPs pose toward living organisms can be recognized, necessitate further research, and encourage preventative measures against the leakage of MPs into the environment.

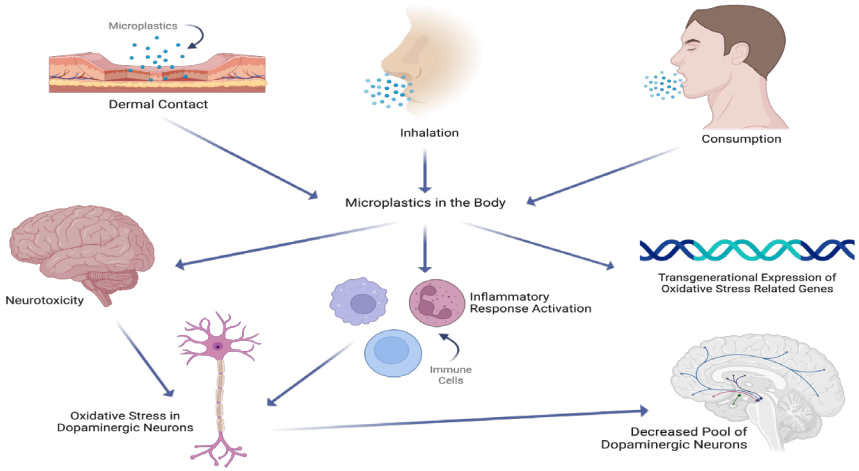

Figure 1. The suggested response in the human body to microplastic exposure through dermal contact, inhalation, or oral consumption. Once in the body, microplastics may follow three pathways: 1) travel to the brain and trigger neurotoxicity, 2) enter the immune system, triggering the inflammatory response after recognition by immune cells, 3) cause transgenerational expression of genes potentially associated with oxidative stress. Neurotoxicity and the inflammatory response are then suggested to induce oxidative stress in dopaminergic neurons, followed by neuronal cell death and decreased numbers of dopaminergic neurons (dopamine pathways of the brain shown in blue, pink, purple, and green). (Created using Biorender.com)

Introduction

It is predicted that, by 2025, 250 million tons of plastic will be in our marine environment (Bouwmeester et al., 2015; Wright & Kelly, 2017). Over time, small particles of these plastics measuring 5 mm or less, called microplastics (MPs), will break off and travel through our drinking water, food, and the air that we breathe (US Department of Commerce & National Oceanic, 2016). Research suggests that, due to their abundance in the environment, microplastics are absorbed by humans and other organisms through dermal contact, oral ingestion, and inhalation (Prata et al., 2020a; Prüst et al., 2020). Microplastics have been found in various processed foods that are consumed daily, such as seafood, sugar, beer, and table salt (Wright & Kelly, 2017). MPs may become airborne when clothing containing plastic is dried outside and small fragments are caught in the wind and travel through the open air, making them available for inhalation by humans (Bouwmeester et al., 2015; Wright & Kelly, 2017).

The effects of MP exposure and consumption have recently come to light, with many researchers finding that microplastics may have an effect on immune function and promote neurotoxicity (Hirt & Body-Malapel, 2020; Prata et al., 2020b; Prüst et al., 2020). In one study, *C. elegans* exposed to microplastics demonstrated neurodegeneration of glutamatergic, serotonergic, and dopaminergic neurons, as well as decreased body movements, including body bends and head thrashes (H. Chen, Hua, Yang, et al., 2021). Another study investigated the effects of microplastic exposure on mice and found decreased motor and memory function along with decreased acetylcholine levels when compared to mice without MP exposure (Wang, 2022). Similarly, neurodegeneration of glutaminergic, serotonergic, and dopaminergic neurons are associated with Parkinson's disease (PD). PD is a disease in which one displays motor function disturbances: including tremors, changes in posture, and rigidity (Tolosa et al., 2021). In a study in which mice were repeatedly exposed to an oral dose of microplastics, researchers found changes in the blood brain barrier, a loss of dopaminergic neurons, and disrupted motor function, suggesting that MPs may play a role in the neurodegeneration found in Parkinson's disease (Liang et al., 2022).

The progression of Parkinson's disease is suggested to be caused by a loss of approxiamtely 80% of dopaminergic nerve cells in the substantia nigra of the brain, followed by a decrease in dopamine levels (Mayo Clinic Staff, n.d.). Dopamine activation is credited for behavior and movement regulation, while, in the onset of PD, its decreased levels are credited for disrupted motor function (Olguín et al., 2016). Nearly 1 million people in the United States have PD, and the number is projected to increase to 1.2 million by 2030 (Kouli et al., 2018; Parkinson's Foundation, n.d.). Evidence suggests that PD could be caused by transgenerational genetic expression of PARK genes, exposure to pesticides, overconsumption of caffeine, or the overuse of cigarettes (Kouli et al., 2018). Although studies have suggested this combination of genetic and environmental factors contributing to Parkinson's disease, the exact triggers are unknown. (Mayo Clinic Staff, n.d.).

Both microplastic exposure and PD result in degeneration of neurons, followed by disrupted locomotive behavior. Currently, studies have examined the correlation between microplastics exposure and the onset of neurodegenerative diseases, although its link to Parkinson's disease has not specifically been studied. The number of diagnoses of Parkinson's disease is projected to double in the next 30 years (Tolosa et al., 2021) while nearly 270,000 tons of microplastic particles continue to collect in the marine environment (Akdogan, 2019). Currently, PD has no cure, and limited therapeutic options are available to treat the symptoms, (National Health Service, n.d.-a). Considering the vast rise in cases of PD and number of MPs entering the environment, it is crucial to investigate their connections and propose possible solutions.

Here, we discuss how the immune response, oxidative stress, neurotoxicity, and gene expression induced by microplastics may contribute to the pathogenesis and progression of Parkinson's disease.

Microplastics

Primary MPs are small particles of plastic created for commercial use (Rochman et al., 2015). One of the most common primary forms of MPs are microbeads, which are industrially manufactured for personal care products (e.g. exfoliants, cosmetics) and cleaning products. Personal use products containing microbeads often wash down drains, then leaking microbeads into the environment through sewage pipes into water treatment plants and aquatic environments (Rochman et al., 2015). Upon this discovery, microbead production has been regulated to slow their leakage into the environment (Rochman et al., 2015). Secondary MPs are another form of MPs that consist of fibers or shards broken off from larger plastic products such as synthetic fabrics, agricultural mulch films, and beach litter (Browne et al., 2011). Their spread is difficult to contain due to their varying sources, making them a large contributor to the ever-increasing level of MPs in the environment (Browne et al., 2011).

Plastic is made of polymers including polyethylene, polyethylene terephthalate, polypropylene, polystyrene, polyvinyl chloride, and polymethyl methacrylate (Cheang et al., 2018; Rodriguez, n.d.). The textures and flexibilities of plastics depend on the type of polymer in the plastic (Cheang et al., 2018; Rodriguez, n.d.). Another main component of plastics are plasticisers: chemical additives used to produce different textures (Cadogan & Howick, 2000; *Plasticisers*, 2018). It has been suggested that these chemical additives can leach from their plastic source into plastic-contained foods and drinks, making them available for consumption (Burgos-Aceves, 2021).

Considering that microplastics are prevalent in the environment and are easily consumed through water and food or through respiration, further research needs to assess how microplastics affect human health.

The Immune Response

Multiple studies suggest that exposure to microplastics has led to the activation of the inflammatory response in both vertebrates and invertebrates (Usman et al., 2021); (Chia-Yu Huangg, 2022; Zhao et al., 2021); (Qiao, 2019; Rodriguez-Seijo, 2017). In one study, mice ingesting microplastics demonstrated liver damage, which is a key organ in detecting pathogens and activating the immune response (Zhao et al., 2021). Additionally, the study found that MPs suppressed T cells and B cells in the liver, enhanced natural killer cell activation, increased infiltration of macrophages and lymphocytes, and induced inflammatory cytokine production through the NF-κB pathway (Zhao et al., 2021). These responses indicate that the immune response has been activated. Inflammation is one of the immune system's responses to foreign bodies, causing a rise in body temperature and swelling in an attempt to kill off the foreign bodies (L. Chen et al., 2018), and it is possible that MPs can induce similar inflammation in the brain through the gut-brain axis (Ding, 2018). A MP exposure study on red tilapia suggested that, upon ingestion, MPs reach the gut, travel through the hemolymph, eventually to the brain crossing the blood-brain-barrier (BBB) (Ding, 2018). Upon MPs crossing the BBB, neurons are easily exposed to the MPs (Daneman & Prat, 2015). If the MPs do cause inflammation in the brain, neurons and neurological processes can be severely damaged by their presence (Ding, 2018). Inflammation commonly occurs in the brain at the onset of neurodegenerative diseases, including PD (L. Chen et al., 2018). In PD, neuroinflammation may be triggered by crosstalk of glial cells, astrocytes, neurons, and endothelial cells (Pajares et al., 2020). Through crosstalk, the homeostatic function of the cells is interrupted by the signal of another pathway. Then, the cells secrete proinflammatory cytokines and chemokines and have increased receptor expression (Pajares et al., 2020). Additionally, peripheral immune cells travel to the brain, causing further inflammation (Pajares et al., 2020). It is suggested that crosstalk of cells followed by inflammation begins in the brain when pattern recognition receptors bind to a pathogen that is presumed to infect the body (Glass et al., 2010). Toll like receptors (TLRs) are a specific type of pattern recognition receptor that recognize varying pathogens then activate microglia to begin the inflammatory process to kill them off (Glass et al., 2010). Upon microglial activation, NF-κB is activated followed by production of reactive oxygen species (ROS) by the mitochondria, (Missiroli et al., 2020) ultimately triggering proinflammatory mediators (Glass et al., 2010). Evidence suggests that this NF-κB cascade is also present in the onset of PD

and responsible for inflammation in the brain upon triggering proinflammatory cytokines and enzymes (Singh et al., 2019). It is suggested that these combined factors destroy dopaminergic neurons, which are the main neurons that are affected in PD and decrease as the disease progresses (Glass et al., 2010). When dopaminergic neurons are destroyed, oxidized proteins, lipids, and DNA are released (Glass et al., 2010). Microglia then recognize these products and initiate production of ROS and increase cytokine production (Dias et al., 2013), thereby creating a positive feedback loop in the brain, and promoting further inflammation (Dias et al., 2013). Perhaps the TLRs recognize MPs as harmful foreign bodies, triggering the NF-κB cascade and oxidative stress, followed by harmful neuronal inflammation that is presumed to be a factor of neurodegenerative diseases. Though research suggests that the immune system plays a part in the toxicity of MPs in the brain, more research needs to evaluate the innate and adaptive immune response to MPs, and how these responses may contribute to the pathology present in PD.

Oxidative Stress and Neuroinflammation

Oxidative stress refers to an interrupted equilibrium between the production of (ROS) and the body's ability to detoxify the ROS, causing cellular damage (Dias et al., 2013). Mitochondria produce ROS through the process of oxidative phosphorylation, in which ATP synthesis is coupled by electron leak (Bottje, 2019). In the central nervous system, mitochondria of glial cells produce excess ROS which causes oxidative stress, then damaging proteins. These damaged proteins then can modulate extracellular pathways and initiate pro-inflammatory pathways (Taylor, 2013). These pathways may initiate inflammation in the brain (Taylor, 2013). In Parkinson's disease, dopamine is easily oxidized, creating ROS. Therefore, ROS may induce apoptosis in dopaminergic neurons and decrease the pool of dopaminergic neurons (Naoi & Maruyama, 1999). It has been shown that microplastics have the potential to create ROS via extracellular and intracellular processes (Hu, 2020). UV exposed MPs have the potential to create their own ROS before cells do through crosslinking reactions on their surface which then react with atmospheric oxygen (Hu, 2020; Jeon, 2021). MPs that are not weathered by UV radiation can also result in the production of ROS through intracellular reactions (Hu, 2020). After entering the body, these MPs are engulfed by cells through endocytosis, which then recognize MPs as a foreign substance, triggering the innate immune response (Hu, 2020).

Neuroinflammation induced by oxidative stress has also been found in the pathogenesis of Parkinson's disease (Dias et al., 2013). ROS is produced as a result of neuroinflammation in PD, creating a repetitive cycle of oxidative stress and inflammation (Dias et al., 2013). MPs and bodily processes can produce ROS and can result in outcomes that are harmful toward the body - like neuroinflammation. The similarity of the progression of neuroinflammation in MP exposure and the onset of PD gives reason to further investigate if the two factors are related.

Neurotoxicity

MPs can alter neuronal populations and behavior through multiple pathways. A recent study in goldfish has shown that nanoplastics may travel to the brain through the olfactory pathway to the olfactory bulb (W. Shi et al., 2021). Upon entrance, the concentration of dopamine in the brain was suppressed incrementally as the size of the microplastic particles during exposure decreased when compared to the control group (W. Shi et al., 2021). The suppression of dopamine was credited for altered behavioral activity in the goldfish ((W. Shi et al., 2021)). Thus, the MPs may have expressed neurotoxic effects in the brain. Similar neurotoxicities are found in the progression of PD, where dopamine suppression correlates with the disease and is credited for the motor dysfunction that is typical with diagnosis (Tolosa et al., 2021). These outcomes are similar to Parkinson's Disease in that patients with PD have lower levels of dopaminergic and glutamatergic neurons and an impairment in motor function. Perhaps exposure to MPs generates neurotoxicity which contributes to the pathology seen in PD patients.

Acetylcholinesterase and Neurotoxicity

In regular conditions, acetylcholinesterase (AChE) is an enzyme that breaks down acetylcholine (ACh), a neurotransmitter that is responsible for smooth muscle contractions, heart rate, blood vessel dilations, and bodily secretions (Britannica, 2022). In one study, AChE activity in the brains of seabass was measured to evaluate neurotoxicity after MP exposure. AChE activity provides information on neuromuscular cholinergic disruption (Kalafatakis et al., 2015). Seabasses exposed to high levels of MPs exhibit inhibited AChE activity in the brain, indicating neurotoxicity (Barboza, 2018). DA and ACh maintain a complicated balance in the brain, with the activation of ACh receptors showing excitation and inhibition of DA activity in the brain (Lester et al., 2010). Recent studies on patients with early onset PD show that there was an increase in cholinergic binding in the brain accompanied by a reduction of DA activity (Sanchez-Catasus et al., 2022). The study also showed a positive correlation with bradykinesia and ACh-DA imbalance, suggesting that the neurotransmitter imbalance influences motor function (Sanchez-Catasus et al., 2022). Thus, MP exposure may inhibit AChE activity, allowing an overabundance of ACh. The overproduction of ACh is then shown to correlate with a reduction of DA in the brain, which is a common finding in PD, credited for the disturbance in motor function. Therefore MPs seem to have a neurotoxic effect on the brain that disturbs the AChE and ACh balance, later disrupting the ACh-DA balance as well.

Genetic Effects

It has been found that *in vivo* maternal exposure to polystyrene nanoplastics in *C. elegans* results in the transgenerational upregulation of genes associated with oxidative stress in offspring, causing transgenerational neurotoxicity (H. Chen, Hua, Li, et al., 2021). The parent generation was exposed to MPs, but the following generations were cultured without direct exposure (H. Chen, Hua, Li, et al., 2021). The neurotoxicity had the effect of decreased motor function, finding that genes related to oxidative stress are passed down, although declining throughout generations. This shows that exposure to microplastics can affect the offspring of the exposed generation before the offspring are even introduced to MPs in the environment. The genes *sod-3, sod-4,* and *sod-5* were some of the upregulated genes expressed in the MP-exposed generation of nematodes; these genes are a part of the SOD enzyme system that is shown in the oxidant stress model of Parkinson's disease (H. Chen, Hua, Li, et al., 2021). The SOD system is referred to as the first line of defense against ROS in the onset of PD because it catalyzes the dismutation of superoxide radicals to hydrogen peroxide, which is later converted to water and oxygen (Yang et al., 2020). Perhaps the discovered upregulation in these genes indicated the need for defense against high levels of ROS in the offspring of MP-exposed organisms, suggesting that MPs may contain high levels of ROS. Another study found that ongoing exposure to MPs can cause alterations in *in vivo* gene expressions resulting in biological toxicity in mice (J. Shi et al., 2022). This study found an expression of *Ace2* in the aorta of mice exposed to MPs. They identified *Ace2* as a hub gene, meaning it has many connections to other RNAs. *Ace2* has been expressed in the cerebrospinal fluid of individuals diagnosed with PD (Li et al., 2020). Although, the specific role of *Ace2* in the pathogenesis of PD is something that requires further investigation. Genetic predisposition to PD may be a serious concern if microplastics have transgenerational effects that result in the progression of the disease.

Discussion

Microplastics pose serious health risks to humans upon consumption and exposure. It is possible that the ingestion of MPs can cause a series of neurodegenerative effects in the human body, potentially leading to Parkinson's disease pathology. The literature continuously demonstrates that the presence of microplastics in living beings can result in the degeneration of dopaminergic neurons, a cell population that generates a circuit largely responsible for voluntary movement and behavioral processes such as reward, mood, and stress (Chinta, 2005). Similar to MP exposure, a

determinant of Parkinson's disease progression is a loss of dopaminergic neurons in the brain (National Health Service, n.d.-b). Through testing on mice, nematodes, fish, and other organisms, MP exposure can result in the activation of inflammation through the immune response, neurotoxicity, oxidative stress, and transgenerational genetic effects through gene expression (Barboza, 2018; H. Chen, Hua, Li, et al., 2021; Liang et al., 2022; Mattsson et al., 2017; J. Shi et al., 2022; W. Shi et al., 2021). All of these processes have been implicated in the progression of PD (Barboza, 2018; H. Chen, Hua, Li, et al., 2021; Liang et al., 2022; Mattsson et al., 2017; J. Shi et al., 2022; W. Shi et al., 2021). Concerns are rising as Parkinson's disease is expected to double in the next thirty years (Tolosa et al., 2021) while MPs continue to enter the environment at unprecedented rates (Akdogan, 2019).

There is minimal research on the specific chemical components of microplastics that have the largest effect on the body, and what specifically causes animals and humans to exhibit PD-like symptoms when exposed to MPs. Many of the studies on MP exposure have used plastics types such as polystyrene and polypropylene. (Wu B 2019; Han 2019; Wang 2022; Lee, et al. 2022; Chen, et al. 2021; Liang, et al. 2022) . Thus, there may be some inconsistency in the findings, considering that different chemicals within plastics can have different effects on the body. For example, in a study that exposed human-derived cells to polystyrene microplastics, the results included inflamed immune cells, excess ROS production, the death of fibroblasts and cancer cells, and cellular membrane damage. The degree of toxicity in the cells was suggested to be due to the physical roughness, sharpness, and concentration of the polystyrene MPs. (Choi, 2020). In a study exposing human-derived cells to polypropylene microplastics, similar results were found, suggested that polypropylene MPs smaller than 20 μm were cytotoxic toward PBMCs and Raw 264.7 cells, showing increased histamine and cytokine production in the results. Larger MPs showed lesser presumed effects in the results, indicating that the effects of polypropylene MPs are dependent on size. Therefore, differing plastic components can yield effects depending on size or depending on concentration. Recent studies have suggested that plasticizers are a common component of almost all plastics that have a direct effect on the body due to their chemical components (Burgos-Aceves, 2021). A very common component of plasticisers used in PVC plastics are Phthalates (Wang & Qian, 2021). They are a family of industrial chemical components, suggested to have negative effects on the endocrine system and neurological system (Wang & Qian, 2021). There are a variety of plasticisers, therefore, future research should identify which Phthalates are particularly hazardous towards humans.

The literature regarding MP exposure generally focuses on animal subjects rather than humans, although the data can still be representative. Many MP studies utilize fish and other marine animals because these organisms are exposed to MPs through aquatic environments, which frequently overlap with the water in which humans use to swim, bathe or drink. Animal studies are also excellent model systems for human disease because of the homology in genes and similarity of expressed phenotypes and pathology between animals and humans. Considering that longitudinal studies on humans exposed to MPs are not currently feasible, studies performed with other organisms will provide insight into the effects of MPs on human disease, particularly PD.

Overall, it is evident that research must elucidate both the connection of MP exposure to Parkinson's disease and MP exposure to human health and disease.

Conclusion

The presence of microplastics has greatly increased in the environment over recent decades.They may be ingested by humans through inhalation, consumption, or dermal contact. Recent evidence from animal studies suggest that MPs may be related to neuroinflammation induced by the immune response and oxidative stress, neurotoxicity, and transgenerational effects. Many of these effects are also associated with the progression of Parkinson's disease, with symptoms including decreased motor function. The increasing numbers of MPs in the environment runs parallel to a predicted increase of PD cases in upcoming generations. Parkinson's disease is degenerative and incurable, thereby highlighting the need for environmental and therapeutic intervention. Therefore, with the possibility of microplastics contributing to the pathogenesis of Parkinson's disease, extensive research must determine MP toxicity, and regulations on plastic production and usage should be implemented.

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