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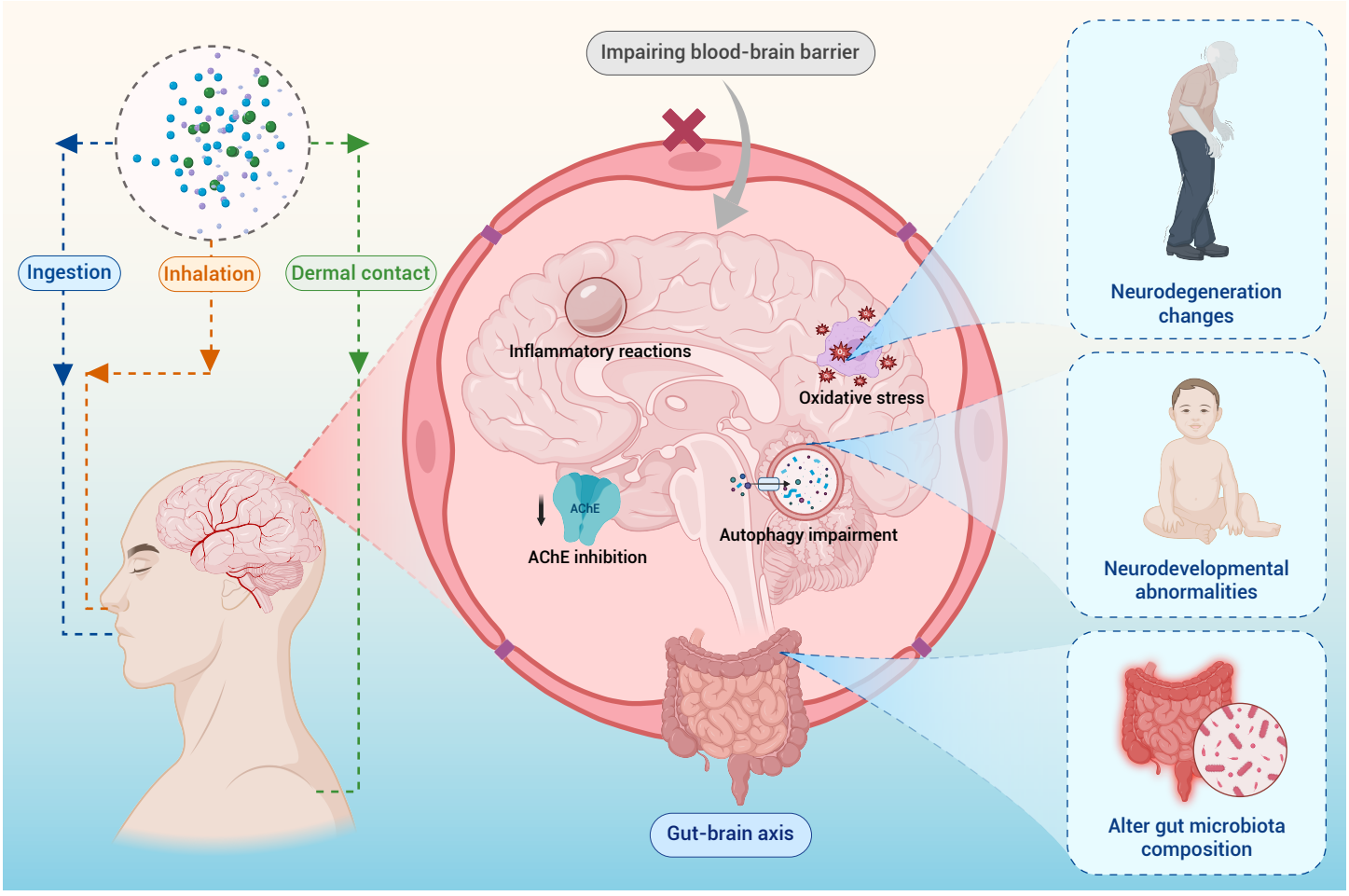
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Microplastics impair intestinal barrier integrity and disrupt gut microbial balance.
- Microplastics induce gut dysbiosis that drives systemic inflammation and oxidative stress.
- Microplastics trigger gut-brain axis signaling that propagates inflammatory stress to the brain.
- Microplastics may contribute to neurodevelopmental and neurodegenerative disorders.

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Microplastics and the gut-brain axis: Unraveling neurotoxic mechanisms and health implications

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Microplastics (MPs) are emerging environmental contaminants with increasing global prevalence, leading to inevitable human exposure through ingestion, inhalation, and dermal absorption. Despite the protective role of the blood-brain barrier (BBB), MPs can translocate and accumulate in the brain, raising concerns about their potential neurotoxicity. This review systematically evaluates the neurotoxic mechanisms of MPs, emphasizing their occurrence in the gastrointestinal tract and interaction with the gut-brain axis. MPs can disrupt intestinal barrier integrity, alter gut microbiota composition, and induce systemic inflammation, ultimately affecting neurotransmitter homeostasis. These disturbances may propagate to the central nervous system through neuroinflammatory pathways, oxidative stress, and dysregulated neurotransmission. Additionally, we discuss potential mechanisms of BBB penetration by MPs and their implications for neurodegenerative and neurodevelopmental disorders. It also highlights environmental exposure risks, technological challenges in assessing MPs' toxicity in real-world conditions, and current research gaps. We emphasize the urgent need for human-based studies to elucidate the long-term health risks associated with MPs exposure, and implementing comprehensive strategies and policies to reduce reliance on conventional plastics and promote sustainable material alternatives can serve as an effective approach to mitigating MPs consumption.

INTRODUCTION

Microplastics (MPs) are generally defined as plastic particles with a diameter of less than 5 mm, have become a prominent global environmental issue. The contamination of MPs, as a significant planetary boundary hazard, is presently a major global environmental problem. MPs are present in nearly all abiotic (including aquatic, terrestrial, and atmospheric) and biotic (containing flora, fauna, and humans) ecosystem compartments on earth.[1] The escalating annual production and disposal of plastic products, combined with inadequate recycling, limited reuse, and the poor degradability of these materials, have made this pollution a significant and challenging environmental dilemma that is difficult to remediate. The physicochemical properties of MPs and interactions with chemicals and bacteria in the environment might affect biological health and environmental quality. Specifically, these particles, which carry adsorbed substances such as chemicals and microbes, traverse biotic and abiotic compartments, leading to cumulative contamination consequences. Moreover, MPs can influence global biogeochemical cycles by altering element cycling and nutrient dynamics in ecosystems. In addition to their global environmental ubiquity, recent human biomonitoring evidence has introduced the concept of a "human plastisphere," which describes a biological particle system formed by non-endogenous plastic debris that accumulates, distributes, and interacts within host tissues.[2-4] This plastisphere is characterized by the long-term persistence of plastic particles that can remain in human organs for decades, along with a highly organized distribution pattern showing clear organotropism across sixty-three biological compartments. Emerging data further indicate that these internally deposited particles can actively participate in human physiology by disrupting cardiovascular, reproductive, metabolic, and immune processes, thereby highlighting the human plastisphere as a novel dimension of MPs exposure and its potential health implications.[5] Furthermore, the toxicity-debt effect (the prospective long-term ramifications of plastic degradation and pollution discharge) associated with MPs may result in a future peak in toxicity.

Notably, recent findings highlight the profound neurotoxic effects of MPs mediated through gut health. Compromised gut health, particularly deficiencies in key antioxidant pathways like Nrf2, can intensify the neurological damage caused by MPs. Research has shown that intestinal epithelial dysfunction exacerbates systemic and neural inflammation, reinforcing the interconnectedness of gut and brain health. The pollution issue of MPs is recognized for its significant complexity in addition to the aspects of ubiquity and ecotoxicity. Contaminated MPs exhibit significant variability in physicochemical characteristics, including dimensions, morphology, polymer composition, additives, duration of aging, and related materials. Divergences in these characteristics of MPs have been shown to result in unique outcomes and have varied ecological repercussions and effects. The complex plastisphere system revealed that environmental and lifestyle factors often exert a greater influence on health than genetic background. For instance, in the case of premature mortality, these factors accounted for nearly ten times the variance explained by the polygenic risk score.[6]

MPs in the environment originate from two primary sources: primary and secondary. Primary sources encompass plastic pellets, microbeads in personal care items, paint, wastewater from laundering, sewage sludge, synthetic sporting surfaces, artificial grass, and wear from automobile tires. Secondary sources originate from the fragmentation of substantial plastic debris, including bags, bottles, fishing gear, and agricultural films. Determining the precise sources of environmental MPs is difficult due to their ubiquitous distribution and overlapping origins. Comprehending and alleviating these causes is essential for tackling the widespread problem of MPs pollution.

To comprehensively grasp the ecological impacts of MPs, it is essential to examine their movement and deposition patterns. MPs are disseminated via natural mechanisms such as water currents, wind, and animal behavior, enabling them to influence populations and ecosystems significantly distant from their sources.[4] The transport dynamics, encompassing the duration and pathways of MP migration, affect their interactions with animals, including ingestion and incorporation into food webs. Moreover, fluctuations in transportation patterns considerably influence the density and dispersion of MP contamination, exacerbating their ecological impacts. Evaluating the destiny of MPs in freshwater ecosystems and their transference to marine habitats is crucial for comprehending their enduring impacts on biodiversity and ecological health. Two primary classifications of MPs distribution have been identified: vertical and horizontal distribution. The classifications are substantially affected by multiple parameters, including the size, structure, density, hydrogeology of MPs, and the presence of organism.[7]

Given the pervasive environmental presence of MPs and the demonstrated vulnerability of the gut-brain axis (GBA) to environmental stressors, this review systematically synthesized the current evidence and correlation of MPs exposure as a novel neurotoxicant via the GBA. Most existing reviews have addressed either MPs neurotoxicity or gut-brain axis disruption independently. In contrast, this work integrates findings across gastrointestinal (GI), microbial, and neural systems to reveal MPs as cross-system disruptors of gut-brain communication. We emphasize unifying mechanistic patterns such as a conserved "GI initiation → systemic propagation → neural impair-

ment" cascade that emerges consistently across taxa.

Moving beyond the broader scope of previous reviews, we provide a unique integrative perspective by tracing the pathogenic journey of MPs from ingestion to neurological impact. Our specific objectives consist of three main aspects: (1) Clarify the role of MPs' physicochemical properties in their bioavailability and interactions within the GI tract; (2) Delineate the mechanistic pathways through which MP-induced gut dysbiosis and barrier disruption propagate inflammatory and metabolic signals to the brain; (3) Assess the empirical evidence connecting MP exposure to adverse neurological outcomes, including altered neurotransmission, neuroinflammation, and the etiology of specific disorders. Through this review, we aim to identify critical knowledge gaps, highlight the urgency of human biomonitoring studies, and underscore the GBA as a critical target in the public health risk assessment of MPs.

MPS PRESENCE IN THE GI TRACT

Recent studies have demonstrated that upon ingestion, MPs interact extensively with GI mucosa, potentially causing physical abrasion and localepithelial barrier. Additionally, MPs can cause systemic inflammation and change the composition of the gut flora, which can ultimately impact neurotransmitter regulation. Human exposure to MPs occurs predominantly through the ingestion of contaminated food and water, leading to direct interaction with the GI tract. While the long-term health implications remain understudied, emerging research leveraging rodent models provides critical insights into their biodistribution and toxicity. In this section, we discuss the presence of MPs in the GI tract from different perspectives, including their impact on the GI system; the influence of size, composition, and charge on MP bioavailability and toxicity; the pathways of MP exposure and the significance of the GBA.

Impact on the GI system

Accumulating evidence from animal studies demonstrates that MPs exert detrimental effects on the GI tract, inducing intestinal mucosal damage, metabolic disturbances, and inflammatory responses in murine and zebrafish models.[8] Exposure to polystyrene (PS) MPs in low-dose (25-30 μg/kg body weight/d with particle size ~5 μm) in C57BL/6J male mice for 14 w either under normal chow or high-fat diet conditions displayed to disrupt gut microbiota composition, compromise intestinal barrier integrity, and trigger metabolic dysfunction, underscoring their potential to drive both localized and systemic pathologies.[9] It exacerbated gut permeability, oxidative stress, inflammation, and hepatic lipid accumulation, further confirming the critical role of MPs in disrupting intestinal and metabolic homeostasis. These effects are mediated through mechanisms such as cellular oxidative damage, dysbiosis, leaching of toxic additives, and impaired nutrient absorption, which may extend to human health.[10] In real-world environments, MPs rarely act alone; they coexist with contaminants like flame retardants, heavy metals, and pharmaceuticals, generating synergistic toxicity. It reported that a pivotal *in vitro* study investigated the interactions between polyethylene (PE) MPs and the flame retardant tetrabromobisphenol A (TBBPA) using Caco-2 intestinal epithelial cells (IECs) and human gut microbiota.[11] In this study, 5 μm PE-MPs were applied at concentrations of 10 to 100 μg/mL with or without TBBPA (20 μM) for 24-48 h exposure. While TBBPA alone caused cytotoxicity; notably, co-exposure of them resulted in an amplified oxidative stress and mitochondrial dysfunction by approximately 40%, likely due to MPs enhancing TBBPA bioavailability through adsorption and prolonged GI retention. In zebrafish test, PS-MPs adsorbed with polychlorinated biphenyls (PCBs) increased intestinal permeability by 60% compared to pristine MPs, facilitating systemic translocation of particles and co-pollutants.[9]

MPs can not only enhance the toxic effects of chemical pollutants but also produce a synergistic enhancement effect on gut pathogenic bacteria and the toxins they produce. MPs alone increase the abundance of *Clostridium*, a genus associated with gut inflammation and opportunistic infections, disrupting microbial metabolic networks essential for host health, including butyrate production that supports intestinal barrier integrity.[12-13]

Mechanistically, this synergistic toxic effect is postulated to arising from the enhanced bioavailability of contaminant/microorganism mediated by MPs, a process facilitated by two key interconnected ways: (1) the high adsorption capacity of MPs toward contaminant, which promotes the formation of stable complexes or microbial carriers; and (2) the prolonged retention of these complexes within the GI tract, which extends the window of toxicant absorption and subsequent systemic exposure. Such findings underscore the critical role of MPs-mediated modulation of xenobiotic bioavailability in amplifying environmental toxicant-induced cellular impairment, also highlight the need to assess MP toxicity under environmentally relevant co-exposure conditions rather than in isolation.

Impact of size, composition, and charge on MPs' bioavailability and toxicity

The GI tract serves as a critical interface for MPs bio-interactions, where physicochemical properties like particle size, chemical composition, and surface charge collectively govern absorption, toxicity, and systemic distribution. Emerging evidence highlights nanoscale particles (<1 μm) as particularly bioavailable due to their ability to exploit paracellular pathways and transcytosis. 20 nm PS particles translocated 5.3-fold more efficiently across murine intestinal epithelium than 200 nm counterparts, accumulating in systemic organs such as the liver.[14] In contrast, larger MPs (1-10 μm), such as polyethylene terephthalate (PET) fibers (5-20 μm), remain confined to the gut lumen but induce mechanical stress, causing mucosal erosion and elevating intestinal permeability by 40% in zebrafish models.[9] Chemical composition influences GI toxicity through hydrophobicity, additive leaching, and degradation byproducts. Hydrophobic polymers like PET and polypropylene (PP) absorb lipophilic toxins such as polychlorinated biphenyls and polycyclic aromatic hydrocarbons, enhancing oxidative stress. Additive-laden MPs, such as phthalate-containing PVC, can release 18-34% of plasticizers like di(2-ethylhexyl) phthalate under simulated GI conditions, disrupting tight junction proteins and increasing epithelial permeability.

Surface charge, defined by functional groups like -COOH or -NH_2, critically influences cohesion, cellular uptake, and organ-specific biodistribution.[15] Carboxylated PS (-25 mV) adheres 2.8-fold more to intestinal mucus, prolonging GI retention, while amine-modified PS (+15 mV) penetrates mucus better but induces 3.5-fold higher cytotoxicity in Caco-2 cells.[16] Biodistribution studies show charge-driven organ targeting, with -NH_2 MPs accumulating in the kidney (35%) and -COOH MPs in the liver (52%).[17] Adverse outcome pathway frameworks (Figure 1) indicate negatively charged MPs have higher intestinal absorption (1.5-1.7%) than neutral or positively charged particles (0.2-0.3%).

These physicochemical traits also drive GI damage, as 50 nm amine-modified PS reduces *Lactobacillus* by 60%, worsening colitis-like symptoms,[19] while PET MPs increase pro-inflammatory cytokines 4-fold via NF-κB activation.[20] Secondary toxicity arises when MPs act as pathogen vectors, as E. coli biofilm-coated MPs enhance bacterial translocation across intestinal barriers.[21]

Pathways of MPs' exposure

Human exposure to MPs and Nanoplastics (MNPs) occurs via three primary routes: dermal contact, inhalation, and oral intake (Figure 2).[22] Inhalation represents a significant exposure route, with synthetic particles detected in atmospheric fallout and airborne particulate matter.[23] The GI tract is considered the dominant entry pathway for MPs, primarily through ingestion of contaminated food and water. Dermal exposure, arising from hygiene products and synthetic textiles, is currently regarded as a minor pathway due to the skin's limited permeability to larger particles.[24] However, uncertainties persist, as studies on deeper dermal penetration remain inconclusive.

Bioaccumulation risks necessitate urgent investigation, particularly given the potential for long-term adverse effects. Seafood, especially from polluted aquatic ecosystems, is the most documented dietary source. Approximately 200 marine species notably sardines and sprats, show significant MPs contamination.[25] Geographic disparities in seafood consumption lead to variable exposure rates; FAO data suggest an annual intake of 54,000 MPs particles per person (147.9 particles/d) from marine sources alone.[26] Beyond seafood, MPs are present in honey, sugar, salt (10-100+ particles/kg), and beverages, with bottled water as a major source. Plastic tea bags release up to 2.3 million MPs and 14.7 billion NPs per cup, meaning two cups daily could add 29.4 billion NPs, far exceeding other foods.[27] These findings highlight

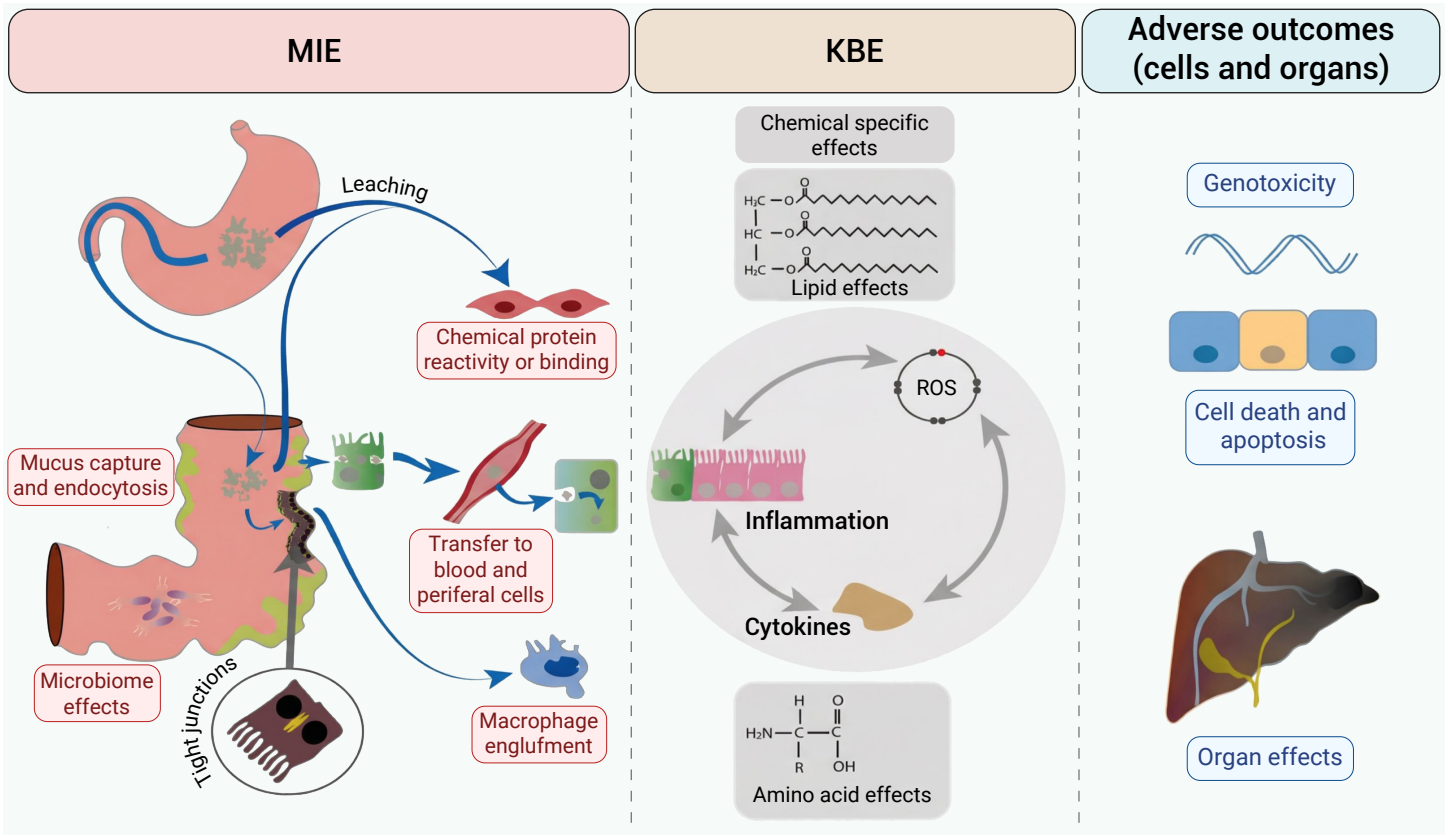

Figure 1. Suggested Adverse Outcome Pathway (AOP) for the oral ingestion of MPs within humans (Crown Copyright © 2023 Published by Elsevier B.V.).[18]

bottled beverages and packaging as priority sources for regulation and toxicological studies.

INTERACTION OF MPS WITH GUT MICROBIOTA

The gut microbiome, a fundamental regulator of host physiology, is increasingly recognized as a critical target for MPs. Ingestion of these environmentally pervasive particles instigates a direct pathophysiological cascade within the gastrointestinal tract. The primary insult involves a significant shift in microbial composition and function, leading to a state of dysbiosis that erodes the foundational symbiosis between the host and its microbiota. This ecological imbalance within the gut community is a pivotal event that compromises intestinal barrier integrity, culminating in increased permeability. The failure of this critical barrier function facilitates the translocation of bacteria and their pro-inflammatory metabolites into systemic circulation. This process propagates a persistent state of low-grade inflammation, which is implicated in the pathogenesis of a spectrum of extra-intestinal disorders, including metabolic syndrome and neurobehavioral deficits. Consequently, the gut microbiome serves not merely as an initial site of MP-induced injury but as a central hub amplifying local damage into systemic disease.

Gut dysbiosis and GBA disruption induced by MPs

The gut microbiome, a pivotal regulator of host physiological homeostasis, is increasingly recognized as a critical target for MPs. Beyond direct GI tract damaging, MPs can also induce gut dysbiosis and disrupt the GBA, thereby triggering a series of pathophysiological consequences.

Ingestion of MPs initiates a cascade of pathophysiological events within the GI tract, initially triggering significant shifts in microbial composition and metabolic function.[28,29] This dysbiosis, characterized by a significant reduction in beneficial commensal bacteria that produce short chain fatty acid (SCFA), particularly butyrate producers. Such a reduction compromises gut barrier integrity and disrupts the host-microbiota symbiosis, decreases SCFA production, impairs epithelial tight junctions, increases intestinal permeability, and subsequently facilitates the translocation of MPs, microbial antigens and pro-inflammatory metabolites into systemic circulation, which in turn elicits triggering persistent low-grade inflammation.

Altered microbial metabolites, impaired epithelial barrier function, and reduced SCFA signaling modulate vagal afferent activity and neuroendocrine pathways, thereby weakening gut-to-brain regulatory mechanisms. Empirical studies demonstrate these disruptive effects across diverse species. In C57BL/6 mice, exposure to PS-MPs induced significant alterations in gut microbiota composition, microbial diversity, and metabolite profiles related to cholesterol, bile acids, and SCFAs.[30,31]

In an *in-vitro* infant gut model, exposure to MPs increased the abundance of potential pathobionts, such as *Dethiosulfovibrionaceae* and *Enterobacteriaceae*, while reducing butyrate synthesis.[32] Epidemiological investigations on coastal and highland populations in Indonesian correlations between MPs contamination and alterations in specific taxa, including *Roseburia*, *Clostridium*, and *Prevotella*, as well as the enrichment of genes encoding plastic-degrading enzymes.[33] Disruptive effects have been observed in invertebrates by MPs for microbial communities in invertebrates, including *Chironomus sancticaroli* and *Bombyx mori*, affecting gut diversity, metabolic pathways, and host development.[34-36]

Microbiota-dependent MPs induced inflammatory responses

MPs promote both intestinal and systemic inflammation primarily by disrupting the homeostatic functions of the gut microbiota.[37,38] This dysbiosis marked by a reduction in beneficial commensals and an overgrowth of opportunistic pathobionts fundamentally alters the gut's metabolic and immunological balance. Functionally, the perturbed microbial community exhibits a loss of protective metabolic outputs and an increase in pro-inflammatory signaling, which collectively compromise the integrity of the intestinal barrier. The resulting increase in gut permeability facilitates the translocation of live bacteria and their immunogenic products, such as lipopolysaccharide (LPS), into systemic circulation. These microbiota-derived factors are recognized by host immune receptors, including Toll-like receptors (TLRs), triggering the activation of inflammasome pathways and the enhanced secretion of pro-inflammatory cytokines such as IL-1β and TNF-α.[39] Thus, the gut microbiota acts not merely as a passive target of MP exposure but as a central

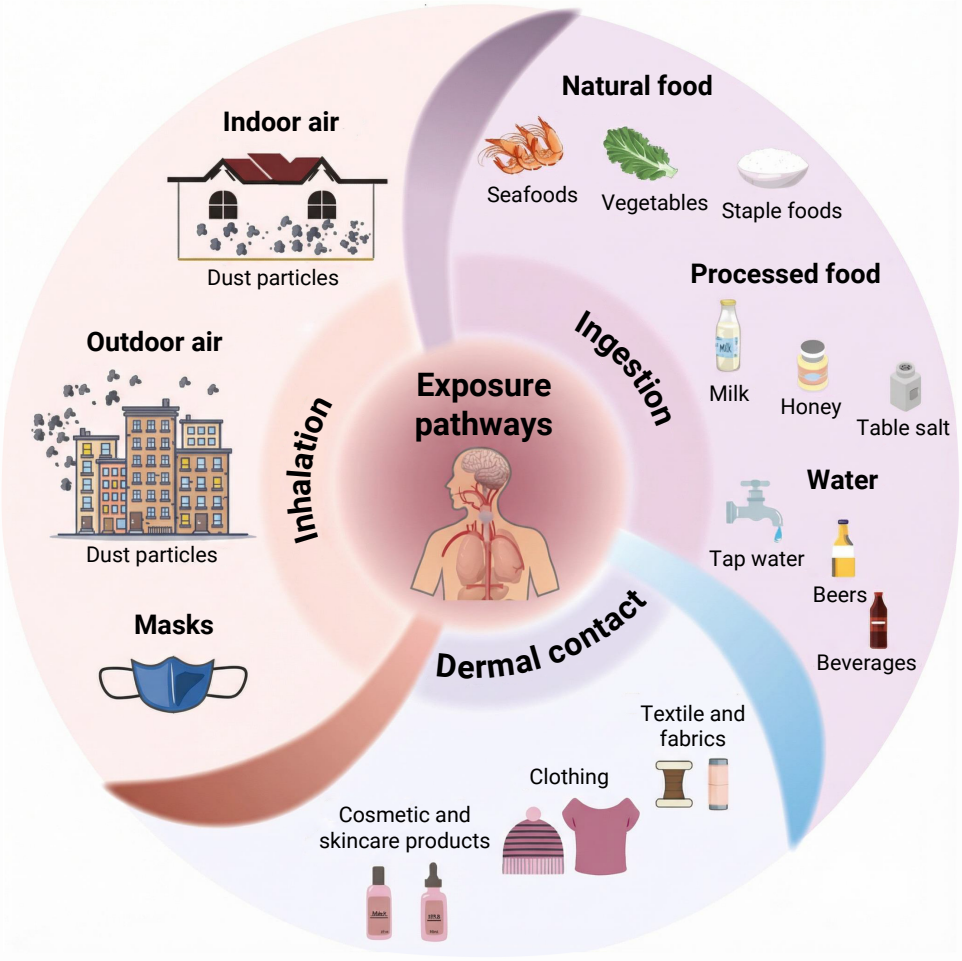

Figure 2. Exposure pathways of MPs (© 2024 Elsevier B.V. All rights reserved).

mediator driving sustained local and systemic inflammation.

In mice, chronic PS-MP ingestion elevates oxidative stress markers-malondialdehyde (MDA, protein carbonyls, myeloperoxidase) and reduces glutathione and superoxide dismutase, correlating with mucosal erosion and decreased tight junction protein expression.[40] Larger size of PS-MPs (5 μm) induce greater barrier dysfunction than that of the smaller ones (0.2-1 μm), mediated via ROS-dependent NF-κB/NLRP3/MLCK pathway activation.[41] NF-κB drives pro-inflammatory cytokine production (IL-6 and TNF-α), while NLRP3 activation increases IL-1β, promoting neutrophil infiltration and chronic inflammation. MLCK activation compromises epithelial integrity by contracting the cytoskeleton and increasing paracellular permeability. MPs also directly trigger TLR4/MyD88 signaling in immune cells, activating MAPK and NF-κB pathways that enhance cytokine production. ROS-induced release of DAMPs from injured epithelial cells further stimulates TLRs and purinergic receptors, creating a self-perpetuating inflammatory cycle. As illustrated in Figure 3.[42] In *Eriocheir sinensis*, MPs restrict immunological function in the hepatopancreas and hemolymph by suppressing antioxidant enzymes and phagocytosis, illustrating conserved inflammatory pathways across species.[43]

Metabolite changes and neural signaling

MPs indirectly disrupt neural signaling pathways via gut microbiota-mediated metabolic dysregulation. MPs alter gut microbial composition and function, which in turn modulates the production of microbiota-derived neurotransmitters and neuroactive metabolites critical for GBA communication. Gut bacteria synthesize key neurotransmitters such as serotonin (90% of total body), gamma-aminobutyric acid (GABA), and dopamine, which are essential for neuronal excitability and synaptic plasticity.[44] MPs exposure reduces microbial diversity and depletes bacteria involved in neurotransmitter and metabolite production, potentially leading to systemic alterations that indirectly influence neural function.[45]

Microbiota-dependent metabolic disruptions compromise synaptic function and neuronal integrity. In murine models, MPs reduce synaptogenesis proteins (PSD-95, synaptophysin) and synaptic density, alongside declines in SCFAs that regulate neuroinflammation and BBB permeability.[46] Dysbiosis also disrupts cholinergic signaling, as microbial conversion of dietary choline to trimethylamine interferes with acetylcholine synthesis.[47] In *C. elegans*, MPs exposure alters dopamine, glutamate, serotonin, and GABA neurotransmission,[48] while in mammals, serotonin depletion and glutamate/GABA imbalance contribute to anxiety-like and cognitive deficits. These findings underscore gut microbiota-derived metabolites as central mediators of MP neurotoxicity.

Across rodent and fish models, MP-induced gut dysbiosis represents a central amplifier of systemic and neural toxicity. Regardless of polymer type or exposure model, MPs consistently diminish commensal taxa, reduce SCFA and neurotransmitter production, and activate chronic inflammatory and oxidative pathways.[49] The convergence of findings across divergent taxa suggests a conserved host-microbe interaction pathway potentially susceptible to MPs interference. It disrupts GBA communication, linking microbial imbalance with impaired neurotransmission and neuroinflammation. However, the dose-response relationship and particle size-dependency remain to be elucidated. It can be concluded that this pattern situates the gut microbiota not only as a target of MP exposure but also as an active mediator that transforms local intestinal stress into widespread neurological consequences. These studies also reveal a recurring signature of MP-induced dysbiosis characterized by reduced SCFA-producing taxa and expansion of pathobionts, a microbial imbalance that propagates systemic inflammation and primes the GBA for dysfunction.

NEUROTRANSMISSION ALTERATIONS AND NEUROLOGICAL DISORDERS

Alterations in neurotransmission and neurological diseases linked to exposure to MPs have emerged as a significant worry due to their potential effects on the nervous system.[50] MPs can disrupt several neurotransmitter systems, such as cholinergic, dopaminergic, and GABAergic pathways, resulting in diverse neurological and behavioral deficits. Here, we've discussed the changes in neurotransmitter levels, MPs-induced neurodegeneration, the potential links to neurodevelopmental and neurodegenerative disorders, and the relationship between MPs and neuroinflammation.

Changes in neurotransmitter levels

MPs impact behaviour, brain function, and neurotoxicity by upsetting the neurological equilibrium. They interfere with the synthesis, release, and metabolism of key neurotransmitters like dopamine, serotonin, glutamate, and GABA through oxidative stress, GBA dysregulation, and direct neuronal damage.[51] Smaller and aged MPs penetrate tissues more readily and release toxins, amplifying neurotoxic effects.

Studies in model organisms, including *C. elegans*, zebrafish, and mice, demonstrate that MPs impair neurotransmitter-related enzymes and signaling pathways, leading to behavioral and cognitive deficits.[52] MPs also compromise gut and brain barriers, allowing inflammatory signals to further disturb neurotransmitter equilibrium. Evidence from aquatic organisms suggests that MP exposure alters enzymatic and neurotransmitter activity,

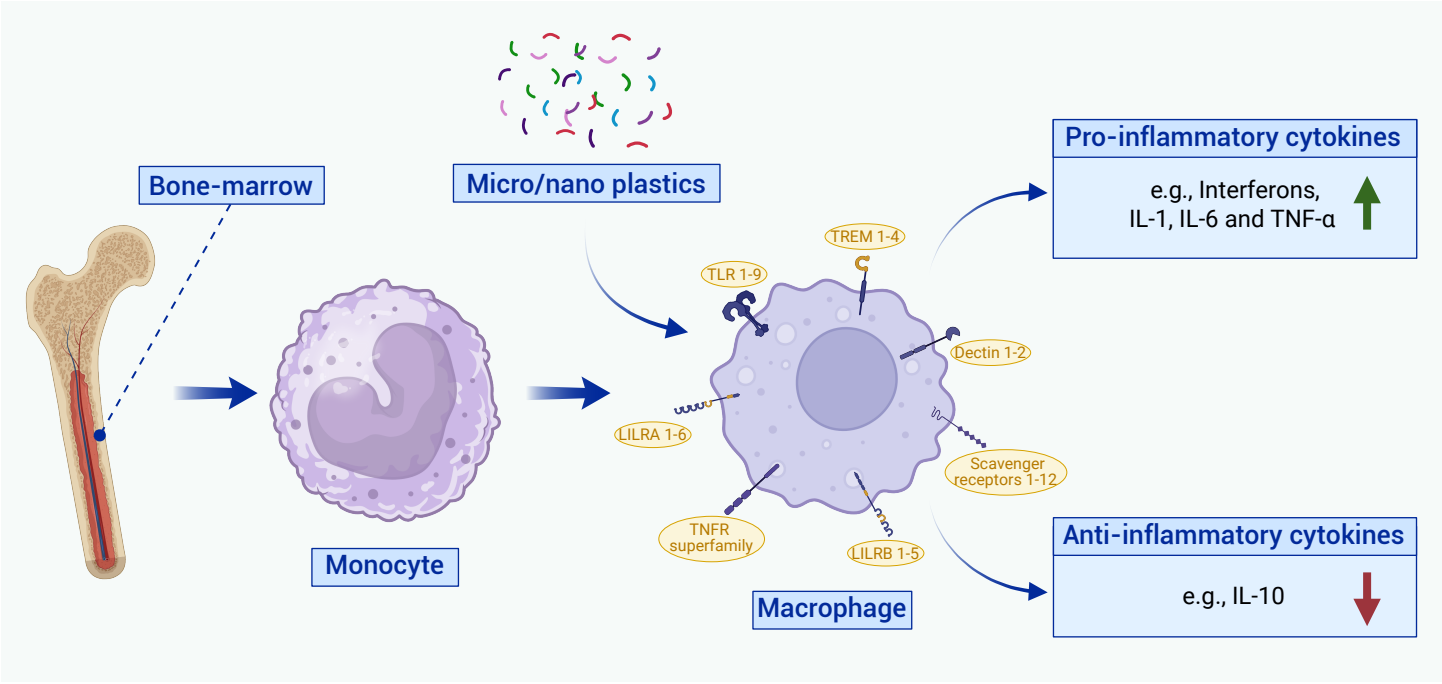

Figure 3. An innate response in producing and regulating both pro- and anti-inflammatory cytokines from bone-marrow-derived macrophages induced by MPs.[42]

though some effects may normalize after depuration.[53] Table 1 illustrates the neurotoxic effects of MPs and their possible mechanisms.

MPs-induced neurodegeneration

MPs impair mitochondrial function by targeting complex I (CI), triggering increased mitophagy via the AMPK/ULK1 pathway, and leading to dopaminergic neuron death. They also disrupt synaptic integrity and axonal structure, contributing to motor deficits. Chronic MP exposure reduces synaptogenesis-related proteins, such as synaptophysin and PSD-95, by up to 40%, resembling pathological features of cognitive decline.[63] Maternal MP exposure can induce axon degeneration in offspring, highlighting intergenerational risks.[64]

Notably, melatonin alleviates MP-induced mitochondrial dysfunction and motor deficits by regulating mitophagy, suggesting a protective strategy against MP-related neurodegeneration. A 28-day murine study revealed incomplete degradation of PLA polymer MPs in the GI tract, whereas PLA oligomer MPs were fully degraded.[65] Conversion of polymers into oligomers increased bioavailability and toxicity, while complete degradation of oligomers reduced toxicity. Both forms induced Parkinson's-like neurotoxicity via MICU3 upregulation and mitochondrial calcium overload, which was mitigated by MCU-i4-mediated calcium influx inhibition or DBcAMP-induced efflux.

Potential links to neurodevelopmental and neurodegenerative disorders

Based on experimental models, MPs link to neurodevelopmental and neurodegenerative disorders through several interconnected mechanisms, including mitochondrial dysfunction, oxidative stress, protein misfolding, and GBA dysregulation.[66] These pathways resemble molecular features observed in Alzheimer's disease (AD), Parkinson's disease (PD), and autism spectrum disorder (ASD), suggesting that MPs might contribute to chronic neurological impairments.[67] It reported that chronic MP exposure may alter neurotransmitter levels and related gene expression.[68] Maternal exposure has been associated with changes in offspring neurotransmitter balance, including glutamate and GABA, which could be linked to behavioral changes such as anxiety, depression, and cognitive impairments.[68] MPs have also been associated with ASD-like behaviors, such as repetitive actions and reduced social interaction, highlighting potential risks to neurodevelopment.[69] Experimental evidence in model systems suggests MPs may impair motor neuron axonal growth, reduce synaptic density, and induce axonal degeneration, which could accelerate neurodegenerative processes.[70] Chronic PS-MPs exposure could inhibit mitochondrial complex I, activate AMPK/ULK1-mediated mitophagy, and induce dopaminergic neuron loss in models, resembling PD-related pathology.[62] Similarly, PE and PP-MPs (5-20 μm) have been observed to colocalize with amyloid-β plaques in the prefrontal cortex and hippocampus, which may suggest a potential role in aggregation processes.[71]

This highlights a fundamental conflict in the literature between correlative observations and mechanistic causation. Furthermore, a significant methodological divergence underpins many conflicting results: the widespread use of pristine, monodisperse MPs in laboratory settings versus the complex, weathered particles found in the environment. Studies employing the former may not accurately recapitulate the bioactivity and toxicity of the latter, which possess altered surface chemistry and often carry adsorbed microbial biofilms and co-pollutants. MPs may reduce synaptogenesis-associated proteins, such as synaptophysin and PSD-95, by up to 40%, correlating with cognitive deficits in experimental model.[72] Exposure of them has also been linked to elevated oxidative stress markers like MDA and reduced antioxidants like glutathione, which could promote neuroinflammation (Figure 4). Human autopsies have detected PP fibers in olfactory bulbs, indicating possible nasal-to-brain translocation.

In neurodevelopmental disorders such as ASD, MPs may influence neurotransmitter balance and GBA function. Maternal exposure to PS-MPs during pregnancy and lactation could impair social behavior in mouse offspring, indicating potential neurotoxic effects.[73] MPs appear to alter gut microbiota, decreasing beneficial bacteria and SCFA production, which might exacerbate inflammation and weaken the BBB, pointing to possible long-term neurological risks.

MPs and neuroinflammation

MPs can lead to neuroinflammation by compromising the BBB and stimulating microglial cells, especially the size under 100 nm.[74] MPs-induced oxidative stress generates ROS, which not only damages cellular structures but also disrupts neurotransmitter metabolism. This disruption is exacerbated by GBA dysregulation, where MPs alter gut microbiota composition, reducing beneficial bacteria and SCFAs. The resultant systemic inflammation interacts with the brain via the vagus nerve, amplifying neuroinflammatory responses and contributing to behavioral abnormalities.[75]

MPs detected in atheroma suggest their potential to promote vascular inflammation and systemic circulation of inflammatory mediators, which can exacerbate neuroinflammation.[76] These particles can cross the BBB, inducing oxidative stress and pro-inflammatory cytokine release, including IL-1β, IL-6, and TNF-α, contributing to chronic neuroinflammation.[77] MPs also indi-

Table 1. Neurotoxic effects of MPs and the mechanism.

Organism		Characteristics of MPs/NPs			Exposure test			Neurotoxic effect and possible mechanism	Reference
Model	Taxonomic specie/cell line	Type	Size	Characteristic	Method of administration	Concentration	Exposure duration		
Nematode	*C. elegans*	PS	50 nm	Plastic sphere	Exposure in medium	1, 10, 100, 1000 μg/L	72 h	Induced oxidative stress, locomotion disorders, apoptosis, decrease in DA content	54
Nematode	*C. elegans*	PS	1 μm	Carboxyl-modified sphere	Exposure in medium	0.1, 1, 10, 100 μg/L	24 h	Altered neurotransmission genes, neuronal damage, changes in glutamate, 5-HT, DA, and GABA levels	55
Blood clam	*Donax trunculus*	PS	490 ± 11 nm	Plastic sphere	Direct exposure to suspensions	5 mg/L	14 d	Immune response and phagocytosis suppression to induce neurotransmitter issues	56
Wedge clam	*Scrobicularia plana*	PE / PP	100-400 μm	Irregular shapes	Mixing plastic particles in sand	60 mg/kg	3 h, 1, 2, 3, 4, 7, 10, and 15 d	Induced AChE inhibition and oxidative stress	57
Zebrafish embryos	*Danio rerio*	PS	100 nm	Plastic sphere	Direct exposure in suspensions	1, 10, and 100 μg/L	2 to 12 hpf	Upregulated antioxidant genes, retinal development inhibition, locomotor activity reduction	58
Zebrafish larvae	*Danio rerio*	PS	100-400 μm	Plastic sphere	Direct exposure in suspensions	1 mg/L	5 d	Enhanced hypoactivity, induced oxidative stress, body length reduction, and AChE inhibition	59
Zebrafish adult	*Danio rerio*	PE	40-47 μm	Plastic sphere	Waterborne and foodborne	0.1, 1, and 10 mg/L	7 d + 48 h	Hyperactivity via both pathways, cholinergic system alteration, significant DA and 5-HT changes	60
Mouse	C57BL/6 J	PS	50 nm	Plastic sphere	Oral gavage	0.5, 2.5, 10, and 50 mg/kg bw	7 d	Microglia activation, neuronal damage, BBB integrity loss, oxidative stress, and inflammatory response	61
Mouse	Hippocampal neuronal cell (HT22)	PS	100 nm, 1 μm	Plastic sphere	In culture medium	5, 25, and 75 μg/mL	24 h	Excess ROS, S-phase cell cycle arrest, particularly with smaller-sized PS particles	62
Human	Microglial cell (HMC-3)	PS	200 nm, 2 μm, 10 μm	Plastic sphere	In culture medium	1, 5, 10 μg/mL	24 and 48 h	Induced immune responses, microglial apoptosis, altered immune gene expression, and microRNA changes	62

Note: *Abbr:* 5-HT: 5-Hydroxytryptamine (Serotonin), AChE: Acetylcholinesterase, BBB: Blood-brain barrier, bw: Body weight, DA: Dopamine, GABA: Gamma-aminobutyricacid, hpf: Hours post-fertilization, PE: Polyethylene, PP: Polypropylene, PS: Polystyrene, ROS: Reactive oxygen species

rectly influence neuroinflammation via the GBA, as ingestion alters gut microbiota composition, causing dysbiosis and systemic inflammation that communicates with the brain through the vagus nerve, amplifying neuroinflammatory responses. Endocrine-disrupting chemicals within MPs, such as bisphenol A (BPA) and phthalates, further exacerbate neuroinflammation by disrupting hormonal balance.[78] Prolonged exposure may lead to chronic neuroinflammation, neurotransmitter dysregulation, mitochondrial dysfunction, and neurodegenerative disorders.[79]

Histological studies in animal models show that high-dose MPs cause GI and brain alterations. In pigs, MPs induced villi damage, cellular debris accumulation, eosinophil infiltration, and hyperemia, indicating GI inflammation that may trigger neuroinflammation via the GBA.[80] Altered nNOS-, substance P-, and galanin-positive neurons, along with reduced cocaine- and amphetamine-regulated transcript and vesicular acetylcholine transporter expression, reflect disrupted neurotransmitter regulation and neuroplasticity.[81] These findings highlight MPs' systemic and neurotoxic effects through oxidative stress, immune dysregulation, hormonal imbalance, and neurochemical disturbances, linking gut and brain dysfunction.

MECHANISMS OF MPS-INDUCED GBA DISRUPTION

Despite MPs interaction with biological systems have been reported, most of the mechanisms of MPs-induced GBA disruption remain largely unaddressed. Impact of MPs' exposure on the GBA is depicted in Figure 5.

MPs disrupt this axis through structural degradation and interference with critical signaling pathways,[83] ultimately compromising neural, metabolic, and immunological homeostasis. MPs induce GBA disruption by compromising structural integrity at multiple levels. In the gut, MPs utilize paracellular routes or transcytosis to traverse intestinal epithelia, reducing transepithelial electrical resistance (TEER) by as much as 20% in animal studies.[84] The "leaky gut" enables the systemic spread of MPs, lipopolysaccharides, and co-adsorbed toxins, which together undermine the enteric nervous system (ENS) and promote neuroinflammation.

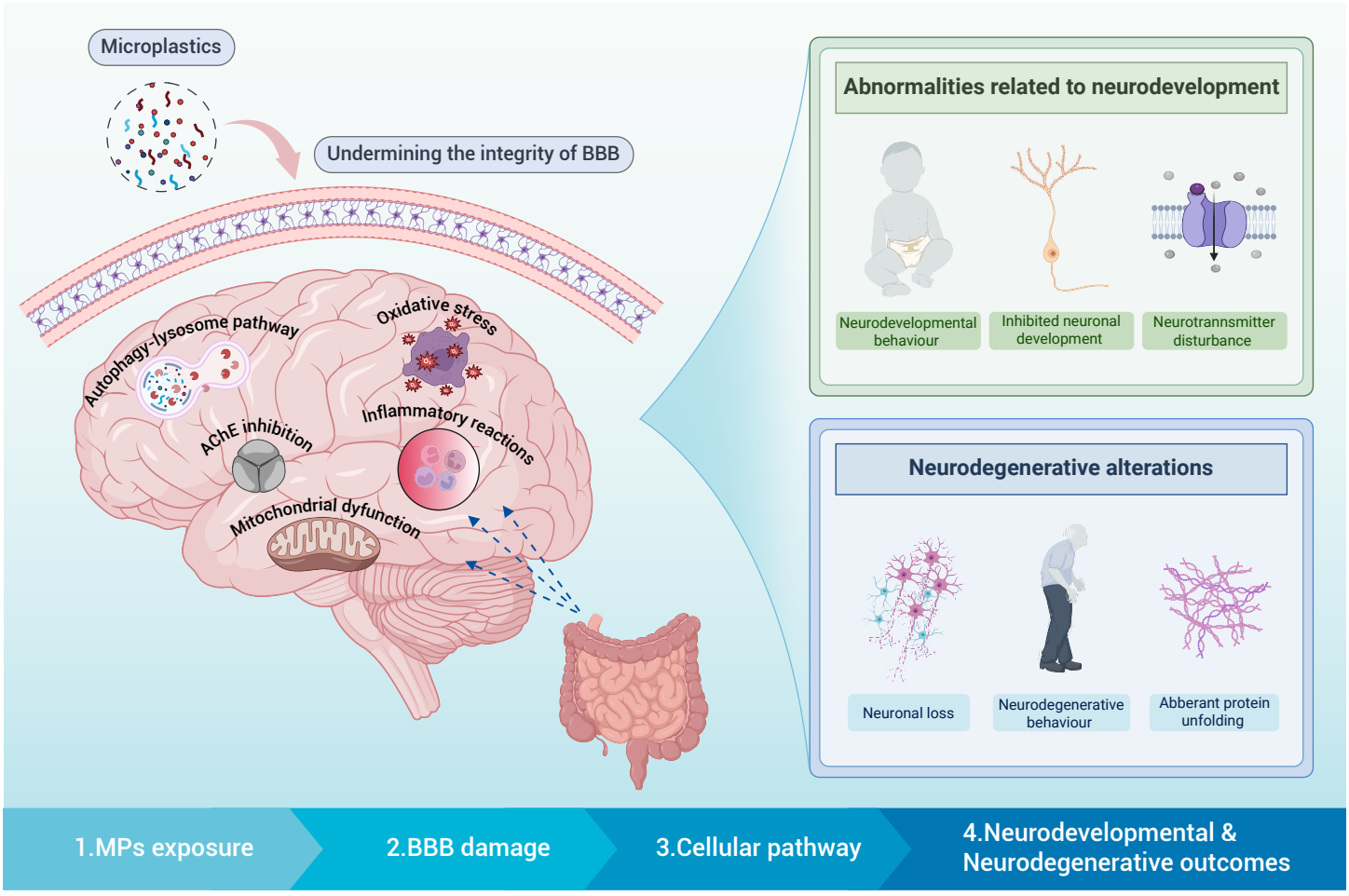

Figure 4. Risks of neurological diseases induced by MPs and possible mechanisms (This figure was created by BioRender.com).

MPs compromise BBB integrity by inducing oxidative stress and degrading tight junction proteins such as ZO-1 and occludin, allowing particle accumulation in brain regions, including the cerebellum and hippocampus.[85]

MPs disrupt GBA communication via molecular mimicry and receptor interactions, acting as PAMP mimetics that activate macrophage NLRP3 inflammasomes and systemic pro-inflammatory cytokine release (IL-6, TNF-α and CCL2).[86] These cytokines recruit monocytes to the brain, inducing astrogliosis and T-cell infiltration, while vagal neurons relay inflammatory signals to the nucleus tractus solitarius. MP-bound additives like bisphenol A and phthalates disrupt thyroid hormone conversion and satiety peptides, such as Glucagon-Like Peptide-1(GLP-1) and Peptide YY (PYY), altering hypothalamic circuits. Serotonergic and dopaminergic pathways are impaired through tryptophan metabolite depletion and mitochondrial dysfunction, evidenced by reduced hippocampal BDNF and motor deficits in zebrafish.[87] Physicochemical properties govern biodistribution and toxicity: NPs (<100 nm) show 5.3-fold higher intestinal translocation than larger particles (>500 nm), hydrophobic polymers absorb lipophilic toxins (PCBs and PAHs), positively charged MPs cause 3.5-fold greater intestinal cytotoxicity, and anionic particles bind mucin, prolonging gut retention.[88]

Transport mechanism of MPs to the brain

The ability of MPs to penetrate biological barriers including the BBB, underscores their neurotoxic potential.[89] The BBB is a protective barrier formed by endothelial cells that are closely interconnected by junctions.[90] Its primary role is to safeguard brain tissue from potentially deleterious chemicals present in the blood plasma.[91] However, growing evidences from *in-vivo* studies demonstrates that MPs, particularly nanometer-sized particles, can traverse the BBB and subsequently infiltrate the brain.[92] Rodent models have confirmed MPs' penetration across the BBB, raising concerns about their accumulation in neural tissues.[93]

An *in-vivo* assay detected the accumulation signals of MPs in mouse brain tissues as early as 2 h post-gavage treatment, indicating the rapidity of this transfer process.[94] The precise mechanisms by which MPs traverse the BBB remain incompletely understood, but numerous studies indicate that MPs may compromise the tight junction architecture essential for BBB integrity, enhancing permeability and facilitating the translocation of particulate pollution into the brain.[95] Molecular dynamics simulations highlight the role of the biomolecular corona in this process, with cholesterol-enriched coronas enhancing MPs' translocation across the BBB.[96] Inhaled MPs can bypass circulation, reach the brain via olfactory and trigeminal pathways, and preferentially accumulate in neural tissues compared to systemic administration.[97] Beyond translocation, persistent MPs may drive delayed neurodegeneration through lysosomal dysfunction and mitochondrial stress. Standardized models incorporating mixed and weathered polymers are essential, particularly in vulnerable populations with impaired BBB integrity, such as the elderly or those with neuroinflammation. The literature presents conflicting evidence regarding the efficiency of MP translocation to the brain, largely stemming from methodological variations. Disparities in the size, surface charge, and polymer composition of MPs used across studies lead to vastly different biodistribution outcomes. For instance, the formation of a biomolecular corona, rarely accounted for in lab studies, can significantly alter translocation potential. The lack of standardized, sensitive protocols for detecting MPs in neural tissue further exacerbates this conflict, making cross-study comparisons and a definitive conclusion on neuroinvasive potential challenging

Translocation dynamics and biomarkers of MPs neurotoxicity

The ability of MPs to penetrate biological barriers, including the BBB, underscores their neurotoxic potential.[98,99] Emerging evidences from *in-vivo* studies demonstrates that MPs can translocate to the brain via systemic

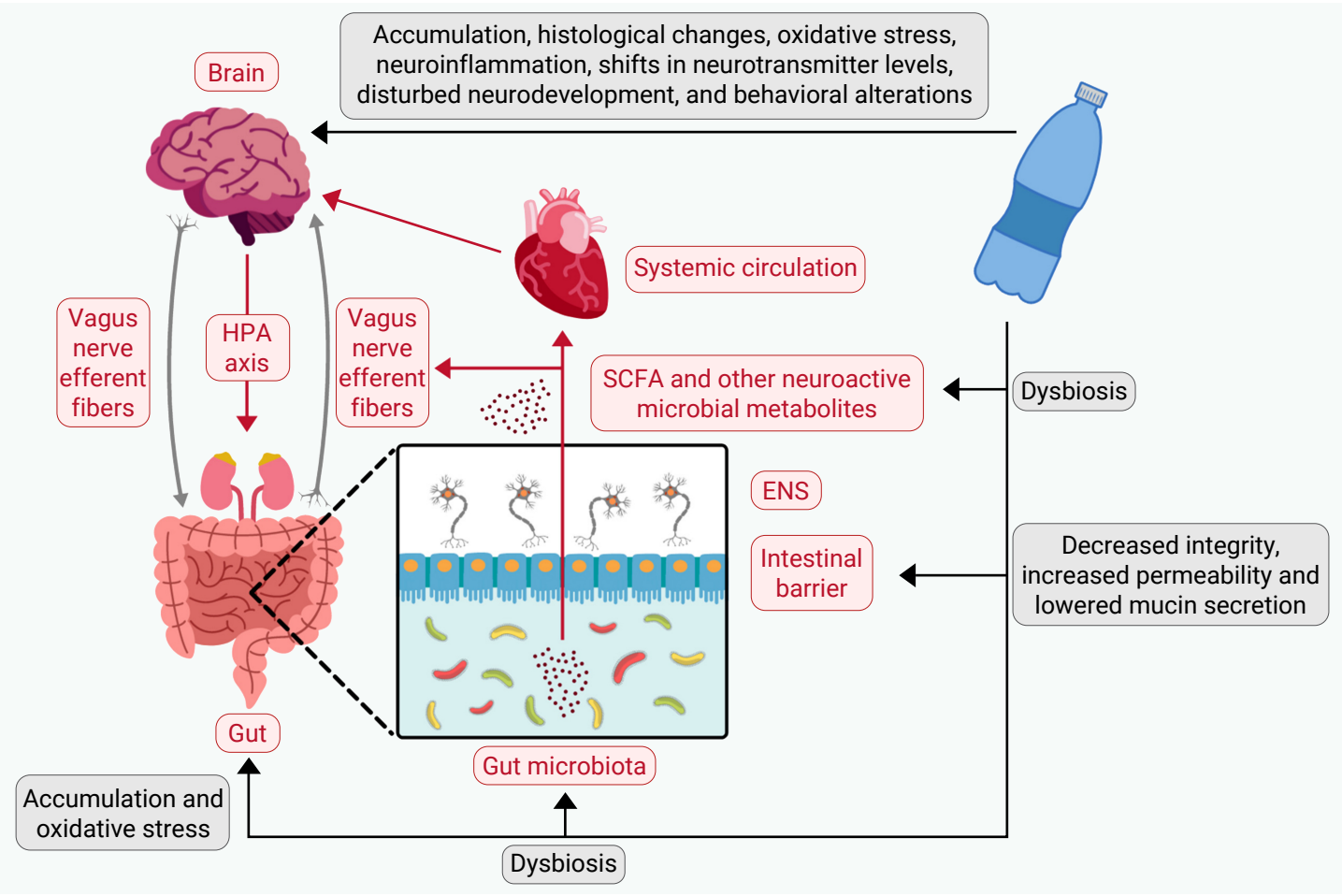

Figure 5. Impact of MPs exposure on the GBA (© 2021 MDPI under CC BY 4.0).[82]

circulation or direct neural pathways, such as the olfactory nerve.[100] Inhaled MPs bypass pulmonary clearance and rapidly accumulate in the olfactory bulb and cerebral cortex, suggesting a unique neuroinvasive route.[101] Computational models further reveal that NPs coated with biomolecular corona exhibit enhanced BBB permeability, enabling neuronal infiltration. Emerging autopsy studies reveal MPs' presence in human brain tissues, particularly in regions vulnerable to neurodegeneration.[102] PET particles (5-20 μm) were detected in the prefrontal cortex and hippocampus of AD patients, colocalizing with amyloid-β plaques.[77]

Beyond translocation, persistent MPs may induce delayed neurodegeneration through lysosomal dysfunction and mitochondrial stress.[103] Standardized experimental models incorporating mixed and weathered polymers are essential to better evaluate these phenomena, particularly in vulnerable populations with impaired BBB integrity such as the elderly or those experiencing neuroinflammation.[104]

Critical to understanding MPs' neurotoxicity are potential biomarkers that reflect cellular and systemic damage. Oxidative stress markers such as ROS and MDA are elevated in MPs-exposed models, correlating with mitochondrial dysfunction and lipid peroxidation.[105] Pro-inflammatory cytokines like IL-6, TNF-α, and IL-1β serve as indicators of neuroinflammation, often preceding behavioral deficits in rodents. Additionally, neuronal-specific biomarkers including tau hyperphosphorylation and α-synuclein aggregation mirror pathological hallmarks of AD and PD.[106] Gut-derived metabolites, such as reduced SCFAs and dysregulated serotonin, further highlight the GBA's role in propagating toxicity.[107] Integrating these biomarkers into clinical and epidemiological studies could enhance early detection of MPs-related neurological risks. However, the current validation of these biomarkers is almost exclusively from animal models. Their predictive value and the causality of the associated pathways in humans remain to be established through rigorous longitudinal studies.[108]

Gut permeability and systemic absorption

The GI tract is a crucial region for the uptake of MPs, and it exhibited size-dependent translocation efficacy.[109] Mechanistic investigations demonstrate that MPs (50-100 nm) diminish TEER by 40-60% in mouse intestinal models, directly compromising tight junction proteins via ROS-induced NF-κB activation. The compromised integrity of the epithelium enables systemic translocation of MPs.[110] A recent study showed that orally administered PS particles of 50, 100, and 500 nm exhibit size-dependent biodistribution in BALB/c mice, with the smaller particles (50 and 100 nm) demonstrating broader systemic dissemination and detectable accumulation in the liver, spleen, and kidneys as quantified by fluorescence microscopy and microplate analysis; however, the study does not provide quantitative percentages of systemic translocation or precise μg/g tissue concentrations.[111]

Upon absorption, MPs interact with TLR4 on macrophages within GALT, thereby activating the NLRP3 inflammasome and increasing the levels of pro-inflammatory cytokines, including TNF-α (350 ± 50 pg/mL) and IL-6 (200 ± 30 pg/mL) in mouse serum.[112] Chronic MP exposure in zebrafish models reduces *Faecalibacterium prausnitzii*, a key SCFA-producing bacterium, by 70%, while increasing pathogenic *Enterobacteriaceae* 3-fold, correlating with a 50% reduction in fecal butyrate levels.[113] This dysbiosis disrupts GBA signaling, decreasing hippocampal BDNF expression by 30% and inducing anxiety-like behaviors in open-field tests.

Signaling pathways involved in MPs-induced GBA disruption

MPs elicit neurotoxicity through interconnected molecular pathways that disrupt cellular homeostasis, drive neuroinflammation, and impair neuronal function. Central to these effects is oxidative stress, where MPs generate ROS, overwhelming endogenous antioxidant defenses such as glutathione and superoxide dismutase. Studies have demonstrated that PS-MPs with varying surface charges accumulate in systemic organs, including the brain,

Table 2. Signaling pathways in MPs-induced neurotoxicity.

Signaling pathway	Mechanism of disruption	Biological impact	Associated pathological outcomes	References
SCFA/GBA	Reducing SCFA-producing microbiota (e.g., *Lactobacillus*) and impairing butyrate synthesis.	Gut barrier dysfunction, systemic inflammation and reduced neuroprotective metabolites.	Neuroinflammation, AD, PD and autism-like behaviors.	116
NF-κB/NLRP3	Triggering ROS-dependent NF-κB/NLRP3 activation and increasing MLCK expression.	Tight junction protein degradation (occludin, ZO-1) and intestinal/BBB hyperpermeability.	Colonic inflammation, neuroinflammatory cascades and synaptic dysfunction.	117
AMPK/ULK1	ROS overproduction, mitochondrial membrane depolarization	Mitochondrial swelling, ATP depletion, neuron apoptosis	Neurotoxicity, locomotor deficits	118
MICU3-Mediated Ca^{2+} Dyshomeostasis	Upregulating MICU3, leading to neuronal mitochondrial Ca^{2+} influx	Calcium overload, mitochondrial swelling and ATP depletion.	PD-like neurotoxicity and neuronal death.	119
VNIA	Altering gut microbiota diversity and disrupting vagal afferent signaling.	Reduced OT in prefrontal cortex and impaired social behavior.	Anxiety, depression and cognitive deficits.	120
AChE/ChAT	Inhibiting acetylcholinesterase and choline acetyltransferase activity.	Altered acetylcholine metabolism and synaptic transmission failure.	Memory impairment and locomotor deficits	121
DA/5-HT	Adsorbing heavy metals and inducing oxidative damage to dopaminergic/serotonergic neurons.	Reduced dopamine, serotonin, and GABA levels; glutamate excitotoxicity.	Motor dysfunction, ASD-like phenotypes, and anxiety.	122

Note: *Abbr:* ASD: Autism spectrum disorder, ATP: Adenosine triphosphate, BBB: Blood-brain barrier, EDCs: Endocrine-disrupting chemicals, MICU3: Mitochondrial calcium uptake family member 3, MLCK: Myosin light-chain kinase, OT: Oxytocin, PLA: Polylactic acid, ROS: Reactive oxygen species, SCFA: Short-chain fatty acids

inducing ROS generation, with charge-dependent bioavailability exacerbating oxidative damage.[114] Further research has linked PS-MPs to gut microbiota dysbiosis and systemic oxidative stress, revealing how intestinal ROS overproduction propagates neuroinflammation via the GBA. Additional findings show that PE-MPs synergize with co-pollutants like TBBPA to amplify oxidative stress, impairing mitochondrial function and glutathione homeostasis.[115] This oxidative imbalance damages lipids, proteins, and DNA, while mitochondrial dysfunction exacerbates cellular vulnerability. Polylactic acid (PLA) oligomers upregulate mitochondrial calcium uptake protein MICU3, inducing calcium overload and neuronal apoptosis via AMPK/ULK1-mediated mitophagy. Table 2 provides an overview of the major signaling pathways implicated in MPs-induced neurotoxicity, highlighting their mechanisms, biological impacts, and associated neurological disorders.

MPs activate neuroinflammatory cascades by stimulating TLRs and NLRP3 inflammasomes in microglia and astrocytes, leading to NF-κB-mediated release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. PS-MPs disrupt intestinal tight junctions and systemic immune responses through NF-κB-dependent cytokine release.[123] The ROS-dependent NF-κB/NLRP3/MLCK pathway is central to MP-induced colonic and neuronal inflammation, linking gut barrier dysfunction to CNS pathology.[124] MPs also activate microglial TLR4 signaling, driving IL-1β and TNF-α release, which compromises BBB integrity and permits peripheral immune cell infiltration.[125] Apoptotic signaling further contributes to neurodegeneration, with MPs triggering intrinsic mitochondrial pathways and extrinsic death receptor pathways; positively charged PS-MPs induce caspase-3 activation and mitochondrial depolarization.[126] Dopaminergic neurons are particularly vulnerable, as MPs impair mitochondrial CI activity, reduce ATP, and promote parkinsonian-like pathology. Maternal exposure studies show prenatal PS-MP exposure alters offspring dopamine and glutamate levels, resulting in autism-like behavior.[127]

Disruption of neurotransmitter systems exacerbates MP-induced neurotoxicity. PS-MPs alter dopamine, serotonin, and acetylcholine levels, impairing locomotion and synaptic plasticity, while glutamate-GABA imbalance predisposes offspring to neurodevelopmental disorders.[128] The GBA mediates these effects, with PE-MPs inducing dysbiosis and reducing butyrate production, impairing intestinal barrier function and neuroprotective SCFA signaling. SCFA depletion further increases BBB permeability and microglial activation in MP-exposed models.[129] MPs also disrupt vagal oxytocin signaling, linking gut-derived inflammation to social behavior deficits, and rising PE-MP accumulation in human brains underscores translational relevance.[130]

Emerging evidence highlights epigenetic perturbations and autophagy dysregulation. PLA oligomers induce DNA methylation changes in neurodevelopmental genes, while co-exposure with environmental toxins inhibits AQP4 and promotes demyelination. MP-induced autophagy dysfunction accelerates toxic protein aggregation, including α-synuclein accumulation, mirroring AD/PD's pathologies.[131]

Systemic disintegration of gut-brain network communication

The GBA is a complex communication network that connects the gut and the brain through neural, hormonal, immune, and chemical signaling (Figure 6). This system helps maintain the body's overall balance.[132,133] However, exposure to MPs can severely disrupt this network, causing different types of cellular damage that combine into a continuous cycle of dysfunction.[134] This breakdown in a two-way communication between the gut and brain plays a key role in linking MP exposure to various brain and metabolic disorders.

In the gut-to-brain direction (afferent pathway), MPs trigger harmful signals. When MPs damage the intestinal barrier, they allow particles, bacterial toxins such as LPS, and inflammatory molecules to enter the bloodstream. These substances can reach the brain directly or through the vagus nerve, causing inflammation, activating microglial cells, and weakening the BBB. Once this barrier becomes leaky, more immune cells and inflammatory factors can enter the brain, maintaining a chronic state of inflammation between the body and the CNS.[135-140]

In the brain-to-gut direction (efferent pathway), regulatory control also breaks down. MPs exposure disturbs the gut microbiota, reducing beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* that produce SCFAs like butyrate. SCFAs are essential for maintaining a healthy gut barrier and protecting the brain. Their reduction weakens both systems, worsening the flow of harmful signals from gut to brain.[141-143] MPs also interfere directly with brain hormonal pathways, lowering oxytocin levels in the medial prefrontal cortex and disturbing vagal control of gut hormones such as GLP-1 and PYY.[144-150] These disruptions are linked to behavioral changes, reduced social interaction, and altered metabolism. Experiments have shown that blocking the vagus nerve worsens these effects, confirming its key role in MP-induced toxicity.[151-153] The main components of the GBA affected by MPs and their related outcomes are summarized in Table 3. This ongoing cycle of dysfunction forms the basis of MP toxicity: gut inflammation promotes brain inflammation and dysfunction which further disrupts gut regulation through stress

Table 3. Role of the GBA in MPs-mediated health effects.

GBA component	Mechanism of MPs action	Health outcomes	Key findings	Potential biomarkers	Therapeutic targets/Interventions	References
Gut microbiota	Inducing dysbiosis, altering microbial diversity, and disrupting key metabolites, including SCFAs and neurotransmitters	GI disorders such as IBS and metabolic diseases, and neurodevelopmental issues	Reduced SCFA-producing bacteria and promoting neuroinflammation	SCFAs, LPS and serotonin	Probiotics, prebiotic and dietary fiber	156
Enteric nervous system	Triggering oxidative stress, inflammation, and ENS neuronal damage	Gut motility disorders such as constipation and visceral hypersensitivity	impaired ENS signaling and gut-brain communication by PS-MPs	ROS, TNF-α and gut motility assays	Antioxidants such as NAC, anti-inflammatories	157
Vagus nerve	Activating vagal afferents through cytokine release or microbial metabolites.	Anxiety, depression and altered satiety signaling	Induce anxiety and systemic inflammation by blocking vagotomy	Pro-inflammatory cytokines (IL-6 and IL-1β)	Vagus nerve stimulation and bioactive diets	158
Immune system	Activating immune cells such as macrophages and promoting systemic inflammation	IBD and neuroinflammation	Increased colonic IL-6 and prime microglia for neuroinflammation	Cytokines (IL-6 and TNF-α), calprotectin	Immunomodulators and anti-IL-6 therapies	159
Central nervous system	Crossing the BBB and inducing neuroinflammation through cytokines or microbial metabolites	Neurodegeneration (AD) and cognitive decline	Induce microglial activation and Aβ aggregation by PS-NPs	GFAP, BDNF, and Aβ plaques	BBB protectants and microglia inhibitors	160

Note: Abbr: Aβ: amyloid-beta, AD: Alzheimer's disease, BBB: Blood-brain barrier, BDNF: Brain-derived neurotrophic factor, ENS: Enteric nervous system, GFAP: Glial fibrillary acidic protein, GBA: Gut-brain axis, GI: Gastrointestinal, IBD: Inflammatory bowel disease, IBS: Irritable bowel syndrome, IL-1β: Interleukin-1 beta, IL-6: Interleukin-6, LPS: Lipopolysaccharide, MPs: Microplastics, NAC: N-acetylcysteine, PD: Parkinson's disease, PS-NPs: Polystyrene nanoparticles, ROS: Reactive oxygen species, SCFAs: Short-chain fatty acids, TNF-α: Tumor necrosis factor-alpha

and vagal pathways. This feedback loop transforms local intestinal injury into a widespread systemic problem.[154] The discovery of PE-MPs in human brain tissue especially in regions prone to neurodegeneration provides concrete evidence of this lasting disruption and its potential role in neurological disease.[155] Therefore, the breakdown of GBA communication is not a secondary outcome but a central mechanism explaining how MPs cause system-wide toxicity.

CHALLENGE AND FUTURE PERSPECTIVES

The growing evidence correlating MPs' exposure to neurotoxicity through the GBA underscores significant public health ramifications; yet substantial obstacles hinder the conversion of preclinical discoveries into practical human health applications. Contemporary research confronts methodological discrepancies in the detection and quantification of MPs, especially submicron particles, within biological matrices, since the absence of established techniques for particle size, polymer composition, and contamination control diminishes cross-study comparability. The technical challenges are exacerbated by heterogeneous exposure dynamics, as MPs interact with various environmental variables such as dietary sources, seasonal particle distribution, and polymer degradation and co-pollutants like heavy metals and pesticides, obscuring causal relationships between exposure and neuropathology. Moreover, there are ongoing epidemiological knowledge gaps, with few human investigations investigating the relationship between MPs' bioaccumulation in vital tissues (blood, placenta, brain) and neurodegenerative illnesses such as AD and PD.

Innovative technologies and regulatory frameworks present viable solutions to these issues. State-of-the-art analytical technologies are improving accuracy in monitoring MPs and their biological interactions, while sophisticated biomimetic models clarify the molecular routes of neurotoxicity. Simultaneously, international regulatory efforts are promoting source reduction and sustainable material innovation to mitigate MP pollution at its source.

Challenges in human health risk assessment

The accurate assessment of human health risks arising from MPs exposure remains a formidable scientific challenge. Despite extensive preclinical evidence demonstrating MP-induced neurotoxicity, translating these findings to human contexts is limited by the absence of standardized methodologies, inconsistencies in exposure quantification, and a lack of mechanistic and longitudinal human studies. Moreover, the complex and heterogeneous nature of real-world MP exposure characterized by diverse particle sizes, polymer compositions, and co-contaminants further obscures causal inference.

Barriers in human risk assessment. The translation of compelling preclinical evidence on MP-induced neurotoxicity into a clear understanding of human health risks faces significant and interconnected barriers. One of the primary challenges lies in the stark scarcity of causal human studies. Although rodent models robustly demonstrate MP-induced gut dysbiosis, systemic inflammation, and hippocampal neuroinflammation, human evidence remains limited and largely correlative. The absence of longitudinal epidemiological studies tracking temporal relationships between MP bioaccumulation and neurological outcomes represents a fundamental knowledge gap, leaving the real-world implications of exposure uncertain. This gap underscores the need to carefully investigate the discrepancies observed between preclinical and human studies, particularly with regard to the variations in study designs, sample populations, and exposure levels. Conflicting findings could arise from several methodological differences, including variations in exposure routes, dosing regimens, and assessment techniques. Discrepancies in the type and concentration of MPs used in animal models, as well as differences in study duration, may contribute to inconsistent results in terms of observed neuroinflammation or behavioral outcomes.

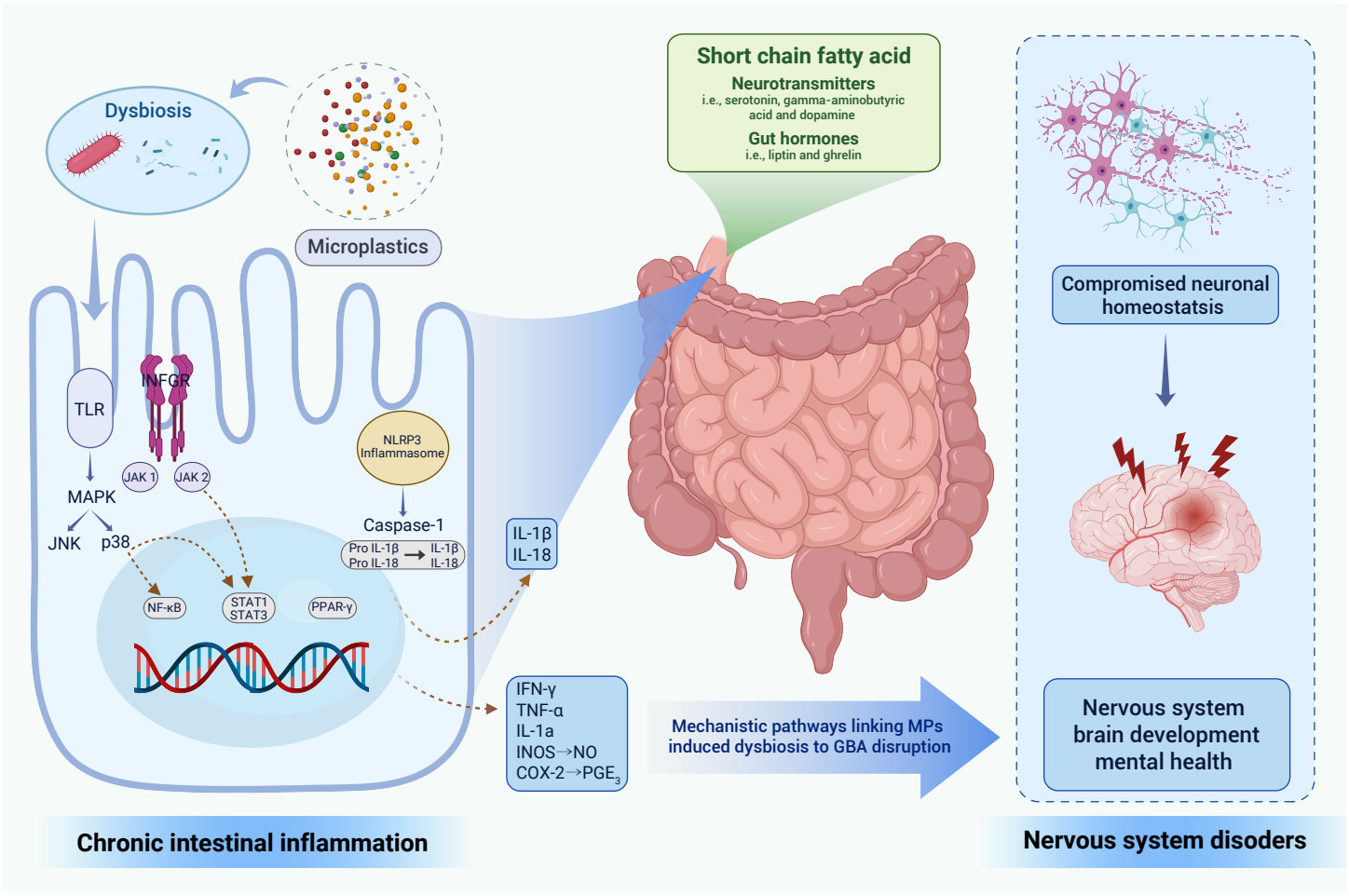

Figure 6. Schematic representation of the correlation between chronic intestinal inflammation and the development of brain disorders by MP exposure (This figure was created by BioRender.com).

Additionally, the lack of standardized protocols for measuring MP bioaccumulation in human tissues further complicates the interpretation of correlative human data. It is essential to consider these factors when comparing findings across studies to understand the reasons for conflicting results.

Limitations of advanced detection technologies. This scarcity of recording on human exposure to MPs is further exacerbated by profound methodological challenges in accurately risk assessment. A major impediment is the absence of standardized and highly sensitive protocols for detecting and quantifying MPs. Advanced imaging techniques, such as Raman spectroscopy and hyperspectral systems, enable precise identification of MPs in complex biological matrices, such as blood, brain, or placenta, at environmentally relevant concentrations, particularly for submicron NPs.[161] However, their sensitivity remains insufficient for nanoscale particles. Fourier-transform infrared and Raman spectroscopy are both powerful tools for polymer identification, yet their spatial resolution is inherently limited, restricting their effectiveness in characterizing fine particle details; as well as pyrolysis-gas chromatography/mass spectrometry, which is capable of identifying the polymer composition of MPs, but is unable to assess particle morphology or count.[162-163] Moreover, microscopic analyses risk false positives and contamination, further compromising data reliability.

Currently, there is no single detection technology capable of comprehensively characterizing all critical attributes of MPs. Consequently, substantial variability in particle characterization and reporting persists across studies, hindering accurate dose-response assessment and comparability of findings across different investigations. This methodological inconsistency remains a major contributor to conflicting results found in literatures, as divergent analytical approaches applied to complex biological samples often yield non-comparable or contradictory findings, impeding the development of a clear understanding of the health implications of MPs exposure.

Complexity of MPs exposure dynamics. There is currently no unified standard exists for the toxicological testing of MPs, resulting in substantial methodological variability. Different model organisms and cell lines show divergent sensitivities to MPs. This lack of standardization hinders the comparability and reproducibility of toxicological findings, contributing to the conflicting conclusions.

Furthermore, the vast complexity of real-world exposure dynamics and multiple pathways of Human exposure present considerable challenges to risk assessment, which is poorly replicated in controlled laboratory settings and clinical research. Of particular concern is the simultaneous exposure of individuals to MPs and a wide range of other environmental contaminants. MPs serve as vectors for these co-contaminants, adsorbing and transporting them, thereby enhancing their bioavailability and synergistic toxicity.[163] This intricate interplay, combined with the lag in regulatory frameworks relative to scientific advancements, complicates efforts to discern the specific neurotoxic effects attributable to MPs and obscures the establishment of clear causal relationships.

Hypotheses derived from critical research gaps

To directly address the methodological conflicts and knowledge gaps outlined in the preceding sections, we propose the following testable hypotheses. These are designed to propel the field beyond correlative observations, advancing our understanding of MPs-induced neurotoxicity by explicitly targeting the sources of inconsistency in the current literature and promoting a mechanistic, environmentally relevant approach.

Hypothesis 1: Environmental weathering enhances MP-induced neurotoxicity. It is hypothesized that MPs subjected to environmentally weathering-characterized by surface oxidation, fragmentation, and biofilm colonization induce a more pronounced gut dysbiosis and neuroinflammatory response

than pristine laboratory MPs. This enhanced toxicity arises from biofilm-driven pathogenicity and increased leaching of adsorbed additives and pollutants, representing the complex reality of environmental exposure conditions.

The inconsistency in reported MP translocation across the BBB is further hypothesized to result from differences in biomolecular corona composition. The formation of a protein or lipid corona on the surfaces of MPs may facilitate receptor-mediated transcytosis, enabling region-specific brain accumulation. This hypothesis offers a testable explanation for the variable neurodistribution patterns observed in previous studies.

Hypothesis 2: Maternal MP exposure induces epigenetic modifications affecting fetal neurodevelopment. We propose that maternal exposure to MPs exerts intergenerational neurodevelopmental effects through epigenetic modifications in fetal brain genes involved in neuronal growth and synaptic function. These alterations are mediated via MP-induced dysbiosis in the maternal gut microbiota, which disrupts SCFA metabolism and alter maternal-fetal signaling. This hypothesis links the gap between acute exposure studies and chronic and multigenerational outcomes, providing a mechanistic framework to understand how persistent MP exposure influences long-term neurodevelopmental trajectories via microbiome-epigenome interactions.

Hypothesis 3: Co-exposure to MPs and environmental contaminants produces synergistic neurotoxicity. It is posited that co-exposure to MPs and co-occurring environmental contaminants, such as heavy metals, pesticides, or persistent organic pollutants leads to a synergistic disruption of intestinal and neural homeostasis. MPs serve as vectors for contaminant adsorption and transport, thereby facilitating the enhanced toxicant delivery to both the gut and neural tissues while impairing hepatic detoxification pathways.

Testing this hypothesis is crucial for moving beyond simplified single-exposure paradigms, enabling more accurate assessment of combined effects of exposures under environmentally relevant conditions. To accurately unravel the neurotoxic complex interactions and mechanisms between MPs and environmental contaminants, standardized models reflecting realistic exposure complexity are imperative.

Emerging technologies for research of health assessment by MPs exposure

The advancement of MPs' research hinges on innovative technologies to address critical challenges in detection, mechanistic modeling, and risk assessment.

Advances in high-resolution imaging drive progress in MPs health assessment. Recent technological advancements have significantly enhanced the precision and depth of MPs-associated health risk assessment. Clustered regularly interspaced short palindromic repeats-derived biosensors now enable rapid, field-deployable monitoring of MPs in diverse complex matrices, including water, food, and clinical specimens, thereby providing a promising strategy for real-time exposure surveillance. The MERSCOPE® platform (www.vizgen.com) offers spatially resolved transcriptomic profiling, which facilitates visualization of gene expression patterns within the native tissue architecture. Using this platform, site-specific dysregulation of pro-inflammatory cytokines and oxidative stress markers, such as superoxide dismutase 2 and glutathione peroxidase 1 has been observed in the intestinal and hippocampal tissues of MPs-exposed mice, correlating with behavioral impairments and reduced BDNF expression.

Furthermore, GBA organ-on-chip models have emerged as powerful tools to for mimicking the intricate crosstalk between IEC and neuron-immune under MPs exposure. These models have revealed that MPs induce mitochondrial dysfunction through inflammatory communication, recapitulating key pathogenic pathways implicated in neurodegenerative diseases such as PD.

Organoid models in MPs toxicology. Traditional animal models exhibit inherent limitations, including species-specific discrepancies and restricted mechanistic interpretability. Establishing a causal relationship between MPs exposure and adverse health outcomes using these models necessitates large sample sizes, prolonged follow-up, extensive data collection, and substantial experimental costs, making these approaches resource-intensive and time-consuming.[164] Given these constraints, there is a growing need for alternative *in vitro* systems capable of effectively assessing health risks with limited sample requirements.

Organoids have emerged as powerful tools for evaluating the toxicological effects of environmental contaminants, organ-specific damage, and drug screening, etc. They have been applied to assess the toxicity of diverse MPs in different organ systems.[165] Recent investigations have demonstrated their potential in environmental toxicology, disease modeling, and precision medicine, as they provide physiologically relevant human-derived platforms that overcome the translational barriers of animal studies.[166-168]

A recent study developed microfluidic human duodenum-chip models derived from primary intestinal epithelial organoids isolated from both healthy donors and individuals with Crohn's disease. This system was employed to evaluate the toxicity and absorption mechanisms of 25 nm PS shell–gold core MPs/NPs (AuPS25). It revealed significant transcriptional dysregulation, especially the downregulation of *IFI6*, a key interferon-α-induced gene essential for antiviral and immunosuppressive functions in the gut. It also implied the potential impairment of innate immunity, raising concerns regarding subtle yet biologically meaningful impacts of MNP exposure on intestinal health. Mechanistic inhibitor analyses further demonstrated that AuPS25 uptake occurred through a combination of passive diffusion and active transport mediated by actin- and dynein-dependent pathways, consistent with previous findings in multicellular intestinal systems.[169] Collectively, organoid-based systems represent a transformative breakthrough in MPs toxicology, offering physiologically relevant, ethically viable, and mechanistically insightful platforms for elucidating MP-induced toxicity.

AI accelerates MPs research. AI and machine learning integrate multi-omics data to predict neurotoxic outcomes and identify synergistic effects with co-pollutants.[170] Machine learning models have demonstrated that exposure duration is a key driver of MPs-induced gut microbiota alterations. Furthermore, *Lactobacillus*, *Helicobacter*, and *Pseudomonas* have been identified as potential microbial biomarkers for assessing intestinal toxicity in animal models. These findings provide valuable insights into the health risks and drivers associated with MPs exposure across diverse animal species.[164]

A recent study introduced an AI-driven analysis framework that goes beyond the traditional "detection and description" paradigm. By extracting over 120-dimensional deep features from Raman imaging data, the researchers constructed the first AI model capable of predicting organ deposition of MPs based on their physicochemical characteristics. This model revealed organ-specific retention patterns such as hepatic and renal accumulation and larger particle aggregation in the lungs and successfully established a predictive link connecting environmental exposure, systemic distribution, and organ-specific health risks.[171]

This discovery bridges a major knowledge gap in understanding the biodistribution and organ-specific toxicity of MPs, offering a new framework for toxicological research, high-risk population stratification, and evidence-based public health policies targeting specific polymer types and morphologies. However, most studies still employ pristine MPs, limiting environmental realism, and AI models may be biased by restricted datasets. Future research should integrate multi-scale data, linking gut-on-chip interactions with hippocampal gene networks to connect subcellular perturbations to systemic disease.

Strategies and policies for controlling MPs

Mitigation of global MPs pollution necessitates a synchronized, multi-level strategy involving international worldwide collaboration, national legislation, and technological innovation. Internationally, frameworks including amendments to the Basel Convention and treaties led by UNEP (United Nations Environment Programme) aim to restrict the transboundary movement of plastic waste, standardize monitoring systems, and enhance the entire lifecycle management of plastics, from production to disposal. National governments have implemented a range of specific policies to address plastic pollution. These include bans on single-use plastics, mandatory recycling requirements, and extended producer responsibility schemes, achieving varied levels of effectiveness in reducing MP emissions across regions.

In developed economies, regulations have targeted microbeads in cosmetics and promoted circular economy principles. Major plastic-producing countries, including China, have implemented comprehensive control strategies and invested in waste management infrastructure. A detailed overview of

policies, timelines, and outcomes is provided in Table S3. Technological innovations, such as advanced wastewater treatment, biodegradable alternatives, and AI-driven risk assessment, complement regulations and enhance the ability to prevent and mitigate MPs pollution effectively.

CONCLUSION

The pervasive presence of MPs into ecosystems and human physiology underscores a rising public health challenge, particularly regarding their potential disruption of the GBA. Findings from experimental and observational studies indicate that MPs can damage intestinal barrier integrity, modulate gut microbiota composition, and trigger systemic inflammation and oxidative stress, ultimately disrupting brain homeostasis to a certain degree. These processes have been linked in preclinical models to neuroinflammatory pathways, mitochondrial malfunction, and changes in neurotransmitter regulation-mechanisms that may be relevant to certain neurodegenerative and neurodevelopmental disorders. Emerging evidence also suggests that MPs can cross biological barriers, such as the BBB, although the extent and consequences of such translocation in human populations remain to be firmly established.

Despite advancements in understanding MPs' mechanisms of toxicity, substantial translational uncertainties persist. Real world exposures typically involve complex mixtures of MPs and co-pollutants such as heavy metals and pesticides, yet these scenarios are rarely replicated in controlled experiments. Human studies are sparse, constrained by technical constraints in detecting MPs within biological samples and in linking exposure levels to specific neurological consequences. Moreover, the biological effects of weathered and environmentally aged MPs, which differ in composition and surface chemistry from pristine particles exhibit stronger interaction, which warrant greater attention. Advancing understanding of the neurotoxic effects of MPs requires interdisciplinary collaboration integrating ecology, neurology, and public health to convert mechanistic findings towards preventive strategies. Emphasizing human biomonitoring, standardizing toxicity evaluations, and promoting sustainable innovation will be crucial in protecting neurological health. While the current evidence base justifies continued investigation and precautionary consideration, translating mechanistic findings into effective preventive strategies will depend on closing critical knowledge gaps. As research progresses, a balanced and data-driven approach will be essential to clarify the potential neurological implications of MPs exposure and to inform evidence-based policy and innovation.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Not applicable.

SUPPLEMENTAL INFORMATION

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