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Micro-nanoplastics and Parkinson's disease: evidence and perspectives

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Abstract

With the intensification of global plastic pollution, the potential threats posed by micro- and nanoplastics (MPs/NPs) to human health have become a major concern. MPs/NPs enter the organism through ingestion, inhalation, and skin contact, subsequently accumulating in multiple organs—particularly the brain. Increasing experimental and epidemiological evidence implicates MPs/NPs in the development of Parkinson's disease (PD). Preclinical research models indicate that MPs/NPs may accelerate both the initiation and progression of PD by facilitating α-synuclein misfolding and aggregation, triggering neuroinflammatory cascades, elevating oxidative stress, and impairing mitochondrial function. To further investigate the causal role of MPs/NPs in PD, upcoming studies should emphasize well-designed, large-scale prospective cohorts to assess individual exposure to plastic-related pollutants, elucidate the pathways of MPs/NPs into the central nervous system, establish safety thresholds for their neurotoxicity, explore the correlation between exposure levels and central nervous system accumulation, clarify the temporal relationship between MPs/NPs accumulation and PD pathology and symptom onset, and identify the neuropathological mechanisms triggered by relevant concentrations of MPs/NPs. Such data will be instrumental in informing preventive and potentially interventional strategies, while offering actionable insights into the interaction between MPs/NPs and PD.

Keywords: Micro-nanoplastics; Parkinson's disease; Pathogenesis; Prospective study

1.Introduction

The continuous expansion of plastic manufacturing and use worldwide has markedly intensified environmental contamination [1]. Under the influence of biological activity, chemical reactions, and physical forces—including hydrolysis and ultraviolet exposure—plastic debris gradually fragments, giving rise to MPs/NPs [2–4]. Consequently, MPs/NPs have become widespread contaminants across diverse ecosystems and have infiltrated nearly every aspect of human life [5,6]. MPs/NPs entering the brain through different pathways may deposit in distinct regions. Following oral ingestion or waterborne exposure, MPs/NPs can penetrate the blood-brain barrier（BBB）via systemic circulation and be transported to various cerebral regions, particularly the midbrain [7]. Additionally, NPs can access the olfactory bulb and cerebral cortex through the olfactory nerve, while the trigeminal nerve pathway enables their transport to the cerebellum and pons [8]. Accumulation of MPs/NPs within the brain leads to histopathological alterations and neurofunctional impairment, potentially promoting the initiation and advancement of neurodegenerative diseases. [7]. PD, ranking as the second most prevalent neurodegenerative condition, exhibits a significantly higher rate of increase in prevalence compared to other neurological diseases amid global population aging. Currently, the number of confirmed cases worldwide exceeds 6 million [9]. In recent years, increasing scientific attention has been directed toward elucidating the relationship between MPs and PD. This review synthesizes extant evidence to explore potential associations between MPs/NPs and outcomes associated with PD. By integrating emerging evidence, we aim to offer novel perspectives on probing PD etiology while establishing a scientific foundation for early preventive and interventional strategies.

2.Overview of MPs

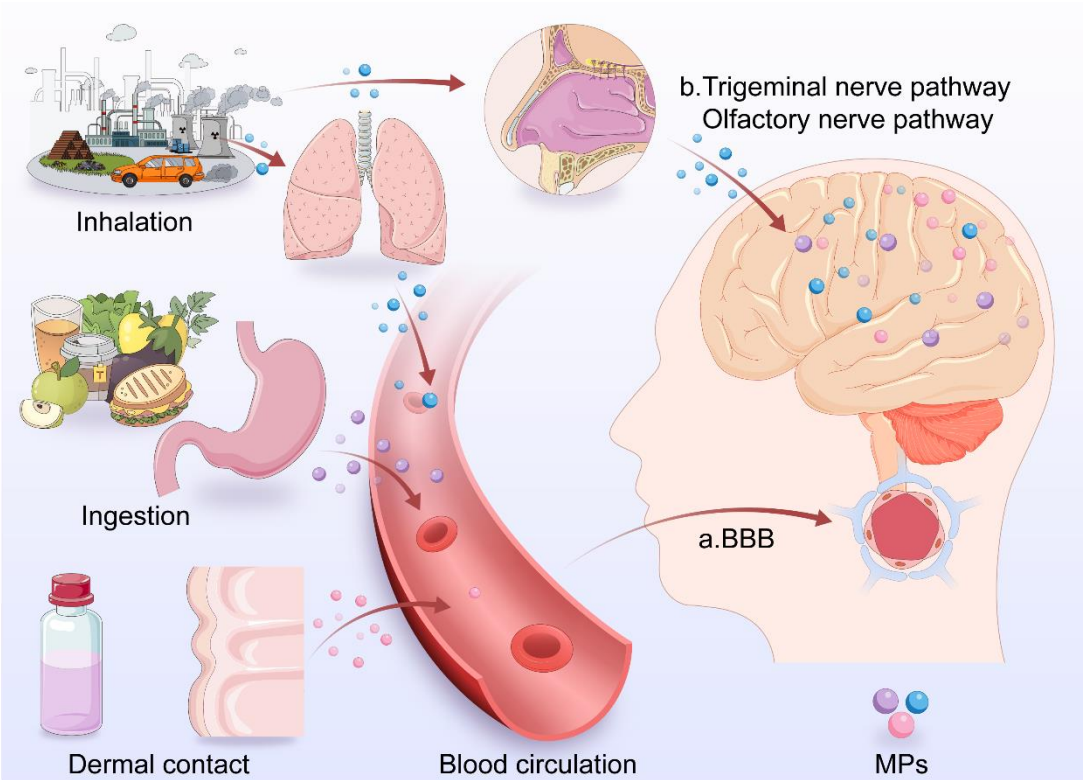
MPs, characterized as solid plastic particles less than 5 mm in size [10], can be classified by dimensions into micrometer-scale MPs (ranging from 1 μm to 5 mm) and NPs, which are smaller than 1 μm [11]. According to their sources, they are classified as primary or secondary MPs. Primary MPs are artificially manufactured micrometer-sized particles designed for use in cosmetics, cleaning agents, pharmaceuticals, and related industries [12]. These particles typically comprise polyethylene (PE), polypropylene (PP), polystyrene (PS), and polyolefin plastic spheres, with sizes generally falling within the 1–5 μm range. By contrast, secondary MPs/NPs are generated when larger plastic materials undergo breakdown driven by factors including ultraviolet exposure, mechanical wear, or biological degradation [13]. Secondary MPs/NPs display a wider range of particle sizes and are frequently present in forms such as fragments, fibers, granules, flakes, or spheres, representing the major contributors to environmental MPs/NPs [14]. NPs, a distinct subclass of MPs, possess smaller dimensions, a larger surface-to-volume ratio, and greater chemical reactivity than MPs, enhancing their capacity to disrupt metabolism and impair reproduction in animals [15,16]. For instance, PS-NPs, with sizes comparable to cell membrane pore diameters (approximately 100 nm),

can penetrate the BBB directly, invade the central nervous system, and interfere with neuronal function, making them a major focus of current research [11].

3.Source and distribution of human MPs

Humans are generally exposed to MPs/NPs through three primary pathways: oral intake, respiratory absorption, and penetration through the skin [17]. Among these, oral intake is generally regarded as the primary means of exposure. [18]. MPs/NPs have been detected across nearly all food categories, and ingestion alone is estimated to result in an average global per capita intake of approximately 39,000 to 52,000 particles annually [19]. Inhalation constitutes another major exposure route. Airborne MPs/NPs in the environment predominantly originate from sources such as synthetic fibers, tire wear, urban dust containing plastics, the erosion of construction materials, as well as residues from waste management and landfill sites. [20–22]. Monitoring data indicate that particulate concentrations span from <1 to >1000 particles/m^3 in outdoor environments, while indoor concentrations range from <1 to 1583 ± 1181 particles/m^3 (mean), with a portion of these particles falling within respirable size ranges [23]. Although less significant, skin absorption can arise when individuals come into contact with water or personal care products that contain MPs [7].

Environmental MPs/NPs are capable of entering the human body, crossing biological barriers, and disseminating systemically through the circulatory system [24,25]. MPs/NPs concentrations exhibit significant variation across different tissues and bodily fluids. Research has quantified MPs at the following concentrations: hair, 3.5 MP/person/day; saliva, 0.33 MP/person/day; sputum, 1.86–9.78 MP/mL; blood, 1.6 μg/mL; breast milk, 20.2 MP/g; liver, 3.2 MP/g; kidney, 0–0.2 MP/g; colon, 28.1 ± 15.4 MP/g; placenta, 0.28–18 MP/g; saphenous vein tissue, 4.99 ± 17.18 MP/g; lungs, 0.69 ± 0.8 MP/g; bronchoalveolar lavage fluid, 0.0918 ± 0.0245 MP/mL; spleen, 1.0 MP/g; meconium, 54.1 MP/g; feces, 3.33–13.99 μg/g; and brain tissue, 4917 μg/g [26,27]. Notably, the brain appears to be a major site for MPs/NPs deposition, and this enrichment may have a strong association with the initiation and progression of neurodegenerative disorders, including PD.



4.MPs and PD pathogenesis

PD represents a prevalent neurodegenerative condition that mainly occurs in middle-aged and older adults. Its clinical manifestations encompasses both motor and non-motor symptoms. The hallmark motor features of PD typically include resting tremor, muscle rigidity, and bradykinesia. Non-motor symptoms involve multisystem manifestations, including gastrointestinal dysfunction, urinary abnormalities (such as voiding difficulties), constipation, depression, and cognitive impairment [28]. Although considerable progress has been made, the precise etiology and pathogenesis of PD are still not fully clarified. A hallmark of the disease is the pathological aggregation of misfolded α-synuclein in peripheral organs as well as within the central nervous system, with subsequent propagation within the brain. This pathological process involves immune activation, neuroinflammation, mitochondrial dysfunction, and lysosomal impairment [29]. During the last thirty years, the global prevalence of PD has risen markedly and is projected to continue rising over the next 30 years [30]. According to data from the Global Burden of Disease (GBD) study, the age-standardized growth incidence of PD in China reached 115.7% from 1990 to 2019—significantly exceeding the global average. In addition to enhanced diagnostic capabilities, emerging environmental pollutants—particularly MPs—have been proposed as potential contributors to this rapid escalation [31].

4.1 Research status of MPs/NPs and PD

Current research on the relationship between MPs/NPs and PD primarily focuses on eight key thematic areas. These include: MPs/NPs mediating mitochondrial dysfunction and energy metabolism disruption, leading to dopaminergic neuronal death [32,33]; the facilitation effect of NPs on the pathological aggregation of α-synuclein[34,35]; the gut-brain axis mechanism, exploring MPs/NPs -induced damage to the intestinal barrier and their interactions with the microbiota [31,36]; neuroinflammation, examining the interactions between MPs/NPs and microglia[31,37]; molecular pathways, focusing on the AMPK/ULK1 pathway inducing excessive mitophagy [32] and aberrant calcium(Ca^{2+}) signaling [38]; the assessment of motor dysfunction, specifically MPs/NPs exposure-induced PD-like symptoms [31]; and the exploration of preventive and therapeutic strategies [32,38].

Research Models: The potential neurotoxicity of MPs/NPs has been investigated through in vivo, in vitro, and computational models, with each approach offering distinct insights.

In Vivo Models

In vivo models dominate current research, primarily utilizing mammals (C57BL/6J mice). These models are frequently employed to study the effects of chronic oral MP exposure, such as through repeated dosing simulating real-world exposure scenarios These studies have revealed that MPs accelerate dopaminergic neuron degeneration and elicit PD-like motor deficits [31,33,38]. Non-mammalian organisms, exemplified by Caenorhabditis elegans (C. elegans), are commonly employed in high-throughput screening and toxicological assessments [31,39]. In C. elegans, NPs accumulate within the digestive tract, leading to increased intestinal permeability and α-synuclein aggregation [39]. Additionally, zebrafish (Danio rerio) are utilized for developmental and toxicity assessments. For instance, NPs exposure in zebrafish has been shown to cause hatching abnormalities, reduced survival rates, and motor dysfunction [34,40].

In Vitro Models

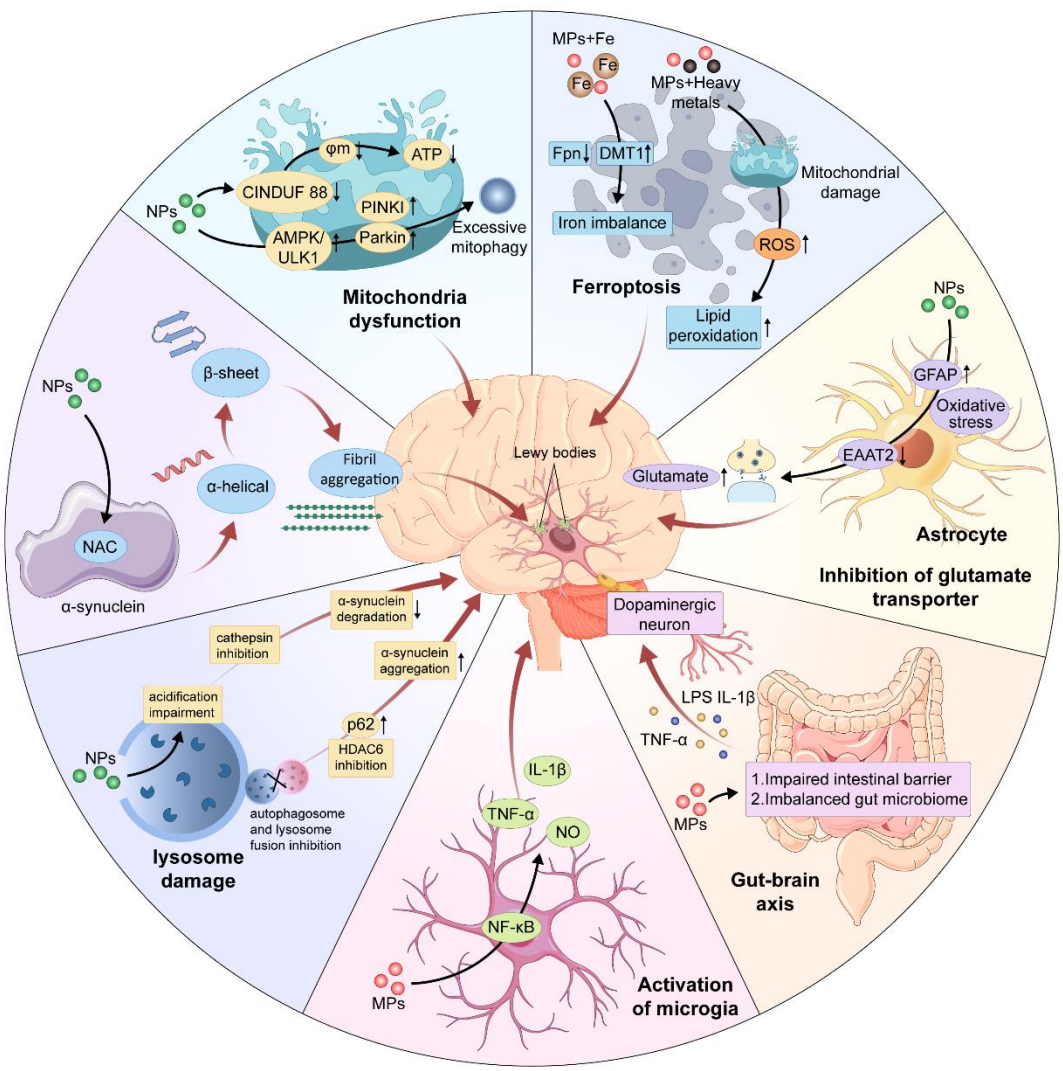
In vitro models enable controlled research on the effects of MPs at the cellular level. The SH-SY5Y dopaminergic neuronal cell model is employed to assess the cytotoxicity of NPs (e.g., PS-NPs) and mechanisms underlying mitochondrial damage [32]. Mouse enteric glial cell models are used to simulate MP/NP-induced intestinal barrier dysfunction and inflammatory signaling, elucidating their contribution to PD-associated neuroinflammation via the gut-brain axis [41].

Computational Models

Although computational models are currently less extensively applied in this field, they provide valuable predictive insights. For example, molecular dynamics simulations have been employed to

model the interactions between NPs and specific biological domains, such as the non-amyloid-β component (NAC) region of α-synuclein and mitochondrial complexes[32,34,35]. While primarily based on molecular simulations, these tools aid in understanding the mechanisms of MP/NP interactions with biomolecules and hold potential for future application in neurotoxicity prediction.

Collectively, these models elucidate the mechanisms linking MPs to PD from diverse dimensions. Subsequent sections will provide a detailed analysis of how MPs/NPs exacerbate PD progression through specific pathways: promoting aberrant α-synuclein aggregation, inducing neuroinflammation, disrupting gut-brain axis homeostasis, interfering with mitochondrial energy metabolism, inhibiting the excitatory amino acid transporter 2(EAAT2), and triggering ferroptosis.



4.2 Mechanism

Aberrant α-Synuclein aggregation

A hallmark pathological feature of PD is the presence of Lewy bodies within neurons, largely consisting of misfolded and aggregated α-synuclein. [42]. α-synuclein, a presynaptic neuronal protein [43], possesses a tripartite domain structure: an amphipathic N-terminal segment, a central NAC domain, and a C-terminal region [44]. The NAC region, enriched in hydrophobic residues, possesses strong amyloidogenic properties and serves as the principal driver of α-synuclein aggregation [44]. Further research indicates that NACore—a specific 11-residue segment (68-GAVVTGVTAVA-78) within the NAC region—constitutes the principal factor driving α-synuclein aggregation and toxicity [34]. Under normal physiological states, α-synuclein maintains a dynamic balance between membrane-bound multimers and soluble monomers, the latter typically adopting a natively unfolded conformation. However, soluble α-synuclein undergoes aggregation and misfolding under various pathological conditions, including compromised membrane-binding capacity, exposure to dopamine oxidation products or metal ions, or impaired autophagy/proteasome degradation system. This process initiates with the formation of soluble oligomers, which subsequently transform into amyloid fibrils, ultimately leading to Lewy body formation [44]. Critically, the soluble oligomeric form of α-synuclein is now widely recognized as the pathogenic species in PD [45].

Liang et al. employed electrospray ionization time-of-flight mass spectrometry to demonstrate that NPs adsorb NACore monomers through hydrophobic interactions, accelerating NACore aggregation kinetics and significantly enhancing oligomerization rates [34]. Specifically, NP hydrophobic surfaces form non-covalent bonds with hydrophobic amino acid residues in NACore monomers. This binding mechanism resembles the hydrophobic burial process observed during protein folding, concentrating NACore monomers on NP surfaces. The resultant increase in monomer collision frequency promotes rapid oligomer formation [34]. Spectroscopic analyses further indicate that diverse MPs, including PE, polyvinyl chloride (PVC), and PS, are capable of modulating the secondary structure of α-synuclein [46]. The secondary conformation of α-synuclein encompasses α-helices, β-sheets, and random coils. Under physiological conditions, α-synuclein predominantly adopts α-helix-rich tetramers, which confer resistance to pathological aggregation. However, under pathological stressors such as chronic inflammation or oxidative stress, α-synuclein undergoes conformational rearrangement: α-helices destabilize, enabling transition into β-sheet-rich oligomers [47,48]. Upon contact with MPs, their hydrophobicity disrupts the intramolecular forces—including hydrogen bonds and van der Waals forces—which normally maintain α-synuclein 's stable secondary structure, ultimately promoting the conversion of α-helical structures into β-sheets. The resultant β-sheet conformation exhibits enhanced intermolecular interaction capacity, thereby facilitating α-synuclein aggregation and leading to the

generation of neurotoxic amyloid oligomers [46]. Of particular note, PS-NPs, owing to their smaller size (100 nm) and stronger hydrophobicity, exhibit the most pronounced effect in promoting amyloid oligomer formation [46]. Animal model studies provide further support for this mechanism. In a C. elegans model of PD, Jeong and colleagues reported that 25-nm PS-NPs significantly increased α-synuclein aggregation, consequently inducing dopaminergic neurodegeneration and motor dysfunction; Complementary studies in PD patient-derived cells confirmed that NPs penetrate cells, primarily localize within the cytoplasm, and increase the number of α-synuclein aggregates by 50.7% [39].

The degradation of α-synuclein is primarily mediated by the autophagy–lysosomal pathway, encompassing macroautophagy, chaperone-mediated autophagy, and related processes. Under physiological conditions, α-synuclein aggregates are identified by autophagy adaptors like p62, incorporated into autophagosomes, and subsequently delivered to lysosomes for degradation by acid hydrolases, including cathepsins B and D. This process is essential for maintaining intracellular protein homeostasis. However, lysosomal dysfunction compromises this clearance mechanism, leading to intraneuronal build-up and aggregation of α-synuclein [49]. Liu et al. demonstrated that anionic NPs enter neurons through clathrin-dependent endocytosis and localize to lysosomes (LAMP1-positive). This lysosomal accumulation induces pH alkalinization and impairs acidification, directly inhibiting hydrolase activity (including cathepsin function) and decelerating β-amyloid fibril degradation[35]. DQ-α-synuclein assays revealed approximately 30% reduced fibril degradation efficiency in NP-exposed neurons compared to controls. Immunoblot analyses further revealed an increased accumulation of insoluble α-synuclein, along with perinuclear aggregation of phosphorylated α-synuclein (pS129-α-synuclein) surrounding lysosomes[35]. Beyond direct lysosomal impairment, NPs further inhibit autophagic flux by interfering with the merger of autophagosomes and lysosomes, thereby blocking aggregate clearance. This leads to the accumulation of autophagy receptor proteins like p62 and impairs HDAC6-mediated retrograde transport as well as exocytotic disposal of misfolded proteins. Together, these effects exacerbate α-synuclein pathology [49]. This degradation deficit exacerbates pathological propagation in vivo. Intracerebral co-injection of NPs with α-synuclein fibrils in mice significantly enhanced fibril aggregation within substantia nigra dopaminergic neurons. Furthermore, it promoted dissemination of pS129-α-synuclein pathology to additional brain regions (striatum and cortex), accelerating PD-like pathogenesis[35].

Neuroinflammation

Neuroinflammation represents a multifaceted biological response, characterized by the activation of resident immune populations in the central nervous system, the release of pro-

inflammatory factors including cytokines and chemokines, and the subsequent recruitment of additional cellular components triggered by neuronal injury [50]. Studies indicate that neuroinflammation plays a pivotal role in driving neurodegenerative processes in PD. Among the key mediators of this response are microglial cells, which act as central players in immune activation and represent the foremost defense mechanism against pathogenic challenges and tissue damage [50,51]. Neuropathological studies in PD have revealed pronounced activation of microglia, accompanied by higher levels of pro-inflammatory cytokines within the substantia nigra pars compacta (SNpc) and striatal regions, when contrasted with findings in non-affected controls [52–55]. Moreover, positron emission tomography (PET) studies demonstrate enhanced activation of microglia in the brainstem, basal ganglia, and frontotemporal cortical regions during early PD stages[56,57]. Microglial cells are capable of differentiating into distinct functional states, including the M1 phenotype, which exerts pro-inflammatory and neurotoxic effects, and the M2 phenotype, which is linked to anti-inflammatory and neuroprotective actions [58]. The pathological shift toward M1 polarization results in heightened secretion of pro-inflammatory cytokines and enzymes—including TNF-α, IL-1β, IL-6, IL-23, IFN-γ, inducible nitric oxide synthase , and cyclooxygenase-2—thereby driving neuroinflammatory processes and contributing to neuronal degeneration [58]. The Nuclear factor kappa B (NF-κB) and Signal Transducer and Activator of Transcription signaling pathways collectively regulate the M1/M2 phenotypic ratio [59].

In vitro studies indicate that exposure to PS-MPs triggers NF-κB pathway activation in microglia, resulting in an overproduction of IL-1β, TNF-α, and nitric oxide (NO)[37]. Extending these findings, using a PD mouse model carrying the A53T α-synuclein mutation, Bai et al. demonstrated that MPs exposure induces significant microglial activation within the substantia nigra of the midbrain. Morphologically, activated microglia exhibited hallmark features of a pro-inflammatory state, including enlarged somata, retracted processes, and increased cell density. Immunohistochemical analyses demonstrated that microglia labeled with ionized calcium-binding adapter molecule 1 were commonly positioned in close proximity to degenerating dopaminergic neurons within the substantia nigra. The activated state correlated with elevated transcription of the pro-inflammatory cytokine IL-1β, indicating that MP exposure triggers microglial activation and subsequent hypersecretion of inflammatory mediators, thereby accelerating neuronal damage [31].

Inhibition of glutamate transporter

Glutamate serves as the primary excitatory neurotransmitter regulating voluntary motor function in PD [60]. Among glutamate transporters, EAAT2 is the most prominent, accounting for approximately 80–90% of synaptic glutamate clearance [61]. Under normal physiological circumstances, glutamate resides in presynaptic vesicles and is released into the synaptic cleft at

high concentrations following neuronal depolarization[62]. Synaptic glutamate is rapidly cleared within 10 milliseconds primarily through EAAT2-mediated uptake. This internalized glutamate is subsequently transformed into glutamine by the action of glutamine synthetase, ultimately recycling into neurons to maintain physiological glutamatergic homeostasis [63,64]. When synaptic glutamate accumulates excessively, it leads to pathological overstimulation of ionotropic glutamate receptors, most notably the N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors. Such hyperactivation leads to an excessive influx of Ca^{2+}, causing intracellular calcium overload. The ensuing dysregulation triggers oxidative stress, mitochondrial dysfunction, neuroinflammation, as well as activation of apoptotic pathways, ultimately culminating in neurodegeneration [60]. Notably, reduced expression of EAAT2—commonly observed in PD as well as other neurodegenerative disorders including amyotrophic lateral sclerosis and Alzheimer's disease—impairs synaptic glutamate clearance and exacerbates excitotoxicity-induced neuronal damage [61].

EAAT2 is predominantly expressed in astrocytes. Pathological alterations in astrocytes—including reactive astrogliosis, α-synuclein aggregation, and oxidative stress—downregulate EAAT2 expression and impair its transport capacity through mechanisms involving epigenetic regulation and protein functional interference [65]. Recent studies suggest that PS-NPs disrupt glutamate cycling by suppressing astrocytic EAAT2, resulting in aberrant synaptic transmission and excitotoxic neuronal damage. Specifically, Su et al. demonstrated that PS-NPs exposure significantly decreases EAAT2 levels in astrocytes of the medial prefrontal cortex (mPFC) in mice, diminishing glutamate uptake capacity. This impairment induces synaptic glutamate accumulation and consequent neuronal hyperexcitation [66]. Pharmacological activation of EAAT2 using compounds such as LDN-212320 has been shown to restore glutamate transport function and ameliorate PS-NPs-induced neurobehavioral deficits [66]. Mechanistically, PS-NPs are believed to suppress EAAT2 expression and function indirectly by inducing astrocytic dysfunction, including upregulated glial fibrillary acidic protein expression and heightened oxidative stress. Pathologically activated astrocytes exhibit disrupted intracellular signaling or metabolic homeostasis, impairing EAAT2 transcription, translation, or trafficking. Concurrently, oxidative stress can reduce EAAT2 activity or expression through oxidative modification of transporter proteins or damage to its encoding gene. These combined mechanisms ultimately compromise glutamate clearance capacity [66].

Gut-brain axis

The gut-brain axis (GBA) has garnered significant attention in PD pathogenesis. Gastrointestinal dysfunction is frequently observed to emerge almost twenty years prior to the manifestation of motor symptoms [67]. The GBA represents a dynamic communication system linking the

gastrointestinal tract with the central nervous system through bidirectional signaling pathways [68]. The gastrointestinal tract constitutes a dynamic interface mediating host-environment interactions and functions as an essential barrier that is pivotal in maintaining immune homeostasis [69]. This semi-permeable barrier performs three primary roles: selective nutrient absorption, regulation of antigen exposure, and the control of microbial populations. Structurally, the mechanical component is formed by intestinal epithelial cells and vascular endothelial cells joined by tight junctions, adherens junctions, and cadherin proteins, thereby ensuring selective nutrient transport. In addition, the immune component of the barrier limits access of environmental antigens, while the biological component is maintained through colonization by commensal microbiota [70]. During PD progression, compromised intestinal barrier integrity with increased permeability—termed "leaky gut"[71]—enables translocation of pro-inflammatory microbial products such as lipopolysaccharide (LPS) and cytokines into the bloodstream, thereby triggering systemic inflammation [72,73]. Such inflammation may induce breakdown of the BBB, enabling the passage of LPS and inflammatory cytokines into the substantia nigra region. Ultimately, these processes induce nigral neuroinflammation and dopaminergic neuronal death [74–76].

Chronic MP exposure induces structural damage to the intestinal mucosa, manifesting as villus atrophy, crypt architectural disorganization, and accumulation of immune cells including lymphocytes and plasma cells [31]. Experimental evidence indicates that prolonged oral exposure to PS-MPs (1 μm and 5 μm) in mice significantly downregulates the expression of tight junction proteins—such as zonula occludens-1 (ZO-1) and occludin—leading to enhanced intestinal permeability. These changes facilitate the translocation of gut-derived endotoxins (e.g., LPS) and pathological proteins (e.g., α-synuclein) into systemic circulation, subsequently activating peripheral immune responses [31,36]. This "leaky gut" state not only disrupts intestinal homeostasis but also enables MPs, along with adsorbed toxicants such as heavy metals and persistent organic pollutants, to translocate into peripheral tissues and the central nervous system [36,77]. Moreover, MPs stimulate activation of gut-resident immune populations, including macrophages and dendritic cells, which subsequently enhance the release of pro-inflammatory mediators such as IL-1β and TNF-α [31,77]. Notably, endotoxins such as LPS bound to the surface of MPs can exacerbate intestinal immune responses through the Toll-like receptor 4 signaling pathway, further compromising barrier integrity [36]. Significantly, these inflammatory mediators intensify intestinal inflammation locally and propagate to the brain via vagal or hematogenous routes, triggering neuroinflammation and microglial activation [31,77].

Alterations in the gut microbial community—termed the microbiota-gut-brain axis—play an essential part in the development of PD [78]. In a physiologically normal state, the stability of the gut microbiota is essential for preserving intestinal barrier and regulating immune homeostasis, which

in turn supports brain maturation and function via bidirectional communication along this axis [79]. Notably, a reduction in the generation of short-chain fatty acids (SCFAs)—crucial microbial metabolites—compromises the protective functions of the BBB [36]. SCFAs exhibit anti-inflammatory and immunomodulatory properties, functioning as signaling molecules that beneficially modulate various intestinal and extra-intestinal disorders [80]. In PD patients, significant alterations in gut microbial taxa have been observed. A meta-analysis examining gut microbial profiles of PD patients and healthy individuals across different regions revealed significantly reduced abundances of Prevotellaceae, Faecalibacterium, and Lachnospiraceae in the PD groups. Conversely, Bifidobacteriaceae, Ruminococcaceae, Verrucomicrobiaceae, and Christensenellaceae exhibited marked enrichment. This PD-associated dysbiosis may impair SCFA biosynthesis, lipid metabolism, immunomodulatory functions, and intestinal permeability, thereby contributing to PD pathogenesis [81]. Emerging evidence suggests that MP exposure disrupts microbial equilibrium by selectively altering gut microbiota composition, thereby promoting neuroinflammation via the microbiota-gut-brain axis. Several animal studies indicate that MPs reduce gut microbial diversity and shift the dominant phylum ratio—particularly elevating the Firmicutes-to-Bacteroidetes (F/B) ratio—while depleting beneficial genera like Bifidobacterium and enriching opportunistic pathogens like Staphylococcus [31,36,77]. For instance, PS-NPs induce enrichment of Fusobacteria and Proteobacteria, concomitant with dysregulation of SCFA metabolism [36]. Critically, MP exposure downregulates microbial SCFA production (e.g., acetate, propionate), thereby weakening their anti-inflammatory effects on microglia. Simultaneously, MPs facilitate the systemic translocation of pro-inflammatory metabolites (e.g., LPS, trimethylamine N-oxide), ultimately triggering central neuroinflammation [77].

Mitochondrial dysfunction

Mitochondria is regarded as a pivotal contributor to the neurodegenerative processes of PD [82]. Early pathogenic events are characterized by synaptic dysfunction and mitochondrial impairment, which are strongly linked to increased reactive oxygen species (ROS) levels, disrupted intracellular Ca^{2+} homeostasis, and decreased adenosine triphosphate (ATP) production [83]. Reports from pharmacologically induced PD models using the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) demonstrate that specific mitochondrial toxins inhibit complex I (CI) activity, thereby promoting degeneration of dopaminergic neurons within the substantia nigra [29]. Reduced CI activity has been documented in PD patients as well as in in vitro and in vivo models induced by neurotoxins or genetic factors [84]. Recent studies indicate that PS-NPs directly compromise mitochondrial energy metabolism by targeting CI. This leads to a loss of mitochondrial membrane potential, a marked reduction in ATP synthesis, and impaired respiratory chain function [32]. Experiments performed in differentiated SH-SY5Y neuroblastoma cells have shown that exposure to PS-NPs downregulates expression of the CI subunit NDUFB8, leading to

diminished basal and maximal oxygen consumption rates alongside increased proton leakage—further confirming mitochondrial CI dysfunction [32]. Similarly, Liang and colleagues employed single-cell RNA sequencing to demonstrate that PS-NPs markedly suppress the transcription of ATP metabolism-associated genes (e.g., *Atp5a1*, *Cox7a2*) in dopamine neurons of the mouse nigrostriatal pathway [33]. These molecular alterations correlate with reduced intracellular ATP levels, suggesting that mitochondrial energy dysregulation is a key mechanistic contributor to PS-NPs-induced, PD-like neurodegeneration.

Mitophagy is a selective lysosome-mediated degradation process that eliminates dysfunctional or excess mitochondria through autophagy, thereby preserving mitochondrial integrity and homeostasis [85]. The proteins PINK1 and Parkin function as central regulators of this process [86]. Inactivating mutations in these genes disrupt mitochondrial quality surveillance, ultimately giving rise to autosomal recessive forms of PD. [87,88]. Recent studies have demonstrated that PS-NPs trigger abnormal upregulation of mitophagy through activation of the AMPK/ ULK1 signaling cascade, further aggravating mitochondrial injury. Huang and colleagues observed that exposure to PS-NPs leads to intracellular ATP depletion, which activates AMPK and subsequently promotes ULK1 phosphorylation. This activation upregulates the expression of key mitophagy-associated proteins, notably LC3-II, PINK1, and Parkin, ultimately driving mitophagosome formation [32]. Notably, pharmacological inhibition of either AMPK or autophagy partially restores cell viability but fails to rescue ATP levels, suggesting that hyperactivated mitophagy consumes residual functional mitochondria, thus perpetuating a deleterious feedback loop [32]. Furthermore, Liang et al. demonstrated in enteric glial cell models that PS-NPs accelerate the aggregation of mutant A53T α-synuclein, disrupt mitochondrial membrane integrity, and impair lysosomal function, collectively exacerbating dysregulation of the mitochondrial-lysosomal axis [41]. Intervention studies reveal that melatonin effectively mitigates PS-NPs-induced mitochondrial dysfunction and dopaminergic neuron loss by modulating mitochondrial autophagy pathways—notably through restoring AMPK/ULK1 signaling equilibrium. [32].

Dysregulation of mitochondrial Ca^{2+} homeostasis is implicated in PD pathogenesis [89]. Mitochondrial calcium dysregulation is a key contributor to mitochondrial dysfunction in PD [90]. Excessive mitochondrial Ca^{2+} uptake or impaired efflux promotes ROS generation and membrane potential dissipation, culminating in neuronal apoptosis [91]. Liang et al. demonstrated that exposure to polylactic acid (PLA) MPs and their oligomers induces mitochondrial calcium overload in midbrain neurons by upregulating MICU3, a key mitochondrial Ca^{2+} uptake regulator, thereby initiating mitochondria-dependent apoptotic pathways [38]. Imbalanced mitochondrial Ca^{2+} homeostasis not only exacerbates oxidative stress but also activates the unfolded protein response and pro-inflammatory signaling cascades, establishing a self-amplifying neurodegenerative loop [31].

In a 28-day repeated oral gavage experiment in mice, Liang et al. established a clear dose-response relationship between the extent of biodegradable MP degradation and mitochondrial dysfunction. Complete gastrointestinal degradation mitigated mitochondrial impairment by limiting NP formation and systemic distribution. In contrast, incomplete degradation released more toxic oligomeric NPs, aggravating Ca^{2+} dysregulation and ultimately inducing PD-like neurodegeneration [38]. These findings provide a new perspective on the possible health risks associated with biodegradable plastics, suggesting that promoting complete gastrointestinal degradation may represent an effective strategy to mitigate NP-associated neurotoxicity.

Ferroptosis

Ferroptosis represents a distinct type of programmed cell death that relies on iron (Fe), and is characterized by mitochondrial dysfunction, dysregulated Fe metabolism, excessive lipid peroxidation (LPO), and glutathione depletion. These interconnected processes collectively promote oxidative stress and neuronal injury, which is now recognized as a potential pathogenic mechanism in PD [92,93]. Neuroimaging and pathological studies establish a correlation between Fe deposition in the SNpc and dopaminergic neuronal loss in PD patients [94,95], indicating that disrupted Fe homeostasis represents a critical factor in PD neurodegeneration. Excessive Fe accumulation triggers ferroptosis in dopaminergic neurons [96]. This form of cell death has also been documented in SH-SY5Y neuroblastoma cells treated with the dopaminergic toxins 1-methyl-4-phenylpyridinium (MPP^+) and 6-hydroxydopamine (6-OHDA) [97,98]. Similar ferroptotic features have been observed in the MPTP-induced murine model of PD [99], further supporting the contribution of ferroptosis to PD-related neurodegeneration.

Mitochondrial dysfunction is intimately associated with ferroptosis. Morphologically, ferroptotic cells retain intact nuclei but exhibit distinct mitochondrial ultrastructural abnormalities. Erastin, a canonical ferroptosis inducer, has been reported to enhance ferroptosis in mitochondria-depleted cells by stimulating mitophagy [100,101]. Mitochondrial dysfunction enhances the production of ROS, which serve as critical regulators of cell fate and central mediators of ferroptosis [102]. Mitochondrial lipid peroxidation is also essential for ferroptosis triggered by depletion of cysteine or glutathione [103]. Additionally, MPs and their adsorbed heavy metals (e.g., cadmium [Cd], Fe) can accumulate in the brain and compromise mitochondrial integrity. Studies indicate that PS exposure induces mitochondrial cristae fragmentation, reduces membrane potential, and inhibits electron transport chain complex activity in murine brains—collectively exacerbating ROS generation. Fe overload triggers direct mitochondrial membrane lipid peroxidation via Fenton reaction-derived hydroxyl radicals, while Cd impairs mitochondrial antioxidant defenses by suppressing glutathione peroxidase 4 (GPX4) activity. This combined action synergistically promotes ferroptosis [92].

Fe balance is maintained through Fe metabolism-associated proteins, such as transferrin receptor 1 (TfR1), divalent metal transporter 1 (DMT1), and ferroportin (Fpn). Cellular Fe uptake primarily involves endocytosis via TfR1 and transmembrane transport mediated by DMT1[104], whereas Fpn functions as the major Fe efflux transporter [105]. Dysregulation of these Fe-regulatory proteins disrupts Fe homeostasis and leads to intracellular Fe overload, a key driver of ferroptosis [106]. Studies demonstrate that MPs act as Fe vectors, facilitating neuronal Fe influx through DMT1 upregulation while concurrently suppressing the Fe exporter Fpn. This dual dysregulation results in pathological accumulation of intracellular ferrous ion (Fe^{2+}). Excess Fe^{2+} accelerates the Fenton reaction, generating hydroxyl radicals that initiate peroxidation of polyunsaturated fatty acids (PUFAs). The resultant toxic lipid peroxides, like 4-hydroxynonenal, compromise membrane integrity and activate ferroptosis execution pathways [92].

5. Conclusions

MPs/NPs, as pervasive environmental contaminants, infiltrate humans through multiple exposure routes, traverse biological barriers, and accumulate in the central nervous system—constituting a novel environmental hazard for PD pathogenesis. This review systematically elucidates core pathways through which MPs/NPs drive PD pathology via multidimensional molecular mechanisms: (1) MPs/NPs facilitate α-synuclein oligomerization and fibrillation by hydrophobically adsorbing its NAC domain. Simultaneously, MPs/NPs impair lysosomal degradation pathways, exacerbating intraneuronal α-synuclein accumulation and promoting the formation of Lewy bodies. (2) Amplification of neuroinflammatory cascades: MPs/NPs activate the microglial NF-κB pathway, inducing M1 polarization and pro-inflammatory cytokine release (TNF-α, IL-1β), ultimately resulting in dopaminergic neurodegeneration in the substantia nigra. (3) Disruption of the bidirectional gut-brain axis: MPs/NPs compromise intestinal barrier integrity by downregulating key tight junction proteins like ZO-1 and occludin, induce dysbiosis (elevated F/B ratio, reduced SCFA), and facilitate systemic translocation of endotoxins. These changes collectively trigger neuroinflammation via hematogenous and vagal pathways. (4) Mitochondrial homeostasis imbalance: MPs/NPs inhibit mitochondrial CI activity, resulting in ATP depletion and accumulation of ROS. Through AMPK/ULK1 signaling pathway activation, they induce excessive mitophagy and initiate calcium overload-dependent apoptosis. (5) Excitotoxicity and ferroptosis induction: MPs/NPs reduce astrocytic glutamate uptake by downregulating EAAT2, resulting in excitotoxic neuronal injury. In parallel, MPs/NPs act as vectors for Fe, promoting intracellular Fe^{2+} accumulation via DMT1 upregulation and Fpn suppression. This facilitates heavy metal-catalyzed lipid peroxidation and inactivation of GPX4, ultimately culminating in ferroptosis.

Current research exploring the relationship between MP exposure and PD pathogenesis is

significantly limited. Foremost, most existing studies rely on animal models (e.g., mice, zebrafish, *C. elegans*) or in vitro cell experiments, whereas the chronic effects of human exposure, as well as toxicity mechanisms at environmentally relevant doses, remain incompletely characterized. Secondly, the pharmacokinetics of MPs in vivo, the mechanism of BBB penetration and their spatial distribution within brain tissue remain poorly understood. The differential effects of particles with varying sizes, surface charges, or chemical properties require systematic evaluation. Moreover, current studies tend to assess MPs as isolated contaminants, whereas real-world exposures involve complex mixtures containing heavy metals and organic pollutants. The synergistic or antagonistic interactions influencing PD pathogenesis need further exploration.

6.Future directions

To address the current research gaps and enhance the scientific rigor of MPs/NPs -PD studies, future research should adopt standardized, interdisciplinary, and translation-oriented designs. The following specific directions are proposed to better elucidate the underlying mechanisms and assess potential risks:

(1) Conduct large-scale longitudinal cohort studies integrating exposure assessment and neurological outcomes.

Future research should prioritize prospective cohort studies designed to integrate detailed assessments of individual MPs/NPs exposure—using methods such as environmental monitoring, biomonitoring, and questionnaires—with longitudinal evaluation of PD progression, including relevant biomarkers, neuroimaging, and clinical symptoms. This approach is essential for establishing causality, quantifying dose-response relationships, and identifying susceptible populations.

(2) Develop advanced experimental models that mimic realistic human exposure scenarios.

Current models often use high-dose or short-term exposures that don't reflect real-world chronic, low-level MPs/NPs accumulation. Future work should employ chronic exposure models with environmentally relevant concentrations, mixed polymer types, and combined pollutants (e.g., MPs with adsorbed heavy metals or organic chemicals). These models should also incorporate aging, genetic susceptibility, and comorbidities to better simulate human disease progression.

(3) Elucidate the pharmacokinetics and neuroinvasive pathways of MPs/NPs in vivo.

Mechanistic studies should focus on the dynamics of MPs/NPs absorption, distribution, metabolism, and excretion, with particular emphasis on their ability to cross the BBB, olfactory nerve, and gut-brain axis. Moving beyond mere detection, research must leverage cutting-edge

spatial-omics and molecular imaging techniques (e.g., PET with radiolabeled polymers) to precisely map accumulation hotspots and unravel consequent molecular perturbations in neuroanatomical areas central to PD pathology, notably the substantia nigra and striatum.

(4) Systematically evaluate the differential neurotoxicity of MPs/NPs based on physical and chemical properties.

Future research must systematically compare how MPs/NPs properties—including size, shape, surface charge, polymer type, and degradation state—influence PD-related pathways. This requires the establishment and adoption of standardized protocols for particle characterization and reporting. Such harmonization is essential to enable meaningful cross-study comparisons, identify the most hazardous particle profiles, and ultimately inform science-based regulatory thresholds and safety guidelines.

(5) Explore preventive and therapeutic strategies targeting MPs/NPs-induced neurotoxicity.

Intervention research should prioritize the evaluation of agents capable of mitigating MPs/NPs toxicity, including antioxidants, anti-inflammatory compounds, enhancers of lysosomal function, and gut microbiota modulators. Concurrently, it is imperative to expand the scope of inquiry beyond biomedical interventions to encompass environmental and policy-oriented studies. Such research should critically assess strategies for reducing human exposure through source control of plastic pollution, improved waste management systems, and the development of safer, effective biodegradable alternatives.

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Author Contributions

L.L. contributed to conceptualization, data curation, and writing the original draft. J.L. and S.Z. performed formal analysis and investigation. Z.Z. provided resources, visualization, and validation. P.X. supervised the work, managed the project, and contributed to writing – review and editing. W.G. supervised the work and participated in writing – review and editing. Z.L. supervised the work and engaged in writing – review and editing. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 1

Overview of the literature investigating MNPs exposure and associated PD-related neurotoxicity effects

Subject	MNPs	Exposure test	Neurotoxic effects	Reference
NACore	PS（50 nm, negatively charged）	In vitro co-incubation; PS (20, 200 μg/mL) for 20 min - 48 h	Promotes NACore amyloid aggregation, induces hydrophobic interaction-mediated NACore-nanoplastic binding, enhances production of toxic oligomers	[34]
Human α-synuclein protein	PE (34-50 μm); PVC (34-50 μm); PS (100 nm)	In vitro co-incubation; MNPs (0-100 μg/mL); Short-term incubation	Alters α-synuclein secondary structure and promotes amyloidogenic oligomer formation. PS-MPs are the most potent due to their small size, impairing protein biological activity	[46]

			relevant to α-synuclein aggregation in PD	
C. elegans; Human neuroblastoma cells (SH-SY5Y)	PS (25 nm)	In culture medium; C. elegans: 10-1000 μg/L PS, 1 day for short-term, 5-7 days for long-term; Human cells :15 mg/L PS, for 1 day	Increases α-synuclein aggregation, induces dopaminergic neuronal degeneration, and causes locomotor dysfunction in C. elegans. PS penetrates human cells and promotes α-synuclein accumulation	[39]
Mouse primary neurons; Nontransgenic CD1 mice	PS (39.5±0.7 nm, 115.6±34.3 nm)	Neurons: in culture medium, 1 nM PS for 12-48 h; Mice: intracranial injection into dorsal striatum (15 μg PS + 4.5 μg α-synuclein	Promotes α-synuclein aggregation and accumulation of pS129-α-synuclein. Impairs lysosomal function and autophagic flux in neurons. Enhances α-synuclein	[35]

		fibrils) for 2 months	pathology aggregation and dissemination in mouse brain, accelerating PD-like pathogenesis	
Mouse microglial BV2 cells	PS (480±30.3 nm)	In culture medium; 25-100 μg/mL PS for 24-72 h	Activates microglia and triggers neuroinflammation via HRAS-PERK-NF-κB pathway, upregulating pro-inflammatory cytokines (TNF-α, IL-1β)	[37]
A53T mice	PS (1 μm, 5 μm)	Oral gavage; 10^5 particles/L per day for 30 weeks	Accelerates PD-like pathogenesis: induces dopamine neuron degeneration, movement disorders, and α-synuclein aggregation. Damages intestinal barrier (mucosal, immune, microbial),	[31]

			triggers excessive ROS and sustained mitochondrial unfolded protein response, promoting neuroinflammation.	
C57BL/6J mice	PS	Oral gavage; 10 mg/kg for 2 months	Inhibits astrocytic EAAT2 expression in mPFC, disrupting glutamate cycling and inducing anxiety/depressive-like behaviors. EAAT2 activation (LDN-212320) rescues these deficits.	[66]
Differentiated SH-SY5Y cells; C57BL/6J mice	PS (50nm)	Cells: in vitro incubation, 0.5-500 μg/mL PS for 48 h. Mice: oral gavage (250 mg/kg/day, PS) + intraperitoneal injection (10	Disrupts mitochondrial complex I function, activates AMPK/ULK1 pathway to induce excessive mitophagy. Causes mitochondrial dysfunction,	[32]

		mg/kg/day, melatonin),28 days	dopaminergic neuron damage, and motor impairments in mice. Melatonin alleviates these deficits by regulating mitophagy.	
C57BL/6J mice	PS (50nm)	Oral gavage, 0.25-250 mg/kg, 28 days	Induces PD-like pathology: causes energy metabolism disorder and dopaminergic neuron loss in SNpc and striatum, and triggers motor dysfunction	[33]
Mouse enteric glial cells	PS (50nm)	In vitro incubation, A53T αS (5-15 μM) + PS (200 μg/mL) for24 h	Accelerates A53T α-synuclein aggregation, impairs mitochondrial membrane integrity and lysosomal function, exacerbates mitochondria-lysosome axis dysfunction. Mediates	[41]

			intestinal barrier dysfunction and inflammatory signaling, contributing to PD neuroinflammation via the gut-brain axis.	
C57BL/6J mice	PLA MPs and their oligomers (~2.5 μm)	Oral gavage (2.5 mg/kg, 25 mg/kg) for 28 days	Upregulates MICU3 expression, induces mitochondrial calcium overload in midbrain neurons and mitochondrial-dependent cell death. Exacerbates PD-like neurodegeneration via incomplete degradation; complete degradation mitigates mitochondrial dysfunction	[38]

MNPs: micro/nanoplastics； PD: Parkinson's disease; PS: polystyrene; PE: polyethylene; PVC: polyvinyl chloride; EAAT2: excitatory amino acid transporter 2; mPFC: medial prefrontal cortex; SNpc: substantia nigra pars compacta.

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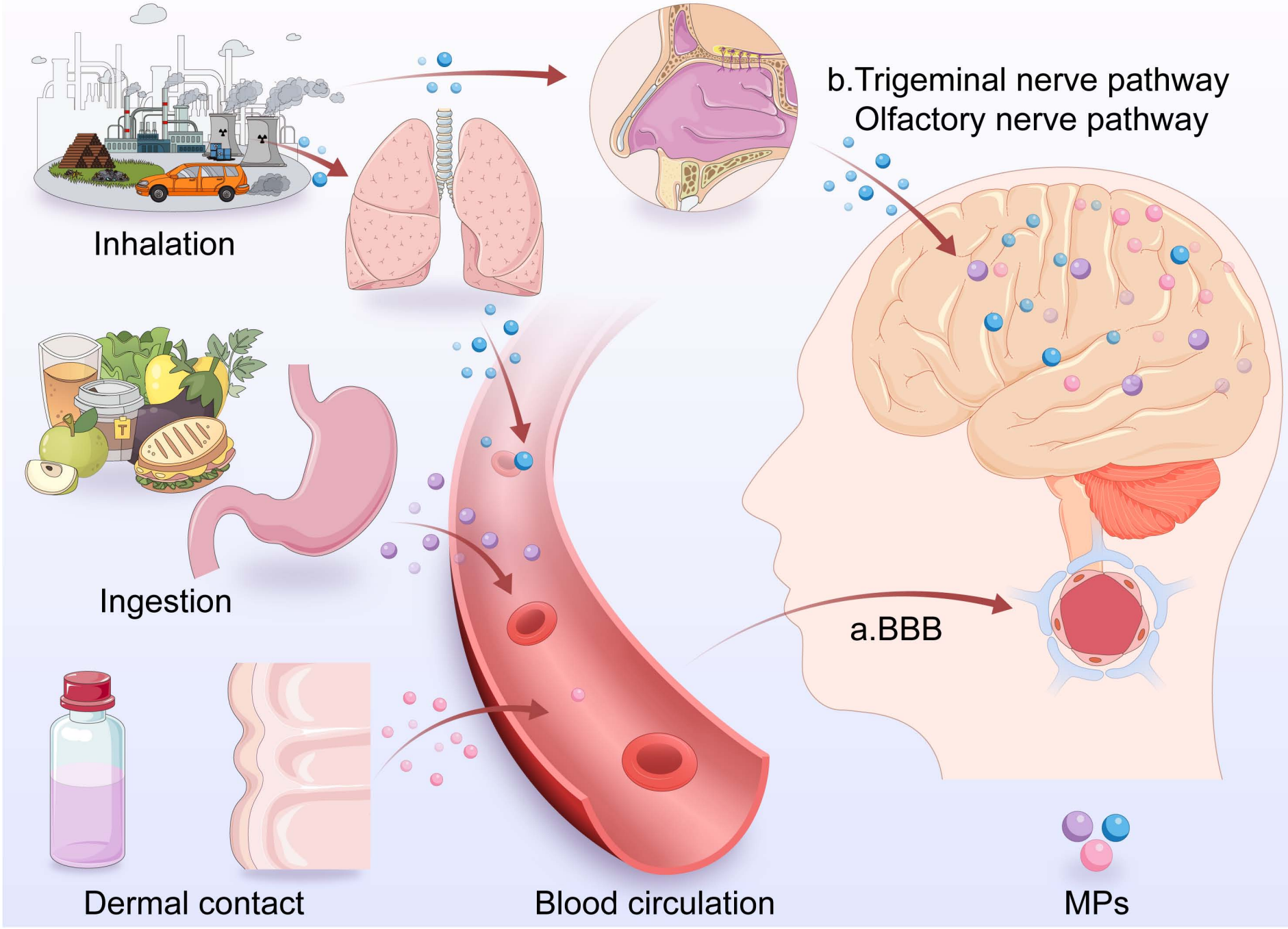
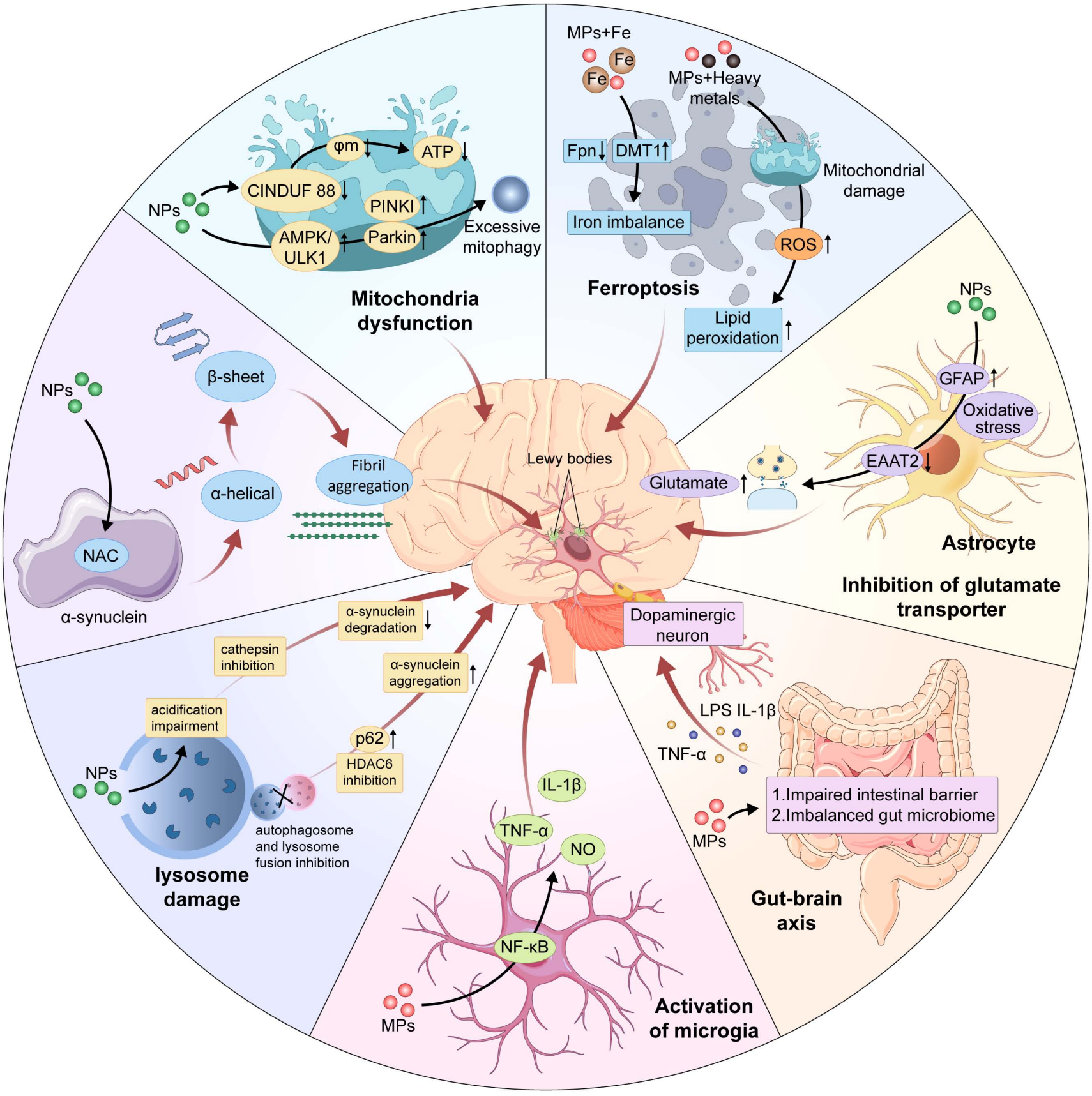
Fig.1.MPs exposure routes and brain entry mechanisms

Fig2. Multipath mechanisms of MPs in exacerbating PD pathogenesis


Inhalation
b.Trigeminal nerve pathway
Olfactory nerve pathway
Ingestion
a.BBB
Dermal contact
Blood circulation
MPs


Mitochondria dysfunction
NPs
φm
ATP
CINDUF 88
PINKI
AMPK/ ULK1
Parkin
Excessive mitophagy
Ferroptosis
MPs+Fe
Fe
Fe
MPs+Heavy metals
Fpn
DMT1
Iron imbalance
Mitochondrial damage
ROS
Lipid peroxidation
Astrocyte
NPs
GFAP
Oxidative stress
EAAT2
Glutamate
Inhibition of glutamate transporter
Lewy bodies
Fibril aggregation
β-sheet
α-helical
NPs
NAC
α-synuclein
Dopaminergic neuron
α-synuclein degradation
cathepsin inhibition
α-synuclein aggregation
acidification impairment
p62
HDAC6 inhibition
NPs
autophagosome and lysosome fusion inhibition
lysosome damage
LPS IL-1β
TNF-α
MPs
1.Impaired intestinal barrier
2.Imbalanced gut microbiome
Gut-brain axis
IL-1β
TNF-α
NO
NF-κB
MPs
Activation of microgia