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■ RESEARCH ARTICLE

The Effects of Micro and Nanoplastics on the Brain and Gene Expression

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ABSTRACT: In today's world, it is impossible to avoid coming into contact with micro- and nanoplastic (MNP) particles: from 1950 to 2015, the world produced approximately 6.3 billion tons of plastic in total. MNP particles infiltrate the air, water, and food. As a result, we ingest plastics every day throughout our lives by using ordinary things, such as tea bags, paper cups, water bottles, or toothpaste, and by eating vegetables and meats. In experimental rodents and fish, plastic particles have been detected within the brain, muscles, lungs, liver, kidneys, heart, and GI tract. MNPs that enter the body and breach the brain-blood barrier (BBB) inhibit crucial enzymes and neurotransmitters, in particular acetylcholinesterase (AChE), and induce oxidative stress in cells, leading to Alzheimer's and Parkinson's diseases. We analyze the mechanisms behind the neurotoxicity of MNPs by examining the causes of neurotransmitter inhibition and cellular damage, and their effects on the brain and gene expression. This review article highlights the existing research gaps and the urgency for more research on this topic to gain a more comprehensive understanding of the potential health risks of MNP exposure. Moving forward, potential solutions, including the use of probiotics, enzymes, and vitamins, must be explored and utilized.

KEYWORDS: Cellular and Molecular Biology, Neurobiology, Neurotoxicity, Micro and Nanoplastics (MNPs), Blood-Brain Barrier (BBB), Oxidative Stress; Acetylcholine (ACh).

■ Introduction

Throughout the past two decades, plastic has been continuously infiltrating our daily lives - through our food, drinks, air, and contact with the skin. On average, the world annually produces approximately 359 million tons of plastic, only about 15% of which has been recycled over the last 30 years.[1] Polystyrene and polyethylene, two of the most widespread types of plastic used in manufacturing, have the highest environmental pollution levels and can absorb a broad range of environmental pollutants. They are often used in plastic-related studies.[2] MNPs are extremely small fragments of plastic that can be categorized as either primary or secondary. Primary MNPs, which are added to cosmetics, fabrics, and paints, were originally manufactured in a very small size on purpose. Secondary MNPs come from larger pieces of plastic, such as car tires and fishing nets, that are degraded through natural means including photodegradation, sand and water abrasion, and erosion.[3] Plastic particles are considered microplastics (MPs) when they are less than 5 mm in size, and nanoplastics (NPs) when they are smaller than 0.1 μm.[4] The extent of plastics' impact on human health has only started to be uncovered. MNPs have been found in several major organs, including the heart, kidneys, gut, lungs, liver, placenta, and brain.[5,6] In multiple studies using adult zebrafish and in one study with tilapia fish, MNP accumulation was present in the intestines, gills, liver, and brain.[3,7-9] It is estimated that humans consume around 80 grams of plastic per day via fruits and vegetables that have been contaminated through the soil.[5]

Information on how plastics impact human organs, especially the brain, is still scarce. Currently, existing experiments observed that interactions between MNPs and brain tissue trigger neurodegenerative processes. These processes included elevated acetylcholine (ACh) levels, which suggests that the MNPs are inhibiting acetylcholinesterase (AChE) activity, and increased malondialdehyde (MDA) levels, which is a marker for oxidative stress.[3] These results indicate that MNPs can be dangerous for brain health and gene expression. This review article aims to explain the potential neurotoxic and genotoxic health risks MNPs pose to human health and emphasizes the critical need for more research to be done on this topic by highlighting research gaps in current studies.

Factors that Influence the Neurotoxicity and Cytotoxicity of Plastic Particles:

Physical Characteristics:

The shape and size of a particle can tell a lot about its neurotoxic potential. Sarasamma *et al.* noted that based on experimental results, the neurotoxicity of polystyrene nanoplastics (PS-NPs) on aquatic biota heavily relies on the size, shape, and composition of the PS-NPs. An experiment on wild-type mice found that only two hours after exposure, the 0.293 μm particles (smallest sized particles out of all the experimental groups - 9.55 μm, 1.14 μm, and 0.293 μm) were detected in brain tissue. This indicates that the smallest-sized particles were able to directly cross the BBB.[2] This suggests that the smaller the particle size, the easier it is for it to permeate the BBB.

Another study that tested the cellular uptake of MNPs in HeLa cells of 10 nm, 15 nm, 25 nm, 40 nm, 50 nm, and 500 nm radii found that only the smaller particles - 10 nm, 15 nm, and 25 nm, were able to penetrate the cell membrane.[10] This

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is similar to the findings of Kopatz *et al*., which stated that NPs less than 0.5 μm in size could come into and out of the cell through the process of transcytosis and potentially interact with intracellular organelles. Size can even influence how deep into an organ an MNP can go. MNPs less than 20 μm in size can penetrate organ barriers and those less than 10 μm in size can cross the cell membrane, cross the BBB, and reach brain tissue.[5]

Intrinsic Additives:

Additives are supplementary chemicals added during the process of plastic manufacturing that give plastics new, unnatural characteristics such as inorganic pigments and increased shininess. Stabilizing additives make plastic more durable by making it more resistant to UV radiation, humidity, bacterial degradation, mold, and weathering. Most of the time, additives are not polymerized with plastic molecules, so they easily contaminate the soil, water, and air in high amounts.[5] When in the natural world, MNPs can reach plants and aquatic biota, which humans consume later on up the food chain. This also means that these toxic additives can be left behind in plastic-packaged food and cause neural and cellular issues (Table 1).

Table 1: Neurotoxic and Cytotoxic Effects of Heavy Metal Additives in Plastic Particles. Adapted from Campanale *et al*., Table 1. "Main use of heavy metals as additives in polymer products and their effects on human health". Heavy metal additives, especially lead, manganese, and mercury, exacerbate the neurotoxic and cytotoxic effects MNPs pose to humans.

Heavy Metal Additive	Purpose of Additive	Neurotoxic/Cytotoxic Effects	References
Lead	Inorganic pigments, heat stabilization, and the prevention of UV degradation	Oxidative stress, Central Nervous System (CNS) disturbance (including damage to motor functions), harm to DNA reparation system, excess Reactive Oxygen Species (ROS) production, changes in apoptosis related genes, blocks neurotransmitter release, lowers Brain-Derived Neurotrophic Factor (BDNF) expression, impaired pre- and postsynaptic signaling systems, increased Blood-Brain Barrier (BBB) leakage, gastrointestinal (GI) tract issues	11, 12
Bromine	Flame retardant	Apoptosis, genotoxicity	5
Manganese	Inorganic pigments	Accumulation in the mitochondria of brain cells and impaired Adenosine Triphosphate (ATP) synthesis, harm to dopaminergic system, emotional dysfunction, neurodegenerative diseases, memory dysfunction, motor incoordination	11, 13
Mercury	Biocide (used to preserve materials by protecting from viruses and stopping microorganism, insect, and animal related degradation)	AChE inhibition, excess ROS formation, changes in DNA structure, interaction with brain macromolecules, changes in activity levels of energy related enzymes, lipid peroxidation, neurobehavioral changes, reduced motor neuron function, neuroinflammation	11, 14, 15
Barium	Inorganic pigment, UV stabilization	Metabolic, mental, and neurological alterations; bioaccumulation in the gut	5, 16
Cadmium	Inorganic pigments, heat stabilization, and prevention of UV degradation	Lipid peroxidation, DNA damage, apoptosis, altered gene expression	11, 17
Cobalt	Inorganic pigments	Development of excess ROS and problems with regulation of bodily senses	5
Chrome	Inorganic pigments	Free radical generation, severe issues throughout the body including in the GI tract and in the brain, potential death	5, 11
Copper	Biocide	ROS formation, excess oxidation, and DNA structural damage	11
Arsenic	Biocide	Neurological disorders, issues with GI tract, inhibited DNA reparation, increased ROS production, oxidative stress	11, 18-20

Extrinsic Co-contaminants:

Particle surface chemistry and charge both influence the neurotoxic potential of MNPs. Several studies have demonstrated that oxygen-containing groups on plastic surfaces make oxidized MNPs more neurotoxic than non-oxidized MNPs. The oxidation aggravates the existing neurotoxic problems the MNPs present.[21] MNPs can also bring co-pollutants such as pathogenesis microorganisms, extrinsically attached heavy metals, pharmaceuticals, and persistent organic pollutants.[3,15] The physicochemical qualities of plastic particles allow co-pollutants to latch onto MNPs through chemical interactions such as hydrophobic interactions and Van der Waals forces.[6]

The biomolecular corona, a layer of proteins, organic matter, biomolecules, and chemical and biological contaminants, that form on the surface of MNPs as they interact with the environment before they enter the body, can also increase or decrease their neurotoxic potential.[2] It contributes to the toxicity of MNPs as it may contain co-pollutants that latch onto the plastic particles and enter the body with them. Depending on the composition of the biomolecular corona, it can also make it easier or harder for the plastic to cross the BBB.[2]

The Entrance and Distribution of MNPs into the Body, Brain, and Cells:

Entrance Pathways:

The three main ways MNPs enter the body are through ingestion, inhalation, or dermal contact.[6] We ingest plastics by using ordinary things, such as tea bags, paper cups, or toothpaste, and by eating vegetables and contaminated meat (especially seafood).[3,6] Bottled water is estimated to contain 0.09 MPs/g, while sugar contains approximately 0.44 MPs/g.[5] Paper cups also have an internal plastic lining that releases MPs and toxic, heavy metals when exposed to hot beverages. Inhalation of MNPs occurs whenever we breathe in polluted air or dust.[6] Lastly, when we come into contact with items that contain primary MNPs, such as personal care products, the plastic particles can enter deep into the skin through dermal contact.[3] Usually, only MNPs less than 20 μm in size are able to enter organs and that 10 μm and less can penetrate the cell membrane, BBB, and brain tissue.[5] People working in nanoparticle manufacturing industries and people living around factories are most at risk for plastic inhalation and dermal contact.[6]

After entering into the body, MNPs immediately join blood circulation which distributes these particles to various organs.[6] For the plastic particles to reach brain tissue, they have to breach the BBB, a semipermeable membrane that lies between the blood and the brain to protect the brain from harmful pathogens and toxic substances. It makes it very difficult for any ions or molecules to pass through without any help. However, there are a few possible ways for a plastic particle to cross this seemingly impenetrable barrier or even enter into a cell.

Blood-Brain Barrier (BBB) Permeability:

The composition of the biomolecular corona of an MNP plays a big role in its ability to cross the BBB. A study conducted at the Medical University of Vienna, Austria, in 2022 simulated four different models of polystyrene plastic transfer through the BBB. Each plastic particle had a different biomolecular corona: pristine plastic, particles with 100 and 150 cholesterol molecules corona, and particles with 40 protein molecules corona. The simulation used a dioleoylphosphatidylcholine (DOPC) membrane (common substitution for BBB in studies) and observed that when an MNP with a cho-

lesterol corona is approaching, the DOPC molecules rearrange by pointing their hydrophobic tails toward the hydrophobic cholesterol particles.[2] Slowly, the plastic is engulfed, and the cholesterol molecules diffuse throughout the membrane, which disentangles the membrane's polymer chains. The plastic gets stuck in the membrane and cannot travel any further because the cholesterol corona diffuses once the MNP is in the BBB. This alters the structure of the membrane, harming its functioning potential as well.[2] After conducting calculations, it was found that pristine plastic particles can be absorbed into the membrane, but the driving force of cholesterol-coronated MNPs was stronger. This suggests that cholesterol molecules facilitate MNP entrance into the BBB, but once the MNP is in, it cannot get out into brain tissue. MNPs with a protein corona necessitated a large amount of energy to enter, which hampered their ability to enter the membrane.[2]

BBB leakage is another potential route for MNPs to pass into brain tissue. This can be caused over time through aging or by neurodegenerative disorders. A study conducted in 2021 at the Department of Life Sciences at the National Central University of Taiwan found that after eight weeks of PS-MP exposure, fragments of polystyrene were detected in the hippocampus. After comparing PS-MP mice and control mice, an increase in BBB leakage was found in the treated mice.[7] This suggests that the BBB becomes more easily permeable when exposed to higher concentrations of MNPs and for longer time periods. One more potential way the MNPs can breach the BBB is by using portions of the brain where the BBB is absent as a pathway. In some brain regions, such as in circumventricular organs, the BBB does not exist to allow for the exchange of hypothalamic hormones between the blood and the brain. MNPs can exploit this function as a way to interact with brain tissue.[7]

Entrance of MNPs Into the Cell and DNA/Gene Expression Damage:

MNPs are also capable of causing DNA damage and changes in gene expression.[2,22] Mediterranean mussels exposed to polyethylene and polystyrene MPs experienced DNA damage and changes to the nucleus.[3] Plastic particles can potentially enter the cell via endocytosis, a process where the cell membrane engulfs and absorbs its target particle.[2] MPs that are 0.5 μm or larger can potentially penetrate the cell membrane by binding to a cell surface receptor that eventually participates in phagocytosis, a process where the cell digests a particle enclosed by part of the cell membrane. NPs 0.5 μm or smaller can be transported across the cell in a vesicle formed by the cell membrane through a process known as transcytosis (Figure 1).[2] Particles that enter the cell can diffuse through either passive or active diffusion. Passive diffusion is when particles have two areas of different concentrations, and the particles from the more highly concentrated portion naturally flow to the less concentrated portion. In this case, it allows the plastic particles to directly enter the cell. This process usually pertains to smaller MNPs, which is dangerous because it could allow them to interact with intracellular organelles.[10] Active transport is when ATP is required to push particles from the lower concentration to the higher concentration, going against the natural flow. Caveolae-mediated endocytosis is a type of active transport that allows cells to select and regulate the substances being brought into the cell and can occur when large MNPs try to enter the cell. The large MNPs form aggregates that are engulfed by the cell membrane and carried into the cell.[10]

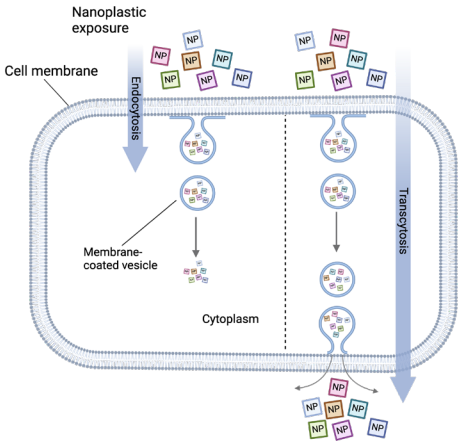

Figure 1: This diagram shows how MNPs penetrate the cell membrane and enter the cell, causing damage and potentially cell death. MNPs 0.5 μm or larger enter via endocytosis, while those 0.5 μm or smaller can enter through transcytosis (Created in BioRender. Ogai, V. (2025) https://BioRender.com/z14k960).

In the previously mentioned study that tested the cellular uptake of MNPs in HeLa cells, they discovered that smaller-sized MNPs were found in the cytoplasm, but not in the nucleus. This means that there was most likely no direct interaction between the MNPs and DNA fragments. However, cell death was nearly 100% at higher concentrations of 10 nm and 15 nm MNPs,[10] indicating that at higher concentrations, MNPs make the cell membrane more easily permeable, which is similar to the findings of Lee *et al*. ROS levels increased as smaller-sized (10 nm and 15 nm) MNP concentrations increased.[10] Elevated ROS levels cause cellular dysfunction and oxidative stress, a common sign of neurodegeneration. This can lead to cell death and the downregulation of anti-apoptotic genes and ROS protection genes. The MNPs in the cytoplasm most likely broke apart after being internalized, which allowed them to directly contact cellular organelles.[10] This demonstrates the obvious cytotoxicity and harmful health effects of the cellular uptake of MNPs. The ability of MNPs to permeate the cell membrane of neuronal cells specifically also has to be investigated to gain a more comprehensive understanding of how the cytotoxic effects of MNPs in other cells like HeLa cells are transferable to the effects of MNPs on brain cells.

Concluding Paragraph:

Plastic particles are able to cross organ barriers and even cellular barriers. Once these MNPs successfully breach the BBB and cell membrane, they can cause a variety of cytotoxic and neurotoxic problems by damaging the natural structure and functioning of cellular components and the organ tissues they interact with. This can cause many chronic issues as MNPs bioaccumulate in the body over time. For example, MNPs in the brain can damage neuronal tissue and thus the natural flow

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of brain activity by inhibiting important neurotransmitters and eventually leading to neurodegeneration.

Neurodegenerative Effects:

Intro Paragraph:

The global number of dementia diagnoses has been rapidly growing over the past two to three decades. Some researchers hypothesize that it is caused by the worsening worldwide plastic pollution crisis.[7] The broad results of research on MNP consequences on the health of the human brain suggest that plastic particles that interact with neural tissue inhibit neurotransmitter activity and contribute to the emergence of ROS and oxidative stress, which causes neuronal cell death.[23] This can cause behavioral changes, neuroinflammation, and the reduced expression of certain genes and proteins involved in brain function. This also contributes to memory loss and can accelerate the development of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS).[3,24] MNPs have even been found to alter brain structure and thus affect neurobehavioral patterns. Crucian carp exposed to MNPs exhibited decreased brain mass and morphological changes in the cerebral gyri. This structural change caused the behavior patterns of the carp to alter.[3] Additionally, the gut-brain axis has also been found to play a role in MNP-induced neurotoxicity. MNPs that damage brain tissue can also damage the gut microbiome, and vice versa.[21]

AChE and Oxidative Stress:

ACh is an excitatory neurotransmitter that helps an electric signal send a certain message throughout the brain. AChE is an enzyme that accelerates the hydrolysis of ACh.[21] AChE breaks ACh down into choline and acetate so that post-synaptic nerves do not get overstimulated (Figure 2). The overstimulation of post-synaptic nerves results in a process known as excitotoxicity, which severely damages neuronal functioning and leads to apoptosis. Since MNPs inhibit AChE activity, this allows cholinergic neurons to secrete ACh unchecked, which leads to a buildup of ACh in the synaptic cleft (Figure 3). This excessively promotes neuron excitability, hampers neurotransmission, and alters neurobehavioral patterns. Cholinergic neurons and cholinergic synaptic signaling have exhibited susceptibility to these problems after MNP exposure.[17] When AChE inhibition is greater than 30%, it disturbs the overall workings of the CNS, making it a reliable indicator for neurotoxicity.[3]

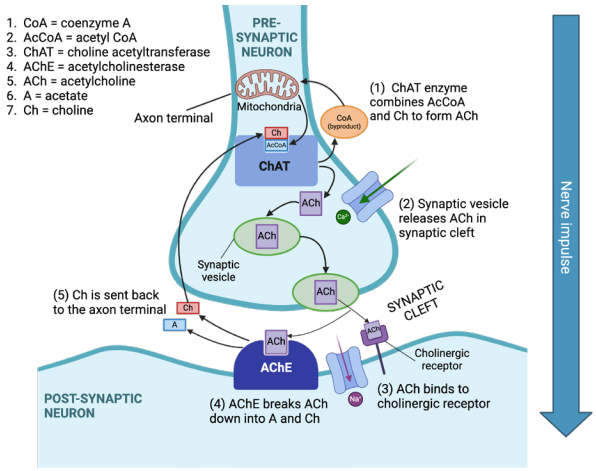

Figure 2: Visual representation of how the ACh (purple) neurotransmitter works within the brain: The ChAT enzyme (light blue) receives an AcCoA (blue rectangle) molecule and combines it with a choline molecule (red rectangle) to create a molecule of ACh. Next, a synaptic vesicle (light green) takes the ACh to the synaptic cleft, where it binds to its cholinergic receptor. While ACh is bound to the cholinergic receptor, sodium ions (dark purple circles) enter the pre-synaptic neuron, while calcium ions (dark green circles) enter the post-synaptic neuron. When the ACh neurotransmitter finishes sending its message to the post-synaptic neuron, it binds to the AChE enzyme (dark blue), which breaks it apart back into acetate (light blue rectangle) and choline. The acetate diffuses into the surrounding medium and the choline gets sent back to the axon terminal. The process repeats (Created in BioRender. Ogai, V. (2025) https://BioRender.com/y29b366).

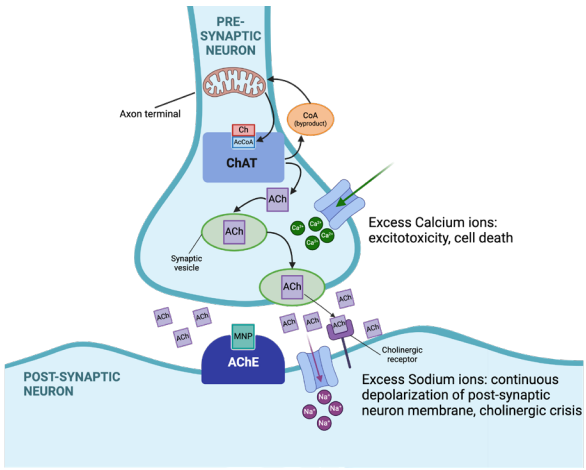

Figure 3: Visual representation of MNPs (turquoise) inhibiting AChE (dark blue) activity. The buildup of ACh (purple) in the synaptic cleft as a result of AChE inhibition causes excitotoxicity, damaging neuronal functioning. While the ACh neurotransmitter is attached to its cholinergic receptor, there is an influx of calcium (dark green circles) into the pre-synaptic neuron (to mobilize synaptic vesicles) and an influx of sodium (dark purple circles) into the post-synaptic neuron to depolarize its membrane. When there is too much ACh in the synaptic cleft, excess calcium ions enter the axon terminal of the pre-synaptic neuron, which can also cause excitotoxicity and cell death. However, when there is too much sodium continuously depolarizing the post-synaptic membrane, it can result in a cholinergic crisis. A cholinergic crisis occurs at the neuromuscular junctions between motor nerves and muscles and can cause paralysis, convulsions, and hypercapnia. This means that MNP inhibition of AChE activity can indirectly trigger a process that results in a cholinergic crisis (Created in BioRender. Ogai, V. (2025) https://BioRender.com/c69w522).

The inhibition of AChE activity has been noted in many organisms participating in studies focused on MNP neurotoxicity and is associated with neurobehavioral changes and neurological disorders.[2,25,26] Juvenile Common Goby fish were exposed to polyethylene MPs, and although there was no actual evidence of MP uptake, the fish experienced significant levels of AChE inhibition.[3] Similarly, a study using European seabass showed that fish exposed to MNPs demonstrated a 50% inhibition of AChE activity in the brain,[15] which means the overall functioning of the CNS was disturbed. This consequence was aggravated by the addition of mercury into the treated fish. The fish displayed decreased predatory performance and signs of oxidative stress.[15] A lack of antioxidants can worsen oxidative stress, cause protein damage, and contribute to cancer and neurodegenerative disease development (Figure 4). In studies surrounding MNP neurotoxicity, growing levels of oxidative stress are often correlated with lowering levels of AChE activity. However, in one study, earthworms exposed to polyethylene MNPs were found to experience increased AChE neurotransmitter activity, MDA levels, and catalase activity.[3] Increased MDA levels and catalase activity are suggestive of oxidative stress, but increased AChE activity is usually not correlated with elevated oxidative stress in the context of MNP neurotoxicity, which poses more questions.[3]

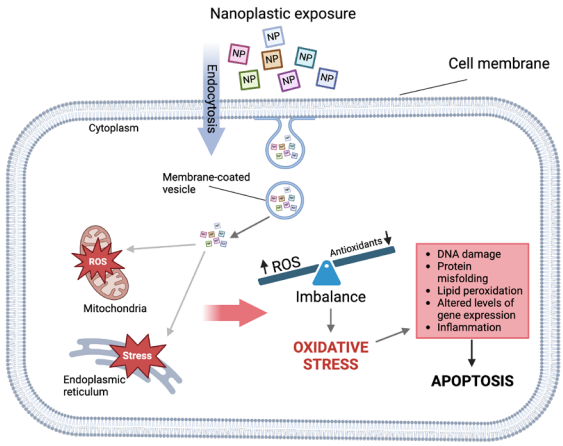

Figure 4: How NPs (multi-color squares) can enter the cell and cause oxidative stress: First, NPs are brought into the cell via a form of endocytosis. Subsequently, a membrane-coated vesicle (light blue circle) brings them to the cytoplasm of the cell. NPs' interaction with intracellular organelles leads to an influx in ROS levels. This triggers oxidative stress within the cell, which results in a variety of negative consequences that all eventually end in apoptosis. If this occurs in too many neurons, it will result in neurodegeneration (Created in BioRender. Ogai, V. (2025) https://BioRender.com/s64b548).

Effects of MNPs on the Behavior and Gene Expression:

Several biomarker analyses of zebrafish exposed to high Bisphenol-A (BPA) levels for one week showed that the plastics accumulated in brain tissue, causing issues including decreased locomotion activity and a dysregulated circadian rhythm.[8,27] Their speed was significantly reduced and they exhibited notable hypoactivity during both the light and dark cycles. At higher concentrations, NP exposure changed predator-induced fear responses, reduced aggressiveness, and altered predator avoidance patterns. The lowered levels of several neurotransmitters including dopamine and Gamma-aminobutyric acid (GABA) contributed to abnormal shoal formation.[8] NPs also elevated ROS levels, an indication of oxidative stress and pro-inflammatory responses. AChE activity was also significantly inhibited at higher NP concentration levels, which was found to correspond with anxiety-like behavior in the fish.[8] It was also found that oxytocin and vasopressin neurotransmitter levels, which both regulate learning, memory formation, and emotional processes, were reduced due to MP exposure in zebrafish.[8]

Similarly, S. Wang *et al.*, and J. Wang *et al.*, both noted that MP exposure in mice damaged learning, memory, and locomotion abilities while promoting depression-like behaviors. In the former study, MP exposure caused oxidative stress and inhibited cAMP-response element binding protein (CREB) phosphorylation which lowered ACh production.[28] In the latter study, it was also found that ACh content was significantly reduced and AChE activity was much higher in the mouse cortex/hippocampus than in the controls. Most other MNP neurotoxicity studies report an increase in ACh levels, as previously mentioned in the study focusing on earthworms, which presents more questions.[3] A reduction in ACh levels can lead to memory, thinking, and concentration problems. Additionally, MP-treated mice exhibited an increase in ROS and MDA levels, along with lowered glutathione levels.[28] It was also discovered that MP exposure inhibited the CREB/BDNF pathway, which causes neuronal death.[28] Hippocampal nerve cells became loose and disordered after MP exposure, which is similar to the irregular arrangement of nerve cells that J. Wang *et al.* observed.

In addition to neurobehavioral impairment, MNPs also hamper the expression of certain genes elicited by brain activity. Based on the findings of J. Wang *et al.* genes (Slc5a7, ChAT, Slc18a3) and proteins (ChAT and Slc18a3) that are important to cholinergic synaptic signaling pathways were damaged and downregulated after being exposed to low-density polyethylene (LDPE) MPs and oxidized-low-density polyethylene (Ox-LDPE) MPs. This disruption lowered ACh levels, induced oxidative stress, and caused neuroinflammation by up-regulating the expression of inflammation-related genes including interleukin 1 beta (IL-1β) and tumor necrosis factor α (TNF-α). This is similar to the biological mechanism that allows Alzheimer's disease to develop.[21] This means that MPs have the potential to cause Alzheimer's disease and other diseases with a similar pathogenesis.

In another study exploring the effects of MNPs on gene expression, fear conditioning, and behavioral tests were run on PS-MP-treated mice. The tests showed that the hippocampus-dependent memory of the mice was damaged and there were lower expression levels of immediate early genes (IEGs - control synaptic plasticity, learning, and memory), especially in the dentate gyrus, CA2, and CA3 subregions.[7] The dentate gyrus, CA2, and CA3 subregions of the hippocampus all play a major role in memory formation and encoding, demonstrating PS-MP's detrimental effects on neuronal activities. Several indicators of neuroinflammation were also found in PS-MP treated mice, including increased tumor-necrosis factor-alpha

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(TNF-α), interleukin 1 beta (IL-1β), and microglia activation levels in the hippocampus, as compared to control mice.[7,29]

The Gut-Brain Axis:

The gut-brain axis is the system through which the gut microbiome communicates with the brain. The vagus nerve and the connection between the BBB and the intestinal immune system are two pathways the gut microbiome uses to communicate with the brain (Figure 5).[7,21] Inflammation caused by MPs in the brain can potentially harm the gut microbiome as well.[21] Once BBB permeability is damaged, endotoxin lipopolysaccharides (LPS) can travel via peripheral circulation, enter the CNS, and accumulate in the brain, which can cause problems in the CNS and the gut.[21] When MPs invade the gut microbiome, they can travel up the gut-brain axis and cause hippocampal and cortical inflammation. In one study, it was found that the gut-brain barrier, including the gut epithelial barrier, the BBB, and the cerebrospinal fluid barrier (CSF), were destroyed in MP-treated mice.[21]

Lipopolysaccharides (LPS) (or endotoxins) are bacterial toxins and proteins that make up the outer membrane of gram-negative bacteria. LPS helps create a barrier around the pathogen to prevent antibiotics from coming into the molecule. MPs have been found to raise LPS levels, which aggravates BBB disruption and in turn, increases the movement of LPS from the blood to the brain.[21] Since the BBB became more easily permeable, this also means that it became easier for other substances including MNPs to pass through, which could worsen the existing neurotoxic effects presented by MNPs.

Since PS-MPs enter the GI tract when ingested, the vagus-nerve pathway is the most probable route PS-MPs travel through to get to the brain.[21] In a study where mice were experiencing MP-induced learning and memory disorders, vagus nerve ablation reversed and stopped any further MP-related issues.[21]

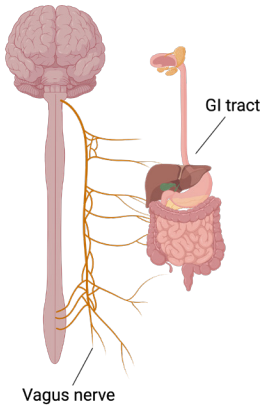

Figure 5: Visual representation of how the vagus nerve connects the brain and the GI tract. The gut microbiome communicates with the brain by sending it signals through neurotransmitters. This is a pathway MNPs can exploit to reach the brain if they originally enter the gut, and vice versa (Created in BioRender. Ogai, V. (2025) https://BioRender.com/x14h240).

In a separate study where Juvenile Discus Fish were exposed to NPs, brain ACh and dopamine concentrations increased while decreasing in the gut.[30] This demonstrates that the brain and the gut communicate to regulate the levels of neurotransmitters traveling through the gut-brain axis. The repression and overexpression of multiple genes in the neuroactive ligand-receptor interaction pathway and the serotonergic synapse pathway (both play important roles in behavioral processes, including appetite, aggression, and eating behavior) caused changes in behavioral patterns by weakening swimming capabilities and predatory instincts.[30] This indicates that ingested MPs that enter the GI tract and then travel to the brain can cause behavioral toxicities.

Concluding Paragraph:

The two main effects of MNPs on the brain are the abnormal AChE and ACh levels, and the triggered oxidative stress. In addition, MNPs have been found to downregulate the expression of genes important to neuroplasticity, memory formation, and behavioral patterns. The GI tract is also involved in how MNPs impact the brain, learning, memory, and BBB integrity via the vagus-nerve-dependent pathway. Further research still must be conducted on all the major effects of MNPs on the brain, especially on how plastics influence the ACh neurotransmitter since there have been some inconsistencies on this throughout the field. All these studies, especially the ones involving aquatic biota, suggest that predators at the top of the food chain such as humans are consuming MNPs and their co-pollutants through meat, especially seafood products.

Probiotics - A Potential Solution?

Probiotics' Reduction of Inflammatory MNP Effects:

Cellular-level probiotics can act as antioxidants, which gives cells and the GI tract the necessary properties to mitigate oxidative stress. When the gut microbiome is imbalanced, it causes an overreaction in the immune system and increases oxidative stress levels.[4] In one study, Wistar rats were exposed to BPA at high concentrations along with a combination of the *Saccharomyces boulardii* (yeast) and Lactobacillus probiotic strains.[4] The combination exhibited antioxidant characteristics by preventing lipid peroxidation (linked to neurodegeneration and free radicals). In a separate study, polybiotics were given to Parkinson's disease patients. The polybiotics were able to improve cognitive function and minimize signs of nerve injury and lipid peroxidation.[4] This is similar to the findings of Cheon *et al.*, who cultured neuroblastoma cell lines, induced neuronal damage similar to Parkinson's disease, and tested three Lactobacillus strains' effectiveness in treating brain damage. The Lactobacillus was able to upregulate the BDNF neurotrophic factor, a protein that helps maintain neuronal growth and survival.

This is comparable to the findings of J. Wang *et al.* also noted that probiotics can help prevent some of the neurotoxic effects MNPs have in mice. A combination of a probiotic strain known as *Lactobacillus plantarum* DP189 combined with galacto-oligosaccharides (GOS) (a prebiotic that increases the number of bacteria in the gut to help the immune system) was tested to see if it could reverse the neurotoxic effects of LDPE-MPs. It was found that DP189&GOS prevented neuron death and mitigated BBB and intestinal destruction.[21] It also restored ACh levels, reduced inflammation, and oxidative stress, and helped increase ChAT and Slc18a3 protein expression to different extents depending on the concentration of

MPs. It also reduced MDA content but not to a significant extent. This suggests that at higher concentrations, DP189&GOS could reverse the cognitive dysfunction caused by MP exposure.[21] Similarly, a separate study was conducted to determine the effectiveness of DP189 in treating Parkinson's disease. It was observed that α-synuclein (α-SYN) aggregation in the substantia nigra was delayed because oxidative stress and inflammation levels were reduced.[31] The Lactobacillus bacteria have been able to stimulate the antioxidant and immune systems, which aids in lowering oxidative stress, inflammation, and intestinal barrier destruction caused by MPs.[21]

Similar to probiotics, vitamins that act as antioxidants can potentially be incorporated into drugs to treat MNP-induced neurotoxicity. Vitamin E, an antioxidant that neutralizes the production of excess ROS, restored neurotransmitter levels and learning/memory functions in MP-treated mice.[28] This indicates that Vitamin E and other vitamins that can act as antioxidants including Vitamin C and Coenzyme Q10 (CoQ10) can be used to treat the harmful neurological effects of MPs. However, more research still must be conducted to corroborate the practicality of their use.

Probiotics and vitamins could potentially help with limiting the genotoxicity of MNPs as well. There have been many studies done solely on how probiotics/vitamins limit DNA fragmentation when being exposed to general pathogens, but few specifically focused on MNPs. This is an area in the field that also must still be further researched.

Discussion

Since the effect of MNPs on human neural health is still a new and developing field, there are many limitations in current experiments that prevent us from gaining a full understanding of how plastic particles act within our bodies. Several important research gaps were noticed while research was being conducted:

(1) The most notable research gap there is right now is that most experiments lack real-life MNP exposure. Virgin particle types, not the ones that are inhaled or ingested, are used in these studies. Most studies order manufactured spherical polystyrene or polyethylene particles when examining the neural effects of MNPs, instead of plastics of variable shapes, sizes, and surface qualities (that all have different levels of neurotoxicity).[3]

(2) Most studies expose their experimental groups to MNPs for short time periods but at high concentrations, which is the opposite of what we undergo in the real world. Humans and animals are exposed to relatively low plastic concentrations but are continuously exposed over their lifespans. This lack of realistic circumstances hinders our acquiring a complete understanding of plastic neurotoxicity.

(3) Some researchers suggest that when we ingest MNP-contaminated food, the plastic comes out through the GI tract, as plastic particles are detected in human feces.[32] Other than that, there is very little research on MNP bioaccumulation in organs and the bloodstream, especially in brain tissue. The way the body expels plastic particles (or what happens with them within the body) is a topic that must be further explored.

(4) NPs can further degrade into monomers once they enter the body. PS-NP monomers have demonstrated even more detrimental effects on several bodily systems, including neural ones, than PS-NPs themselves.[6] The immune system's response and the neurological response to invading MNPs and monomers must be researched further.

(5) Exposure to higher temperatures in the environment allows plastic particles to more easily adsorb co-pollutants, which broadens their range of potential health risks.[3]

(6) Another question that still has to be answered is what groups of people: age/race/gender/medical records - are more vulnerable to the harmful effects of plastic particles.

(7) More research must be conducted to corroborate the MNP neutralizing capabilities of probiotics. This analysis could also help find other substances or make new medications that could be even more effective.

(8) Since coming into contact with plastic is inevitable, another angle on this problem that has to be considered is if there is any way to prevent plastic particles from coming into our bodies in the first place. For example, we know chemicals and enzymes that can break down plastic exist, such as PETase and MHETase.[33] We must conduct other studies to understand whether such enzymes can safely be used in natural ecosystems and if they can be consumed to break down plastic in the body.

Conclusion

In 2022 alone, the global level of plastic manufacturing reached 400.3 million tons, a number that is expected to increase exponentially in the years to come. It is also approximated that by 2035 the amount of plastic in the ocean will equal the amount of fish in the ocean by weight.[1] These alarming numbers combined with the recent discovery that MNPs can enter the brain by crossing the BBB highlight the critical need for more research to be done on the topic of MNP neurotoxicity. There are also a variety of factors that can influence the neurotoxic potential of a plastic particle, including the size and shape of the particles, its manufactured company additives, and its environmental co-pollutants. MNPs that breach the cell membrane can damage DNA and gene expression, mess with AChE levels, and cause oxidative stress, all of which contribute to the development of neurodegenerative diseases and memory loss. The gut-brain axis and its role with regard to MNP ingestion is also a newly developing area of study. MPs that travel to the brain through the gut-brain axis can impair learning, memory, and behavioral patterns. As demonstrated through multiple different studies, probiotics, and vitamins that act as antioxidants have been showing promising results in terms of reversing or at least reducing the neurotoxic effects of MNPs. However, we still have yet to learn how we can prevent MNPs from entering the body in the first place using plastic-dissolving enzymes released into the environment and if they can be used in the human body along with probiotics.

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