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The Toxicological Mechanisms of Microplastics in Aquatic and Mammalian Animals

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Abstract. Microplastics, as global environmental pollutants, have been widely distributed in water bodies, soil and the food chain. The ingestion of microplastics can induce a series of continuous toxicological effects in organisms. However, existing research mostly focuses on a single biological group and lacks a systematic summary of the commonalities and differences in toxicological mechanisms among different species. This review aims to summarize the toxicological pathways of microplastics in aquatic organisms and mammals, with a focus on discussing the similarities and differences in their toxicological effects ranging from oxidative stress, inflammatory responses to energy metabolism disorders. According to the research in this article, the overall process of toxicological effects of microplastics in different organisms has cross-species commonalities. However, aquatic organisms are more prone to acute, high-intensity, and irreversible tissue damage, while mammals show chronic, controllable inflammatory responses and systemic energy metabolism inhibition across organs. This review can provide an important reference for a deeper understanding of the toxicity of microplastics and for improving the health risk assessment system.

Keywords: Microplastics, cross-species toxicological mechanisms, aquatic organisms, mammals.

1. Introduction

Since the 1950s, global plastic production has continued to rise exponentially [1]. Plastic is widely used in various fields due to its light weight, strength, low cost and chemical stability. However, the excellent chemical stability of plastics makes them extremely difficult to decompose in the natural environment, gradually accumulating and evolving into a global environmental pollution problem. Microplastics are plastics with a particle size of less than 5 millimeters that are decomposed under the influence of light, mechanical friction and microbial action. Microplastics are one of the most common pollutants nowadays. A systematic review shows that at least 822 species of marine organisms were found to have ingested microplastics between 1972 and 2021, including 513 species of bony fish, 97 species of mollusks, 73 species of crustaceans and 22 species of echinoderms [2]. In the detection of plastic polymers in seven small terrestrial mammals, more than half of the species

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were plastic positive [3]. It is evident that microplastic pollution has extended from aquatic environments to terrestrial ecosystems, causing harm to life forms at different nutritional levels.

More and more studies have shown that microplastic particles can cause various toxicological effects in organisms, such as oxidative stress, inflammatory responses, and energy metabolism disorders, ultimately leading to tissue and organ damage. Microplastic exposure significantly increases the level of reactive oxygen species in aquatic organisms and mammalian tissues, induces a decline in antioxidant enzyme activity and activates inflammation-related pathways, ultimately leading to functional damage to organ structures such as the liver, kidneys and heart. In severe cases, it can cause organ failure and endanger life [4]. The physiological damage caused by microplastics may weaken the reproductive and survival capabilities of aquatic organisms and mammals, ultimately affecting ecological balance and food chain security.

However, most of the existing reviews focus on the toxicological mechanisms of microplastics on a single biological group, lacking systematic research on the commonalities and differences among different life forms. Therefore, this article will integrate the toxicological mechanisms of microplastics on aquatic organisms and mammals, focus on exploring their continuous action pathways from oxidative stress to tissue and organ damage, and analyze the similarities and differences in stress response and damage patterns among different organisms, which can provide references for subsequent risk assessment and health protection.

2. Common toxicological mechanisms of microplastics

To reveal the universal mode of action of microplastics in aquatic organisms and mammals, the core toxicological mechanisms shared across species will be outlined below. According to the investigation literature, microplastic exposure usually starts with the accumulation of reactive oxygen species, which then triggers the activation of inflammatory signaling pathways and further causes disorders in multiple energy metabolism networks, resulting in a cascade of damage from molecules to tissues. Therefore, this article will conduct a systematic discussion around these three major steps.

2.1. Oxidative stress initiation

At the molecular level, microplastics (MPs/NPs) generate reactive oxygen species (ROS) once they enter the body, disrupting the oxidation-antioxidant balance.

As shown in Table 1, different oxidative stress patterns were presented in various aquatic and mammalian models in terms of ROS, hydrolase activity and ATP changes. In aquatic biological models, when roxithromycin (ROX) and aged microplastics (AMPs) act together on goldfish, they promote oxidative stress responses in the liver and intestine, manifested as increased activities of superoxide dismutase (SOD) and catalase (CAT), and the smaller the diameter of the microplastics, the greater the impact on them. In the study of its intensity, it was found that it also has long-term residue and delayed oxidation reaction [5]. In the experiment of combined exposure of microplastics and brominated flame retardant TBBPA on motile marine microalgae, the intracellular ATP content decreased and energy was impaired. At the same time, a large amount of ROS accumulated, and the activities of antioxidant enzymes such as SOD, CAT and glutathione transferase (GST) significantly increased. The microalgae showed intense antioxidant defense in a short period of time. Moreover, algae lack organ-level structures. After being ingested with microplastics, their energy systems directly collapse, and the damage is irreversible [6]. In the ovarian and hepatocyte models of mammalian mice, an increase in ROS content was observed. The ovarian tissues of mice showed a

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collapse in antioxidant defense and significant lipid peroxidation. When microplastics are exposed to AML12 cells, it is manifested as a rapid increase in ROS, but SOD/CAT/GSH basically tends to be stable. This is because the larger diameter microplastics cannot be phagocytosed by mouse liver cells into the cells to cause damage to mitochondria and lysosomes, and mainly remain on the cell membrane surface, causing a mild membrane-related oxidative stress response [7]. This is not a comprehensive oxidative damage, but rather the cell as a whole is in a low-intensity, adjustable oxidative stress state.

Table 1. Comparison of oxidative stress levels in aquatic organisms and mammals after exposure to microplastics

Species model	Plastic type	Measurement indicators and trends	Types of oxidative stress	References
Carassius auratus	AMPs	SOD ↑ CAT ↑ GST ↑ AChE ↓	Compensatory-activated OS	[5]
Platymonas subcordiformis, Dicrateria zhanjiangensis	PS	ROS ↑ MDA ↑ SOD/CAT ↑ ATP ↓	Acute outbreak type OS	[6]
Mouse hepatocytes	PS-MPs	ROS ↑ SOD/CAT/GSH ↔ MDA ↔	Low-intensity ROS outbreak	[7]

Overall, aquatic organisms and mammals share both commonalities and significant differences in the oxidative stress response induced by microplastics. From a commonality perspective, both aquatic organisms and mammals will induce excessive ROS generation under microplastic exposure conditions, disrupt the intracellular oxidation-antioxidant balance, and cause changes in the activity of the antioxidant enzyme system. However, there are also some differences between them. The oxidative stress response of aquatic organisms is more urgent and non-compensatory. Microalgae and fish exhibit ROS outbreaks and rapid collapse of their energy systems under short-term exposure to microplastics, which are irreversible and manifest as typical acute high-intensity oxidative stress. In contrast, mammalian cells exhibit regulated or chronic oxidative stress. For instance, although ROS increased in mouse hepatocytes under exposure to large-sized microplastics, the activity of antioxidant enzymes remained basically stable, presenting membrane-related, low-intensity and recoverable oxidative stimulation. However, in ovarian tissue, the defense system can gradually collapse under high doses or long-term exposure to microplastics.

2.2. Inflammatory and immune responses

At the cellular and signaling pathway levels, inflammatory responses are induced by oxidative stress responses. When microplastics enter the body, excessive reactive oxygen species (ROS) activate multiple inflammatory signaling pathways, such as the NF-κB pathway and the upregulation of cytokine and chemokine-related genes, leading to cytokine release and immune system imbalance.

As shown in Table 2, the various biological models exhibit significant differences in the inflammatory core pathways and tissue damage manifestations. In the study on the subacute toxicity mechanism of polypropylene microplastics (PP-MPs) on the gut-liver axis of zebrafish, it was found that the presence of PP-MPs not only disrupted the intestinal mucosal barrier to induce inflammatory cell infiltration, but also inhibited the gene expression of key pathways such as DNA replication and repair, cell cycle, and Fanconi anemia (FANCA) [8]. These changes cause the proliferation of liver cells to be hindered and their repair capacity to decline, leading to a chronic inflammatory state in zebrafish. Moreover, changes in the structure of the intestinal flora lead to gut-

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liver axis linkage, affecting the immune and metabolic balance of the liver. In another group of experiments, different particle sizes of polyethylene terephthalate (PET) microplastics induced significant tissue lesions in the hepatopancreas of white shrimp: glandular duct atrophy, cell necrosis and inflammatory cell infiltration were particularly obvious, with the smaller particle size group showing the strongest performance [9]. In most studies on mammals, mice are used as research subjects. In experiments where microplastics induce premature testicular aging in mice, the number of p65-positive cells in the exposed group's testicles increased significantly, and the NF-κB signal was activated. The increase of pro-inflammatory cytokines in the local testicles of mice leads to premature aging of Sertoli cells. In another example, exposure to polystyrene microplastics led to an increase in pro-inflammatory factor levels and inflammatory cell infiltration in the colonic mucosa of mice. Among them, mature IL-1β is catalyzed by activated caspase-1 and then released outside the cell, triggering a strong inflammatory response, which is a typical inflammatory response of the lamina propria of the mucosa [10].

Table 2. Comparison of inflammation and immune response mechanisms induced by microplastics in different biological models

Species model	Plastic type	Inflammatory core pathway	Manifestations of tissue inflammation	Reference
Zebrafish	PP	Inflammatory flora + gut-liver axis	Intestinal wall thinning, goblet cells ↓, hepatitis	[8]
White shrimp from South America	PET	Small particles: Inflammation/apoptosis; Large particles: Compensation	Collapse of the hepatopancreas structure and shedding of intestinal microvilli	[9]
Mouse colon	PS	ROS → NF-κB/NLRP3 → IL-1β/MLCK	Epithelial inflammation, destruction of tight junctions	[10]

Overall, the inflammatory and immune responses induced by microplastics in aquatic organisms and mammals share commonalities in molecular mechanisms, but there are differences in response patterns. The commonality is that both aquatic organisms and mammals activate typical inflammatory signaling pathways, especially the NF-κB pathway, after oxidative stress responses, and cause the upregulation of pro-inflammatory factors. The difference is that aquatic organisms are more prone to acute inflammation and tissue structural damage. In contrast, mammals mainly exhibit chronic, cell-level abnormal immune regulation. In conclusion, the inflammatory response induced by microplastics has the characteristics of a common mechanism but significant biological specificity. In aquatic organisms, it is mainly acute tissue damage type, while in mammals, it is chronic immune dysregulation type.

2.3. Metabolic disruption

The inflammatory response will further spread to the energy metabolism system, manifested as damage and remodeling of multiple metabolic pathways. Common ones include damage to core energy pathways such as the tricarboxylic acid cycle (TCA cycle), amino acid metabolism and lipid metabolism.

In the study on the effects of microplastics on the gills of aquatic organisms such as tilapia, it was found that small particle PS-MPs directly weakened the ATP energy supply capacity of the respiratory tissue of tilapia by inhibiting glycolysis, the TCA cycle and oxidative phosphorylation. Moreover, this process is accompanied by abnormalities in key energy metabolism intermediate

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products such as citric acid and ADP, ultimately leading to respiratory dysfunction [11]. PS-MPs exposure induces significant fat production in the liver of Microphysogobio hanhuensis by remodeling the glycolipid metabolic network. Histological studies have found that the liver abnormally stores energy in the form of lipids, which is a typical phenotype of lipid metabolism disorder. The results of the transcriptome and metabolome jointly indicated that multiple glucose metabolism pathways, including pentose/glucuronic acid conversion, fructose/mannose metabolism, and carbon metabolism, were significantly disturbed [12]. Exposure to microplastics can also lead to intestinal microbiota imbalance and serum metabolic disorders in mammals, such as rats. Metabolomics analysis revealed that both the carbon skeleton energy metabolism pathway and the connection pathway between amino acids and the TCA cycle were significantly affected. At the same time, the fatty acid profile has also undergone significant changes. Fatty acid β-oxidation plays a key role in maintaining the energy homeostasis of the body. Long-chain fatty acids, after conversion, enter the tricarboxylic acid cycle for energy supply. When this process is disturbed, both fatty acid oxidation and overall energy metabolism are disrupted, thereby exacerbating metabolic imbalance [13].

Overall, the three types of models jointly show that glycolysis - TCA-oxidative phosphorylation of the central carbon metabolism network is the key attack point of microplastic toxicity, and microplastic exposure will damage and reshape multiple pathways of the energy metabolism network. The disorder of energy metabolism in aquatic organisms is mainly manifested as the collapse of local energy supply in tissues and the remodeling of metabolic stress. Mammals, on the other hand, exhibit systemic metabolic inhibition across organs, with overall down-regulation of energy metabolism. At the same time, the function of the gut microbiota is also related to energy metabolism pathways. These differences reflect the different levels of action of microplastics in various species: in aquatic organisms, it is mostly local metabolic pathway damage, while in mammals, it is manifested as an imbalance of the entire metabolic system.

3. Conclusion

This review systematically summarizes the continuous toxicological effects induced by microplastics in aquatic organisms and mammals, ranging from oxidative stress, inflammatory responses to energy metabolism disorders, revealing the commonalities and differences in the harm caused by microplastic exposure in different organisms. For commonalities, both aquatic organisms and mammals start with oxidative stress responses, which stimulate inflammatory signaling pathways and further disrupt core energy metabolism pathways such as glycolysis - TCA - oxidative phosphorylation, ultimately leading to cell damage and organ structure destruction. The toxicity is essentially an ecological-health chain reaction arising from the long-term interaction between microplastics and biological systems, reflecting the profound disturbance of artificial micro-pollutants on the homeostasis of the biological world.

However, there are also some differences in the damage patterns caused by the ingestion of microplastics by aquatic organisms and mammals. Due to the single tissue structure and low metabolic redundancy of aquatic organisms, the damage patterns they exhibit are mostly acute, high-intensity and irreversible. Disorders of energy metabolism mainly present as local energy supply collapse and rapid stress remodeling. In contrast, mammals have a stronger compensatory ability. After the intake of microplastics, they mostly show chronic, cell-level inflammatory activation and systemic metabolic inhibition across organs, and can regulate themselves to reduce damage.

Based on the existing research, the toxicological effects of microplastics have cross-species commonalities, while presenting different damage patterns due to differences in biological structure

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and metabolic levels. Future research should mainly focus on the influence mechanism of different microplastic particle sizes, morphologies and surface aging characteristics on toxicological effects. These studies are of great significance for guiding environmental governance strategies and assessing human health risks.

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