Microplastic pollution: A potent threat for metabolic disruption in mammals

Sudipta Pal

ABSTRACT

Polystyrene (PS) is one of the major primary microplastics that are factory-made and widely used as consumer goods, insulation materials, and equipment used in information technology. Animals are exposed to PS *via* freshwater, marine water, drinking water, food, and atmosphere, as well as via agroecosystems due to their low density, strong durability, and small size characteristics. Several health problems are caused by polystyrene, such as neurotoxicity, digestive disorders, reproductive dysfunction, immunotoxicity, genotoxicity, and oxidative damage in marine creatures. Sub-acute oral exposure to different doses of polystyrene microplastic (PS-MP) in male Wistar rats stimulated glycogenolysis in skeletal muscle as evidenced by depletion of tissue glycogen. Pyruvic acid in the kidney and skeletal muscle was reduced in a dose-dependent fashion after PS-MP exposure. Free amino nitrogen was significantly increased in muscle, whereas it decreased in the kidney. The LDH function was compromised in skeletal muscle, whereas it enhanced in the kidney following PS-MP exposure. Glucose 6-phosphatase and succinate dehydrogenase activities were stimulated in the kidneys of the PS-MP-exposed rats, whereas transaminase activities were decreased in both kidney and skeletal muscle after polystyrene exposure. It is submitted that sub-acute polystyrene exposure significantly altered glucose metabolism in renal and skeletal muscle by decreasing glycolysis, as well as by stimulating the TCA cycle and gluconeogenic activities in the renal tissue of rats. Metabolic adjustment was made differentially in skeletal muscle and kidney of exposed animals in accordance with dose-dependent alteration of biochemical and enzymatic parameters.

Keywords: Polystyrene microplastic, Glycolysis, TCA cycle, Transamination, Gluconeogenesis, *In-vivo* studies.

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INTRODUCTION

Plastics are found in various fields, including industry, agriculture, and everyday life.[1] India is the second-most populated nation in the world, manufacturing about 5.6 million tons of plastic waste each year.[2] According to different estimates, India recycles about 60% of its plastic garbage, although only 9% of all plastic waste ever produced worldwide has been reused again, according to the United Nations report.[2] "White pollution," a term for the phenomena of environmental pollution produced by waste made of plastic, has gradually threatened the world due to increased manufacturing and widespread usage of non-degradable plastic materials.[3] Microplastics (MPs), an unusually persistent organic pollutant, have come under more attention in the past few years. Microplastics are plastic pieces that are less than 5 mm (0.2 inch) in length.[4] Humans get microplastics from diverse sources like seafood, contaminated drinking water, plastic bottles, cosmetics, and toothpaste (Figure 1).

Microplastics (MPs) particles are categorized into primary and secondary microplastics (Figure 2). Primary microplastics can enter the environment unintentionally through spills during production or transport, product use (such as household wastewater systems washing personal care products into them), or abrasion during washing (such as washing clothing made of synthetic textiles). When much larger plastics are subjected to wave action, wind abrasion, and UV radiation from sunlight, secondary microplastics are produced as a product for all of these. For better recycling and making it reusable, the microplastic products can be melted by heating and made thermoplastics. Polyethylene (PE), polypropylene (PP), polystyrene (PS), polyvinyl chloride (PVC), and polyethylene terephthalate (PET) are produced at a level that is reflected in the degree of microplastic contamination. For example, the order of MPs detected globally in fresh and drinking water is PE ≈ PP > PS > PVC > PET.[5] PS is a major primary microplastics factory-made and widely used as consumer goods, insulation materials, and equipment used for information technology. Chronic human exposure reveals PS-mediated vascular and endothelial dysfunction, autophagy, and other health issues.[6] Research also revealed several health problems caused by polystyrene, such as metabolic disruption, neurotoxicity, digestive disorders, reproductive dysfunction, immunotoxicity, genotoxicity, and oxidative damage in marine creatures.[7,8]

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Polystyrene-Mediated Metabolic Disintegration: Existing Scenario

The harmful effects of microplastics are mostly reported to disturb lipid and energy metabolisms in different tissue

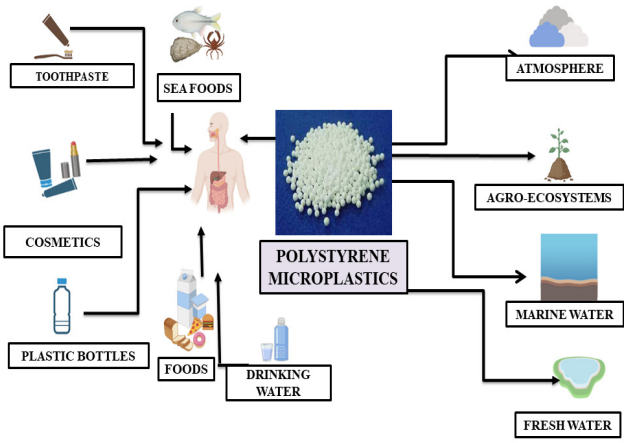

Figure 1: Sources of polystyrene microplastics in the environment and human body

and animal systems.[9-13] Alteration in metabolic integrity is one of the major health concerns in microplastic contamination.[14] It was reported that lactic acid production in the zebrafish intestine was affected by polystyrene.[15,16] Hepatic transcriptome studies exhibited inhibition of expression of genes of hexokinase, Glut2, glucokinase, PEPCKC, and pyruvate kinase by PS-MP, providing evidence in support of alteration of glycolysis/neoglucogenesis in mice and zebrafish.[12,14] Perturbation in energy metabolism was mostly studied in the reproductive system of mice in terms of decreased succinate dehydrogenase and lactate dehydrogenase functions after PS-MP exposure.[17] Additionally, increased expression of isocitrate dehydrogenase and lactate dehydrogenase was evaluated in the muscular tissue of European seabass.[16,18] Moreover, the metabolic intervention of PS-MP was also observed by histopathological studies, LC-MS metabolomics, and RNA sequence transcriptomic analyses, indicating metabolic interference of PS-MPs in rare minnow fish.[19] It was suggested that PS-MP may inspire immune response and oxidative risk and may also interrupt glycolipid metabolisms in fish model.[19] Hepatotoxicity and altered lipid metabolism were also observed in the human pluripotent stem cells derived liver organoids exposed to PS-MP.[20] Moreover, *in vitro* studies revealed that PS-MPs could result in energy deficit by inhibiting gene expression of the glyceraldehyde 3-phosphate dehydrogenase in Hep G2 cells and human kidney 2 cells.[21] *In vitro* mechanistic research revealed that PS-MPs caused an inhibitory effect on myogenic differentiation of C2C12 myoblast by inhibiting p38 MAPK phosphorylation and promoting adipogenic differentiation by stimulating NF-κB expression and ROS production.[22] The oxidative stress was considered a crucial factor for metabolome disorder in polystyrene toxicity.[23] Recent reports suggest that sub-acute exposure to polystyrene dose-dependently caused metabolic dysfunctions in hepatic and cerebral tissue of Wistar rats by inducing hypoglycemia and also by modulating glycolysis, gluconeogenesis and TCA cycle activities.[24]

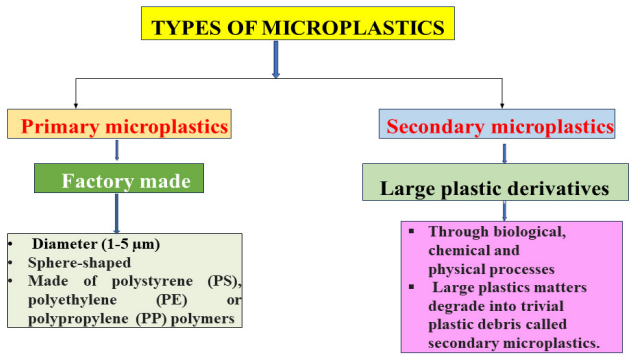

Figure 2: Types of microplastics

Current Experimental Studies: Dose-Dependent Effect of PS-MP on Renal and Muscular Energy Metabolism of Wistar Rats

A dose-dependent *in-vivo* study was carried out in Wistar rats to evaluate the effect of sub-acute polystyrene microplastic (PS-MP) exposure on certain aspects of carbohydrate metabolism in the kidney and skeletal muscle of Wistar rats. The animals were divided into one control and three PS-MP exposed groups (Figure 3). Ethical clearance was taken from IAEC, Tripura University. The treated groups of rats were fed with PS-MP *via* drinking water at three graded doses of PS-MP for four weeks. After treatment, rats were sacrificed by cervical dislocation, and kidney and skeletal muscle were collected for analyses. Parameters of carbohydrate metabolism like muscle glycogen, glycolytic intermediates, free amino nitrogen, glucose 6-phosphatase, lactate dehydrogenase, and transaminase enzyme activities were evaluated. Results indicated a dose-dependent alteration in carbohydrate metabolism in the studied tissues of rats following tissue-specific changes after PS-MP exposure.

Changes in skeletomuscular metabolism in rats following polystyrene exposure

Sub-acute polystyrene exposure significantly decreased muscle glycogen content dose-dependently (Table 1).

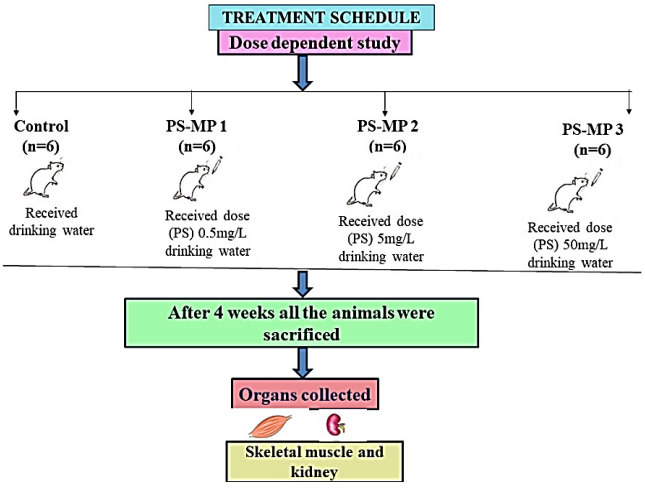

Figure 3: Treatment schedule for dose-dependent study

Table 1: Alteration in muscle glycogen content, pyruvic acid, and free amino nitrogen in skeletal muscle and kidney following PS-MP exposure

Groups	*Muscle glycogen (mg/100g tissue)*	*Pyruvic acid (g/100g tissue)*		*Free amino nitrogen (g/100g tissue)*	
		Muscle	*Kidney*	*Muscle*	*Kidney*
Control	9.15 ± 0.09	0.16 ± 0.01	0.50 ± 0.05	0.13 ± 0.01	0.24 ± 0.09
PS-MP1	7.14 ± 0.59*	0.07 ± 0.01*	0.31 ± 0.05*	0.16 ± 0.01*	0.14 ± 0.01*
PS-MP2	4.11 ± 0.39*	0.05 ± 0.01*	0.22 ± 0.02*	0.21 ± 0.02*	0.14 ± 0.02*
PS-MP3	5.45 ± 0.51*	0.09 ± 0.01*	0.19 ± 0.02*	0.25 ± 0.01*	0.13 ± 0.01*

Values are Means ± SEM. * represents $p < 0.05$. Comparison was made in between control and the respective PS-MP treated group by multiple comparison t test.

Glycogen depletion indicates enhanced glycogenolysis in response to PS-MP-mediated stress. Earlier studies revealed that polystyrene decreased blood glucose levels in rats and enhanced blood cortisol levels in zebrafish,[24,25], both may motivate glycogen breakdown from liver and skeletal muscle to compensate for hypoglycemia. Additionally, a dose-responsive decrease in muscle pyruvate level is evident from the present study (Table 1), suggesting decreased glycolytic conversion of muscle glucose to pyruvate following PS-MP exposure. As PS-MP induces hypoglycemia, the skeletal muscle may get less glucose from the blood, and due to substrate scarcity, pyruvate production is hampered. It is supported by the hepatic transcriptome studies, which exhibited inhibited expression of genes of hexokinase, Glut2, glucokinase, PEPCKC, and pyruvate kinase by PS-MP, providing evidence in support of alteration of glycolysis/neo glucogenesis in mice and zebrafish.[12,14] It is further revealed that the lactate dehydrogenase function in the skeletal muscle of rats was compromised after PS-MP exposure, which may be due to substrate (pyruvate) unavailability, indicating that pyruvate is preserved for maintaining energy metabolism (Table 2). A decrease in lactate dehydrogenase function was also reported in mice testicular tissue, indicating disturbed energy metabolism in sperm cells after PS-MP exposure.[17]

Moreover, free amino acid nitrogen was increased gradually following sub-acute polystyrene exposure at different doses, assuming enhanced gluconeogenesis to provide glucose to blood as a compensatory mechanism for loss of blood glucose (Table 1). Alternatively, free amino acids may be mobilized from blood to skeletal muscle to provide more substrates for gluconeogenesis for maintaining tissue energy status in PS-MP-stressed condition. Additionally, transaminase functions (both glutamate-pyruvate transaminase and glutamate-oxaloacetate transaminase) were declined in PS-MP-treated animals, which might be suggestive of muscular tissue damage following PS-MP exposure at the present doses and duration (Table 2). Energy depletion and oxidative stress are supposed to be potent modulators of tissue degeneration in PS-exposed animals.

Polystyrene modulates renal metabolism in a dose-responsive fashion

Further studies indicated that PS-MP also significantly altered glucose metabolism in rat kidneys. Renal glycolysis was retarded in response to the hypoglycaemic situation and resulted in decreased pyruvate production following a dose-dependent pattern (Table 1). Further, it was associated with increased lactate dehydrogenase function (Table 2), indicating anaerobic conversion of pyruvate to lactate that might induce renal tissue damage. Glucose 6-phosphatase activity in the renal tissue was found to be suppressed following PS-MP exposure (Table 2), which might result in hypoglycemia and accumulation of glucose 6-phosphate in that tissue to preserve metabolites for maintenance of tissue metabolism. Free amino acid nitrogen may be mobilized from renal tissue to blood due to metabolic stress or may be used as an alternative energy source via gluconeogenesis for maintaining energy balance in PS-stressed condition. Additionally, stimulated succinate dehydrogenase function

Table 2: Alteration in GOT, GPT and LDH activities in skeletal muscle and kidney, and G6Pase and SDH functions in kidney following PS-MP exposure

Groups	GOT activity (µg/min/100g tissue)		GPT activity (µg/min/100g tissue)		LDH activity (µmol/min/mg protein)		Renal G6Pase activity (µg Pi liberated/min/g protein)	Renal SDH activity (µmol/min/mg protein)
	Muscle	Kidney	Muscle	Kidney	Muscle	Kidney		
Control	90.01 ± 1.91	96.11 ± 1.31	3.90 ± 0.18	32.00 ± 0.17	1080 ± 50	510.26 ± 10.94	185.01 ± 9.51	11.10 ± 2.60
PS-MP1	84.16 ± 2.11*	94.20 ± 0.71	2.99 ± 0.19*	29.21 ± 1.01	825 ± 35*	690.82 ± 10.12*	130.06 ± 2.60*	39.52 ± 4.91*
PS-MP2	76.81 ± 1.80*	94.11 ± 0.59	2.50 ± 0.18*	22.80 ± 1.50*	690 ± 40*	758.09 ± 11.03*	110.02 ± 10.20*	27.21 ± 3.90*
PS-MP3	81.01 ± 4.11*	63.00 ± 1.30*	3.21 ± 0.09	27.11 ± 0.31*	415 ± 25*	734.20 ± 6.90*	116.01 ± 10.01*	26.01 ± 8.11*

Values are Means ± SEM. * represents $p < 0.05$. The comparison was made between the control and the respective PS-MP treated group by multiple comparison t test.

by polystyrene may help in maintaining energy level *via* the TCA cycle in renal tissue (Table 2).

CONCLUSION

Dose-dependent alteration in glucose metabolism was observed in renal and skeletomuscular tissue after four weeks of polystyrene microplastic exposure. Disruption of energy metabolism was observed in terms of decreased pyruvic acid production in kidney and skeletal muscle, indicating retardation of glycolysis. Muscle glycogen was depleted to release glucose into the blood as a compensatory adjustment of hypoglycemia. Altered LDH function in muscle and kidney was in accordance with the substrate availability. Renal glucose 6-phosphatase function was suppressed, indicating decreased gluconeogenesis; TCA cycle function was stimulated in that tissue to maintain energy balance. Decreased transaminase activities in both tissues suggest degenerative changes in response to polystyrene.

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