The Glycolysis-Lactate-Histone Lactylation Axis in Polystyrene Microplastic-Induced Cognitive Impairment: A Proposed Mechanistic Framework

Haodong Xiang[1*]

[1*]Department of Clinical Medicine, Southwest Medical University, Luzhou, Sichuan, China.

Corresponding author(s). E-mail(s): 20230202330130@stu.swmu.edu.cn;

Abstract

Polystyrene microplastics (PS-MPs) are ubiquitous environmental contaminants repeatedly shown to impair cognitive function in mouse models. Existing literature converges on oxidative stress, blood-brain barrier disruption, and neuroinflammation as central mechanisms, yet the precise molecular pathways linking these phenomena to hippocampal dysfunction remain incompletely understood. This review synthesizes current evidence to evaluate the hypothesis that PS-MP exposure triggers a metabolic shift toward aerobic glycolysis, enhancing lactate production. This lactate, in turn, may mediate neuroinflammation and impair synaptic plasticity through epigenetic reprogramming via histone lactylation (e.g., H3K18la). We construct a mechanistic model based on this hypothesis, integrating findings on microglial activation, astrocyte-neuron metabolic coupling, and innate immune signaling. While the glycolysis-lactate-histone lactylation axis presents a biologically plausible mechanism for PS-MP neurotoxicity, we identify critical evidence gaps, primarily the lack of direct measurements of lactate, glycolytic flux, and histone lactylation in the brain following PS-MP exposure. Finally, we propose key regulatory proteins—including LDHA, MCTs, p300, and HIF-1$\boldsymbol{\alpha}$—as high-priority targets for future research to validate this emerging metabolic-epigenetic pathway.

Keywords: Polystyrene microplastics, Neurotoxicity, Cognitive function, Glycolysis, Lactate, Histone lactylation, Neuroinflammation

1 Introduction

Polystyrene microplastics (PS-MPs) are pervasive environmental pollutants that have been shown to accumulate in various organs, including the brain, raising significant concerns about their potential neurotoxicity [1, 2]. A growing body of evidence from mouse models demonstrates that exposure to PS-MPs impairs cognitive function, as evidenced by deficits in spatial memory and recognition tasks [1, 3, 4]. Multiple studies converge on oxidative stress, blood-brain barrier (BBB) disruption, and neuroinflammation as central mechanisms underlying these deficits, with alterations in synaptic proteins and inflammatory mediators noted across diverse exposure paradigms [1, 3].

A particularly intriguing yet underexplored hypothesis posits that PS-MP-induced oxidative stress may trigger a metabolic shift from oxidative phosphorylation to aerobic glycolysis, a phenomenon known as the Warburg effect. This metabolic reprogramming would enhance the production of lactate. In support of this concept, studies have shown that lipopolysaccharide (LPS)-driven M1 microglial polarization, a key feature of neuroinflammation, is accompanied by such a glycolytic shift [3]. Lactate is no longer considered merely a metabolic waste product; it is a critical signaling molecule and an epigenetic regulator. Specifically, lactate can serve as a precursor for histone lysine lactylation (e.g., H3K18la), a post-translational modification that directly influences gene expression [5].

This review synthesizes the existing literature to critically evaluate whether a glycolysis-lactate-histone lactylation axis mediates the neurotoxic effects of PS-MPs. We propose a mechanistic model wherein PS-MP-induced oxidative stress enhances lactate production, which in turn promotes histone lactylation, leading to neuroinflammation and hippocampal dysfunction. We analyze points of agreement and disagreement across studies, identify crucial gaps in the current research, and suggest future directions to validate this proposed pathway, including key regulatory genes and proteins such as lactate dehydrogenase A (LDHA), monocarboxylate transporters (MCTs), histone acetyltransferase p300, and hypoxia-inducible factor 1-alpha (HIF-1α).

2 Dose-Dependent Cognitive Impairment and Neuroinflammation after Polystyrene Microplastic Exposure

Mouse studies converge on a dose-dependent relationship between polystyrene microplastic exposure and deficits in spatial and recognition memory, accompanied by oxidative stress, blood-brain barrier disruption, neuroinflammation, and synaptic alterations. While particle size effects remain unresolved, the absence of consistent endotoxemia or cytokinemia in normal-diet mice shifts attention to brain-intrinsic mechanisms, motivating a glycolysis-lactate-histone lactylation model to explain hippocampal dysfunction.

2.1 Background

Microplastics are now ubiquitous in air, water, and food, raising concern that chronic low-level exposures may impair brain function. In mice, the hippocampus is particularly vulnerable to inflammatory and metabolic stressors that disrupt synaptic plasticity and memory. Emerging epigenetic mechanisms link cellular metabolism to gene regulation, including histone lactylation, a modification derived from glycolytic lactate. This creates a biologically plausible axis whereby redox stress and metabolic reprogramming could rewire neuroimmune and synaptic gene expression in the hippocampus after environmental exposures. However, the field lacks standardized exposure metrics and quantitative systemic inflammatory readouts, complicating causal inference and cross-study comparisons.

2.2 Results & Discussion

Across independent laboratories, oral or systemic polystyrene microplastic (PS-MP) exposures reproducibly impair spatial and recognition memory in mice, with deficits in Morris water maze and novel object recognition tests co-occurring with oxidative stress, blood-brain barrier compromise, neuroinflammation, and loss of synaptic proteins in brain tissue [1, 3, 4]. A synthesis of in vivo data supports a clear dose-response relationship for PS-MP neurotoxicity, whereas particle size-dependent effects remain inconclusive due to heterogeneous designs and reporting, precluding pooled analyses [1, 6]. These behavioral and molecular endpoints provide a consistent pathophysiological footprint that is compatible with microglial activation and synaptic vulnerability within the hippocampus [1, 3].

Notably, the available literature provides no quantitative plasma or serum endotoxin data after oral PS exposure in normal-diet mice; Limulus Amebocyte Lysate (LAL) assays were used mainly for material quality control rather than blood measurement [7]. Similarly, direct circulating cytokine quantification (e.g., TNFα, IL-1β, IL-6) is largely absent in normal-diet cohorts [7–9]. This lack of consistent systemic inflammatory signals, together with robust brain changes, sharpens the focus on brain-intrinsic mechanisms, including metabolic reprogramming and cell-autonomous neuroimmune activation, as proximal drivers of hippocampal dysfunction after PS-MP exposure [8].

A mechanistic model consistent with current evidence posits that PS-MP-induced oxidative stress shifts microglia and possibly astrocytes and neurons from oxidative phosphorylation to aerobic glycolysis, increasing lactate production. This lactate can be retained or shuttled via monocarboxylate transporters, thereby enabling histone lactylation in target cells (for example, at H3K18) to reprogram inflammatory and synaptic gene expression in the hippocampus [3, 4]. Support for the glycolysis arm comes from studies showing that lipopolysaccharide-driven M1 microglial polarization is accompanied by a glycolytic shift, although PS-MP studies to date have not directly measured brain lactate or histone lactylation (e.g., H3K18la), defining a critical gap [3, 4]. On this basis, prioritized regulatory nodes for validation include lactate dehydrogenase A (LDHA) as the proximal generator of pyruvate-to-lactate flux,

monocarboxylate transporters MCT1 and MCT4 to control lactate trafficking, the histone acetyltransferase p300 as a candidate acylation writer, and HIF-1α as a master transcriptional regulator of glycolytic gene expression under oxidative stress [4].

This model yields testable predictions tightly linked to the reported dose-response. Increasing PS-MP dose should proportionally elevate hippocampal glycolytic indices and lactate alongside microglial M1 markers and IL-1β, with correlated declines in memory performance, while particle size effects may remain variable unless dosing and quantitative endpoints are standardized across studies [1]. To enable rigorous cross-study synthesis, exposure should be converted to mass-per-body-weight-per-day (e.g., mg kg^{-1} day^{-1}), and behavioral outputs harmonized, along with common molecular endpoints [1]. Batch effects can be mitigated by randomizing particle lots, verifying endotoxin-free suspensions by LAL at the time of dosing, and pre-specifying normalization strategies for tissue assays across cohorts. Concurrent measurement of plasma LPS and cytokines in normal-diet mice will help rule out systemic drivers and strengthen causal inference for the brain-intrinsic glycolysis-lactate-histone lactylation axis [7, 8]. Together, the literature supports a dose-dependent PS-MP neurotoxicity that plausibly converges on a glycolysis-lactate epigenetic mechanism in hippocampus, with LDHA, MCT1/4, p300, and HIF-1α highlighted as actionable targets for validation in future experiments [1, 3].

3 The Glycolysis-Lactate-Histone Lactylation Axis: Plausibility Versus Evidence Gaps

Polystyrene microplastics (PS-MPs) impair cognition in mice and consistently trigger oxidative stress, barrier disruption, and neuroinflammation. A mechanistic model is proposed in which PS-MP-evoked oxidative stress biases brain myeloid cells toward glycolysis and lactate production that fuels microglial histone lactylation (e.g., H3K18la) to amplify inflammatory programs, whereas neuronal lactate supports synaptic function; however, PS-MP-specific evidence for hippocampal lactate elevation, glycolytic reprogramming, and histone lactylation remains unreported.

3.1 Background

Microplastics are emerging neurotoxicants that can access the central nervous system, where they perturb redox balance, immune tone, and synaptic integrity. In parallel, immunometabolism research has revealed that glycolysis-derived lactate is not just a metabolite but also a chromatin substrate for histone lactylation, a modification that can tune gene expression. Microglia and neurons differ in their metabolic wiring and lactate handling: microglia often upshift glycolysis under inflammatory stress, whereas neurons exploit lactate for activity-dependent plasticity. Mapping how PS-MPs intersect with the glycolysis-lactate-histone lactylation axis is therefore central to explaining their cognitive impact and to identifying actionable molecular targets.

3.2 Results & Discussion

Multiple mouse studies converge that PS-MP exposure impairs spatial memory and recognition performance, with oxidative stress, BBB disruption, neuroinflammation, and synaptic protein alterations recurrently observed across exposure paradigms [1, 3, 4]. On mechanistic grounds, PS-MP-induced oxidative stress could drive aerobic glycolysis and lactate accumulation, consistent with the association of lipopolysaccharide-driven M1 microglial polarization with a glycolytic shift. However, no PS-MP study has directly measured lactate or histone lactylation in the brain to date [3, 4]. Specifically, no in vivo PS-MP mouse study has quantified hippocampal or CSF lactate [10], no microglial PS-MP study has assayed glycolytic flux (e.g., lactate efflux, glucose consumption, extracellular acidification rate) [11], hippocampal glycolytic enzyme induction has not been reported [3], and PS-MP-induced histone lactylation in microglia has not been demonstrated [12, 13]. Upstream metabolic regulators such as HIF-1α or PI3K/Akt/mTOR have also not been shown to be engaged in the brain by PS-MPs with concomitant glycolytic readouts, underscoring a critical evidence gap for this pathway in the PS-MP context [14, 15].

Indirect evidence from non-plastic neuroinflammatory models supports the plausibility of the glycolysis-lactate-histone lactylation axis in brain myeloid cells. Elevating intracellular lactate in microglia by oxygen-glucose deprivation, doxorubicin-induced senescence, or exogenous sodium lactate is sufficient to increase histone lactylation, including H3K18la, whereas pharmacological inhibition of lactate production decreases lactylation, establishing a causal link between lactate abundance and lactylation levels [5]. Mechanistically, p300 functions as a histone lactylation writer in microglia: the p300 inhibitor A485 suppresses oxygen-glucose deprivation-induced H3K9la and reduces iNOS and TNFα [16]. Genomewide mapping further shows H3K18la enrichment at promoters of NF-κB regulatory genes (e.g., Rela, Nfkb1) in senescent or lactate-treated microglia, suggesting that H3K18la potentiates inflammatory signaling via upstream pathway regulators [5].

In vivo, lactate exerts cell-type-specific effects that are favorable in neurons but potentially detrimental in microglia. In mouse models, exercise or systemic L-lactate improves cognition and increases synapse-associated proteins; direct hippocampal lactate infusion enhances memory, elevates synaptic markers, and increases histone lactylation, with benefits requiring neuronal MCT2 [17]. Conversely, in a diabetes model, heightened lactate drives microglial H3K18la, activates TLR4/NF-κB signaling, and associates with spatial memory deficits, indicating that lactylation-dependent pathology can be microglia-centered [18]. Coupled with PS-MP-evoked neuroinflammation, these data support a framework in which microglial lactate-driven histone lactylation amplifies inflammatory tone and contributes to PS-MP neurotoxicity, whereas neuronal lactate may serve as a compensatory pro-plasticity signal [17, 18].

Integrating across these strands, a testable mechanistic model is proposed: PS-MPs induce oxidative stress and barrier dysfunction that could stabilize HIF-1α or engage PI3K/Akt/mTOR, upregulating glycolytic enzymes (HK2, PFK, PKM2, LDHA) and elevating intracellular lactate. Lactate is exported via MCT4 and taken up by neighboring cells via MCT1/2, where in microglia it fuels p300-mediated H3K18la at NF-κB pathway genes to potentiate cytokine production and impair hippocampal function,

while in neurons it supports activity-dependent synaptic programs [5, 14–17]. The decisive PS-MP-specific links remain unproven [10–12]. A focused agenda should therefore pair PS-MP exposures with (i) hippocampal lactate quantification; (ii) microglial metabolic flux analysis; (iii) HIF-1α and pAkt/pmTOR measurements; and (iv) H3K18la ChIP-seq/CUT&Tag, integrated with behavioral endpoints [5, 11, 14, 15]. Supportive macrophage data showing PS-MP-induced glycolytic shifts reinforce the plausibility of similar reprogramming in brain myeloid cells [19].

Five regulatory nodes emerge as priorities for validation: LDHA, EP300/p300, Monocarboxylate transporters (MCT4/MCT1/2), HIF-1α, and PKM2. Experimental designs must control for dose, size, and batch effects to enable cross-study synthesis [3, 11].

4 Microglial Sensing of Polystyrene Plastics via TLR4 and Inflammasome Pathways

Polystyrene plastics activate microglial innate immune pathways through TLR4 signaling and inflammasome engagement under oxidative stress, with evidence for ROS- and JNK-dependent caspase-1 processing and IL-1β/IL-18 release. A plausible but as yet untested link connects TLR4-driven glycolysis to lactate accumulation and histone lactylation (H3K18la), offering a mechanistic route by which polystyrene exposures could epigenetically reinforce neuroinflammation and contribute to hippocampal dysfunction.

4.1 Background

Micro- and nanoplastics have emerged as biologically active environmental particles that engage innate immune pathways. In the brain, microglia act as sentinels that integrate pattern-recognition receptor signaling with metabolic state to shape inflammatory outputs and synaptic remodeling. Immunometabolic reprogramming toward glycolysis can fuel lactate production, and lactate-derived histone lactylation has recently been recognized as an epigenetic modification that can tune transcription. Connecting these axes provides a framework to understand how particle exposures might drive durable neuroinflammatory states.

4.2 Results & Discussion

Multiple lines of evidence converge on a model in which polystyrene plastics activate microglia through TLR4 and inflammasome pathways, potentiated by oxidative stress. In N9 microglia, polystyrene nanoplastics increased inflammatory markers, and the TLR4 inhibitor TAK-242 prevented these inductions [20]. In BV-2 microglia, 50 nm polystyrene nanoplastics upregulated NLRP3 and ASC, increased the cleaved caspase-1/pro-caspase-1 ratio, and elevated IL-1β and IL-18 release, with ROS scavenging (NAC) attenuating these endpoints and JNK inhibition reducing caspase-1 activation [21]. Although these datasets strongly support inflammasome engagement, NLRP3 necessity has not been demonstrated with MCC950 or loss-of-function approaches in

microglia [22]. Evidence for NF-κB p65 activation is also incomplete [23], yet conditioned media from PS-MP-stressed hippocampal neurons increased microglial TLR4, phosphorylated NF-κB, NLRP3, ASC, cleaved caspase-1, and IL-1β, indicating that neuron-derived damage signals can prime microglial inflammasome pathways [24]. By contrast, a purinergic ATP-P2X7 route is not supported by the current excerpts in brain-relevant systems [25].

Immunometabolic data provide a mechanistic bridge. Activation of TLR4 by LPS is sufficient to impose an aerobic glycolytic shift in microglia, with increased HK2 and PKM2 expression and elevated extracellular lactate [26, 27]. However, no primary study has measured glycolytic endpoints in microglia after polystyrene exposure, so a PS-MP-induced glycolytic switch remains an inference [11].

The epigenetic arm of this model is anchored by causality between intracellular lactate and histone lactylation. In cultured microglia, manipulations that elevate lactate are sufficient to increase histone lactylation, including H3K18la [5]. Conversely, no study has examined whether polystyrene exposure increases histone lactylation in microglia [12, 13]. Thus, the PS-MP-specific steps connecting microglial glycolysis to histone lactylation are untested [11–13].

Integrating these findings yields a mechanistic hypothesis: polystyrene plastics engage microglial TLR4 signaling and ROS/JNK-dependent inflammasome activation, culminating in IL-1β/IL-18 release [20, 21, 24]. In parallel, TLR4-driven immunometabolic reprogramming could increase lactate, fostering H3K18la, although these steps require direct validation [5, 11–13, 26]. The most informative regulatory targets for validation are TLR4, HK2, PKM2, LDHA, and NLRP3 [5, 20, 21, 26].

5 Astrocyte-Neuron Metabolic Coupling: An Untested Link in PS-MP Neurotoxicity

Mouse evidence indicates that polystyrene exposure impairs hippocampal structure and memory but has not interrogated lactate transport or histone lactylation, leaving the glycolysis-lactate-lactylation axis untested in this context. Independent studies show that lactate and its transport generally support hippocampal plasticity, whereas microglial histone lactylation can potentiate inflammatory signaling, motivating a cell-type-resolved model for PS-MP neurotoxicity.

5.1 Background

Lactate shuttling from astrocytes to neurons sustains synaptic transmission and memory through monocarboxylate transporters. Histone lysine lactylation links cellular glycolytic state to transcriptional control, with neuronal lactate often supporting plasticity programs, while microglial lactylation can amplify inflammatory cascades. Polystyrene plastics are detectable in the brain, but their specific impacts on astrocyte-neuron metabolic coupling and lactate-dependent signaling remain largely unmeasured.

5.2 Results & Discussion

A cohesive picture emerges from mouse studies manipulating lactate independent of plastic exposure. Raising brain lactate improves cognition, increases synapse-associated proteins, and enriches hippocampal synapse gene programs [17]. Mechanistically, lactate can induce immediate early genes (e.g., c-Fos, Arc, Bdnf) [28], and astrocyte-neuron lactate transfer is required for long-term memory. The strongest causal link between histone lactylation and behavior to date is in microglia, where elevated lactate drives H3K18la, activates TLR4/NF-κB, and associates with spatial memory deficits [18]. This underscores a cell-type-specific valence: lactate appears pro-plasticity in neurons, but its epigenetic consequences can be pro-inflammatory in microglia [17].

In vivo PS-MP exposure produces hippocampal phenotypes compatible with disrupted plasticity but has not been mechanistically tied to lactate transport or histone lactylation. Chronic PS-MP exposure reduces dendritic spines, lowers synaptic proteins (synapsin 1, synaptophysin, PSD95), decreases Bdnf and Syt1 mRNA, and impairs memory, yet MCT1/2/4 expression and lactate flux were not measured [1].

Primary astrocyte studies suggest impaired metabolic support after polystyrene exposure. Astrocytes avidly internalize PS-NPs, exhibit dose-dependent cytotoxicity, and transition to reactive states with transcriptomic evidence for downregulation of lipid metabolic programs [29, 30]. However, direct measurements of astrocyte glucose uptake, lactate production, or MCT abundance after PS exposure are lacking [29–31]. Similarly, in neuronal cells, PS-NPs reduce mitochondrial respiration and ATP production, but compensatory glycolytic changes and lactate production remain unquantified [32].

Two non-exclusive pathways are plausible after PS exposure: (i) astrocyte metabolic stress diminishes lactate export, starving neurons and depressing synaptic programs; and (ii) altered cellular redox and lactate handling shifts microenvironmental lactate availability, enabling microglial H3K18la-dependent neuroinflammation [17, 29, 32]. The most parsimonious working model is that PS-MPs impair cognition by disrupting astrocyte-neuron metabolic coupling and biasing microglial epigenetic states via lactate. High-priority targets for validation are SLC16A7/MCT2 (neuronal lactate uptake), SLC16A3/MCT4 and SLC16A1/MCT1 (astrocytic lactate export), HCAR1/GPR81 (lactate receptor), and TLR4 (microglial inflammatory node) [1, 17, 29].

6 Conclusion

This review consolidates evidence demonstrating that PS-MP exposure impairs cognitive function in mouse models, consistently triggering oxidative stress, BBB damage, and neuroinflammation. We propose and evaluate a novel mechanistic hypothesis centered on the glycolysis-lactate-histone lactylation axis. The existing literature lends strong plausibility to this model: PS-MP-induced stress is well-positioned to drive a metabolic shift in glial cells, and the resulting increase in lactate could epigenetically regulate gene expression through histone lactylation, thereby perpetuating neuroinflammation and impairing synaptic function.

However, a critical evidence gap exists. There is a clear lack of direct experimental data from PS-MP exposure models measuring key components of this proposed pathway in the brain, including lactate concentrations, glycolytic flux rates, and the status of histone lactylation marks like H3K18la. While the necessary molecular tools and conceptual frameworks are established in related fields, their application to PS-MP neurotoxicology is conspicuously absent.

Future research must prioritize filling these gaps. Studies should directly quantify hippocampal lactate levels and the expression of rate-limiting glycolytic enzymes after PS-MP exposure. The functional role of histone lactylation should be interrogated using ChIP-seq and targeted inhibition of writer enzymes like p300. Furthermore, clarifying the distinct roles of microglia and astrocytes in this metabolic-epigenetic cascade is essential. Validating this pathway will not only deepen our understanding of how microplastics impact brain health but also potentially reveal novel therapeutic targets for mitigating their neurotoxic effects. Standardizing experimental variables, such as dosage and batch effects, will be crucial for building a robust and reproducible body of evidence.

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