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# NEURAL AND INTESTINAL IMPACT OF BIODEGRADABLE POLYLACTIC ACID NANOPLASTICS: RESULTS FROM THE PLASTAMINATION PROJECT

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The increasing use of biodegradable plastics has raised new concerns about the potential health impact of their degradation products. Polylactic acid (PLA), one of the most widely used bio-based plastics, can rapidly fragment into micro- and nanoplastics (MPs/NPs), whose health effects are still poorly understood. Within the PRIN PNRR 2022 project *PLASTAMINATION*, the effects of PLA NPs (size ~170 ± 64 nm) on central nervous system (CNS) cellular models, and epithelial cells representing key components of the intestinal barrier were investigated. In CNS models, PLA NPs were efficiently internalized by both neuronal (PC12) and glial (C6) cells. In differentiating PC12 cells, PLA NPs exposure impaired NGF-induced neuronal differentiation, reducing neurite number and length, altering cell cycle progression, and downregulating ERK and AKT signaling, while increasing oxidative stress and pro-inflammatory cytokine release. In C6 glial cells, PLA NPs induced a reactive phenotype characterized by increased GFAP expression, AKT pathway activation, and elevated reactive oxygen species (ROS) levels. In parallel, *in vitro* studies on human intestinal Caco2 and HT29 cells also showed that PLA NPs can be internalized by the cells and PLA NPs exposure induced a significant increase in ROS production in both cell types, while HT29 cells also displayed enhanced release of the pro-inflammatory cytokines. Further investigations on differentiated Caco-2/HT29 co-cultures, set up to mimic the intestinal barrier, showed that chronic exposure to PLA NPs (100 µg/mL for 21 days) led to a persistent increase in transepithelial electrical resistance (TEER), associated with enhanced expression of tight junction proteins ZO-1 and E-cadherin in differentiated Caco2 cells while increasing mucin production in differentiated HT29 cells. These findings suggest a structural reinforcement of the epithelial barrier accompanied by oxidative stress and inflammatory signaling, suggesting an adaptive response that may evolve toward a chronic inflammatory condition. Untargeted metabolomic analyses supported the overall results indicating that PLA NPs can affect redox balance and nitrogen metabolism in C6 cells as well as glucose and lipid metabolism in HT29. Across both intestinal and CNS cellular models, PLA NPs exposure consistently induced oxidative stress and activation of inflammatory related pathways, in the absence of acute cytotoxicity. These shared responses suggest a common cellular stress signature triggered by PLA-derived NPs, despite tissue-specific functional outcomes. However, compared to intestinal epithelial cells, CNS cellular models seem to show more pronounced functional alterations. In particular, neuronal and glial cells displayed impaired differentiation, activation phenotypes, and marked changes in intracellular signaling, suggesting a higher sensitivity of neural cells to PLA NPs. Overall, these results demonstrate that PLA NPs can interact with intestinal and neural cells, inducing molecular and functional alterations. The findings highlight the need to carefully evaluate the long-term biological impact of biodegradable plastic-derived NPs to support truly sustainable plastic alternatives.

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