

Hydroxyphenyllactic Acid Promotes Intestinal Homeostasis Through Antioxidant, Anti-inflammatory, and Barrier-Protective Effects

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Background: *Lactobacillus* species are known to support intestinal development and homeostasis early in life. These effects are partly mediated by metabolites produced from dietary substrates. In a previous study, we identified that hydroxyphenyllactic acid (HPLA), a tyrosine-derived metabolite, was robustly produced by multiple *Lactobacillus* species in response to human milk, but not infant formula. Although HPLA has demonstrated to have free-radical-scavenging activity *in vitro*, its other potential functions, particularly in the gut, remain uncharacterized. Here, we investigated the effects of HPLA on intestinal oxidative stress, inflammation, and barrier function. **Methods:** Antioxidant activity of HPLA was assessed in fetal intestinal epithelial cells (CCD-841CoN) using H₂DCFDA to measure intracellular reactive oxygen species (ROS) induced by H₂O₂. Anti-inflammatory effects were evaluated in CCD-841CoN cells stimulated with lipopolysaccharide and flagellin, followed by RNA-seq analysis. Barrier function was tested in human colonic monolayers using lucifer yellow permeability assays and RT-qPCR analysis of tight junction gene expression. *In vivo*, the effects of orally administered HPLA (20 mg/kg) were examined in adult C57BL/6 mice with 7-day dextran sulfate sodium (DSS)-induced colitis; inflammation was assessed by H&E histology and colonic cytokine expression by RT-qPCR. **Results:** *In vitro*, HPLA significantly reduced H₂O₂-induced ROS accumulation in fetal intestinal cells. Transcriptomic analysis revealed that HPLA attenuated activation of key inflammatory pathways, including TNF- α , IFN- α/γ , and IL-6/JAK/STAT3 signaling. HPLA also enhanced epithelial barrier integrity, evidenced by reduced monolayer permeability and increased expression of tight junctional genes *Cldn1*, *Cldn3*, and *Ocln*. In the DSS colitis model, HPLA administration upregulated the anti-inflammatory cytokine *Il10*, although no differences were noted for the pro-inflammatory genes *Kc*, *Tnfa*, or *Ifng*. HPLA treatment also rescued DSS-induced suppression of *Cldn3* and increased expression of *Cldn1* and *Cldn4* relative to the control and DSS vehicle group, respectively. **Conclusions:** HPLA is a diet-dependent microbial metabolite that mitigates oxidative stress, inflammation, and barrier dysfunction, providing a potential mechanistic link between human milk-microbe interactions and intestinal homeostasis.