Deoxycholic Acid Modulates Cell-Junction Gene Expression and Increases Intestinal Barrier Dysfunction in Caco-2 Cell Monolayers

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Objectives: Diet-related obesity is associated with an increased risk of developing intestinal hyperpermeability. High dietary fat intake causes an increase in colonic bile acids (BAs), particularly deoxycholic acid (DCA, secondary BA), which may disrupt the intestinal epithelial barrier. To determine the potential role of bile acids in barrier dysfunction, we hypothesize that DCA modulates the gene expression in multiple cell junction pathways and increases intestinal permeability.

Methods: With a Caco-2 cell intestinal barrier model, we used cell proliferation, PCR array, biochemical, western blotting and immunofluorescent assays to examine the impact of DCA on the integrity of intestinal barrier and gene expression.

Results: Human intestinal Caco-2 cells were grown in monolayers and challenged with DCA at physiological concentrations (sub mM levels). DCA increased transcellular and paracellular permeability (>30%) via transepithelial electrical resistance and phenol red flux measurements. Similarly, DCA increased intracellular reactive oxidative species production (>1-fold) and accompanied a modification of cellular p38 and ERK1/2 signaling pathways. Further characterization of underlying genes related to epithelial barrier with PCR array analysis identified that 23 genes (in tight junction, focal adhesion, gap junction and adhere junction pathways) were decreased at least 40% in (0.25 mM) DCA-treated Caco-2 cells when compared to untreated cells. Finally, we demonstrated that DCA decreased the protein levels of occludin gene at both cellular tight junction and nucleus in epithelial cells.

Conclusions: Collectively, our data suggest that at physiological concentrations, DCA alters the gene expression of multiple pathways related to cell junctions and increases permeability in a Caco-2 intestinal barrier model. These molecular events may represent the underlying mechanistic pathways that are responsible for DCA-induced transcellular and paracellular permeation.

Funding Sources: This work was supported by U.S. Department of Agriculture, Agricultural Research Service, research project 3062-51,000-056-00D.