Effects of Chronic Hypervitaminosis a on Global Plasma Metabolome Changes and Liver Gene Expression (OR05-06-19)

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Objectives: Concerns about inadvertent chronic excessive vitamin A (VA) intakes due to overly frequent supplementation, fortification and voluntarily fortified products have been raised. Although chronic excessive VA intake can create liver abnormalities, clinically detectable signs of VA toxicity are rare, indicating the need for early biomarkers of tissue damage induced by excessive VA intake.

Methods: To identify early markers of VA toxicity, we induced chronic hypervitaminosis A in pigs (64 pigs, 8 per group) dosed with an oral supplement of retinyl propionate (0 up to 10,000 μg/KgBW) for 17 weeks. To assess the regulatory role of vitamin A in liver metabolism, a microarray analysis was performed to identify genetic regulation in liver tissue. Gene expression data were confirmed using qRT-PCR, and differentially expressed transcripts and pathways were identified using Genespring and Ingenuity Pathway Analysis (IPA). Additionally, two untargeted UPLC-MS assays (HILIC and C_{18} reversed phase) were applied to analyse plasma metabolites followed by univariate and multivariate analysis.

Results: Metabolomics analysis indicated that between 228 to 949 plasma metabolites were statistically significant between VA treated and control animals. The majority of metabolic changes observed in plasma were lipids, with ceramides, glycerophospholipids, lysoglycerophospholipids, sterol lipids and triacylglycerides enriched in both low and high VA dosed animals. Gene expression analysis confirmed significant changes in lipid metabolism, with pathways in metabolism of terpenoids and membrane lipids significantly increased by 2.4 fold.

Conclusions: The combined analysis of gene expression with untargeted metabolomics data confirm that changes in liver function and lipid metabolism offers an opportunity to develop a biomarker panel to diagnose pre-symptomatic hypervitaminosis A in humans.

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