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## Monday June 26th: Physiology and Endocrinology 1

### Systemic transcriptomic analysis in lactating cows with elevated peripheral serotonin

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The objective of this study was to investigate the systemic transcriptional response to elevated peripheral serotonin in lactating cows. In a cross-over design, multiparous Holstein cows (187±34 DIM, n=8) were intravenously infused with saline or the serotonin precursor 5-HTP (1mg/kg bodyweight) on days 1–3 and 8–10 of each period, for 1h/d, starting at 7am. Adipose tissue (WAT), liver, and mammary were biopsied 6 h after d10 infusion. Extracted RNA was sequenced, mapped to the cattle reference genome (ARS-UCD 1.2), and analyzed with DEseq2 for differentially expressed genes (DEG) using a combinatory cutoff of mean read-count ≥ 5, fold-change ≥ 2, and p-value < 0.01. 5-HTP downregulated 71 and upregulated 14 identified genes in WAT, 59 genes were downregulated and 95 upregulated in the liver, and 43 downregulated and 29 upregulated in mammary tissue. Expression patterns were analyzed by QIAGEN Ingenuity Pathway Analysis (IPA) with absolute Z-score ≥ 2 as cut-off. Based on IPA prediction, 5-HTP decreased activity of 54 upstream regulators of the DEG in WAT, including insulin, PPAR gamma, and FOXO-1; and increased activity of 17 regulators. In line, *synthesis and metabolism of triacylglycerol* and *uptake of monosaccharides* were predicted to be inhibited in response to 5-HTP. In the mammary glands, 5-HTP increased the activity of 90 upstream regulators and decreased activity 220 of them. In addition, IPA predicted that 5-HTP increased mammary lipids trafficking. In the liver, 90 upstream regulators had decreased activity, including insulin receptor, PKC, FOXO-1 and 2, and SREBF-1 and 2; and 61 had increased activity, including the cholesterol synthesis inhibitors INSIG-1 and 2. In line, the *superpathway of cholesterol biosynthesis* was predicted to be inhibited by 5-HTP in the liver. In conclusion, lactating cows with elevated peripheral serotonin developed a systemic response, altering the expression of genes in energy metabolic pathways, including reduced lipid synthesis in WAT, reduced cholesterol synthesis in the liver, and increased lipid trafficking in the mammary tissue. Together, these changes may function to shift energy partitioning towards milk synthesis.

**Adisseo Message:**

Among its many functions in the body, serotonin plays a role in energy metabolism. 5-hydroxytryptophan (5-HTP) is the precursor to serotonin and infusing 5-HTP has been documented to increase peripheral serotonin concentrations in lactating dairy cows. This study aimed to investigate the effects of serotonin on liver, mammary and adipose tissue metabolism using 5-HTP. In particular, changes across the three tissues indicated a systemic change in lipid metabolism, suggesting a shift in energy partitioning towards milk rather than storage in adipose tissue.