Lipid Mobilization in Transition Dairy Cows Alters Endothelial Inflammatory Response

G.A. Contreras, *DVM, MSc;* **L.M. Sordillo,** *PhD*
Large Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, E. Lansing, MI 48824

Introduction

A hallmark of the transition period in dairy cows is intense lipid mobilization. This mechanism of adaptation is necessary to fulfill the energy deficits experienced by cows in late gestation and early lactation. Lipid mobilization is a dynamic process involving lipolysis and lipogenesis. During the transition period, the rate of lipolysis surpasses that of lipogenesis, inducing the release of non-esterified fatty acids (NEFA) into the blood stream. As a consequence, increased NEFA concentrations disrupt systemic lipid homeostasis not only quantitatively, but also relative to composition. Previous research demonstrated that enhanced lipolysis during the transition period altered the fatty acid composition of different organs and cell populations including blood, liver, adipose tissue, and peripheral blood mononuclear cells. A common change was the increment in the concentrations of saturated fatty acids (palmitic and stearic). Although increments in plasma NEFA are linked to transition cow diseases such as ketosis and displaced abomasum, less is known about the consequences of shifts in fatty acid profiles of endothelial cells and how these changes contribute to dairy cows increased susceptibility to disease. Immune responses are highly dependent on the interactions between immune cells with the vasculature. Indeed, endothelial cells regulate the trafficking of the immune cell migration to and from tissues. We hypothesize that shifts in plasma NEFA content and composition in transition dairy cows modify endothelial cells inflammatory response by enhancing lipid mediator biosynthesis and expression of adhesion molecules.

Materials and Methods

Bovine aortic endothelial cells (BAEC) were cultured for four and 24 hours with 0, 0.25, 0.5, and 0.75 mM concentrations of NEFA mixture complexed to bovine serum albumin. The NEFA mixture included myristic (3%), palmitic (30%), stearic acid (45%), oleic (16%), linoleic (5%), and DHA (1%) fatty acids. This complex reflected plasma NEFA fraction during the first week of lactation. To evaluate shifts in the fatty acid profile of BAEC, phospholipids were extracted and analyzed using gas chromatography. BAEC inflammatory responses were assessed at both the gene and protein level. BAEC RNA was extracted for q-PCR of IL-6, IL-8, ICAM1, TLR4, COX-1, COX-2, and 15-LOX1. Protein quantification was performed by Western blot analysis in whole cell lysates using antibodies specific to COX-1, COX-2, TLR4, and ICAM1.

Results

Addition of NEFA-albumin complex to culture media altered the fatty acid profile of BAEC by increasing the concentration of saturated fatty acids (stearic and palmitic) in the phospholipid fraction. Changes in the NEFA content in cultured media induced a significant time and concentration dependent increase of mRNA expression of COX-2, IL-6, IL8, ICAM1, and TLR-4. Changes in gene expression were directly reflected in protein expression by a significant time and concentration dependent increment in the biosynthesis of COX-2. The expression of 15-LOX1, a major enzyme in eicosanoid biosynthesis, also increased significantly with time.

Significance

The transition period is characterized by abrupt changes in lipid homeostasis that could enhance dairy cows' susceptibility to disease. This research demonstrated for the first time that in dairy cows, lipid mobilization augments the expression of pro-inflammatory interleukins and adhesion molecules in endothelial cells. Furthermore, quantitative and compositional alterations of plasma NEFA modify the components of inflammatory lipid mediator biosynthetic pathways at the substrate level by changing phospholipid fatty acid profile and at the enzyme level by enhancing the expression of COX-2 and 15-LOX1. Understanding the dynamics of lipid mobilization during the transition period could lead to novel nutraceutical or pharmacological interventions that modulate inflammatory responses, potentially improving the health of dairy cows during the transition period.