Lipid Mobilization and Inflammation During the Transition Period

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Abstract

The transition period of dairy cows is characterized by changes in the lipid mobilization process in adipose tissues (**AT**) that include enhanced lipolysis and reduced lipogenesis. This imbalance leads to a net release of non-esterified fatty acids (**NEFA**) into the AT environment and circulation. Increasing the availability of these energy dense molecules is a mechanism of metabolic adaptation that is necessary to fulfill energy deficits driven by fetal growth and the onset of lactation. However, intense lipolysis and limited rates of lipogenesis lead to a considerable reduction in AT mass during the first 3 weeks after parturition. At the same time, lipolysis induces a remodeling process in AT that is characterized by a moderate inflammatory response with infiltration of macrophages. In cows that transition well into peak lactation, lipolysis decreases and AT inflammation resolves as lactation progresses. Nevertheless, if lipolysis dysregulation occurs and lipolysis rate does not decrease, AT inflammation becomes chronic and leads to poor lactation performance, reproductive failure, and increased risk for culling. This article summarizes the process of lipid mobilization in transition dairy cows, elaborates on the concept of AT remodeling and inflammation, and discusses how these biological processes affect transition cow health and lactation performance.

Introduction

Lipid mobilization is a bioenergetic process that includes lipogenesis and lipolysis. The AT, as the major body of energy reserve in mammals, is specialized in the storage and release of fatty acids through lipid mobilization. AT lipogenesis comprises the assembly of triglycerides through a stepwise addition of fatty acids catalyzed by glycerol-3-phosphate acyltransferase, 1-acylglycerol-3-phosphate acyltransferase, lipins, and diacylglycerol acyltransferase (Takeuchi and Reue, 2009). During lipolysis, AT's adipose triglyceride lipase, hormone-sensitive lipase, and monoacylglycerol lipase breakdown the triglyceride molecule into glycerol and NEFA [reviewed by Arner and Langin (2014)]. Released NEFA are either re-esterified to triglycerides through lipogenesis or exported into the bloodstream where they are transported by albumin and Fetuin-A for use in other tissues as fuel or secreted in milkfat (Strieder-Barboza et al., 2018). During the transition period, the net release of NEFA from AT into circulation is the result of reduced lipogenesis and enhanced lipolysis within adipocytes (De Koster et al., 2018). Normally, lipolysis decreases and lipogenesis replenishes adipocytes' triglyceride stores as lactation progresses. However, when AT exhibits an impaired response to the anti-lipolytic effects of insulin, lipolysis becomes intense and protracted, and lipogenesis is

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drastically reduced. Cows that exhibit high lipolysis rates around parturition are at a higher risk for inflammatory and metabolic diseases and have impaired lactation and reproductive performance. Among the mechanisms driving these deleterious effects, there are alterations in the inflammatory responses within the AT that lead to dysregulation of metabolic and immune functions in AT and systemically.

Adipose Tissue Remodeling in Transition Dairy Cows is an Inflammatory Process Induced by Lipolysis

The consequences of enhanced lipolysis and reduced lipogenesis in AT of transition cows go beyond the release of NEFA into circulation. Body weight loss during the first 3 weeks after calving is largely explained by a 25 to 35% reduction in the total AT mass and is driven by lipid mobilization (Akter et al., 2011). Excessive lipolysis also induces a remodeling process in AT that is characterized by an inflammatory response that includes infiltration of macrophages and changes in the structure and composition of its extracellular matrix (Contreras et al., 2017b).

Macrophages are the most abundant immune cell type in the AT of ruminants, accounting for 5 to 10% of its stromal vascular cells [i.e. non-adipocytes; Ampem et al. (2016)]. In transition dairy cows and in mid-lactation cows in negative energy balance induced by feed restriction protocols, lipolysis enhances the migration of macrophages into the adipose organ (Contreras et al., 2015; Contreras et al., 2016; Vailati-Riboni et al., 2017; Newman et al., 2019). During excessive lipolysis induced by clinical diseases, such as displaced abomasum and ketosis, AT macrophage populations increase to more than 20% of the cells in the stromal vascular fraction or 2% of the total number of cells in AT (Contreras et al., 2015; Häussler et al., 2017). The role of AT macrophages during lipolysis is to contain and eliminate the highly cytotoxic products of triglycerides breakdown that include NEFA, diglycerides, and monoglycerides (Lee et al., 2013).

The phenotype of AT macrophages is broadly classified as classical (**M1**), which characterizes those cells that are active in pro-inflammatory responses, and alternative (**M2**), which include macrophages that promote inflammation resolution. At any given time, AT macrophages are a combination of M1, M2, and intermediate phenotypes. In transition cows with pronounced negative energy balance, including those with displaced abomasum and ketosis, AT macrophages are predominantly M1 and accumulate in aggregates within omental and subcutaneous depots (Contreras et al., 2015; Newman et al., 2019). In mid-lactation cows exhibiting moderate lipolysis induced by a short 4 day feed restriction protocol, macrophage infiltration into the same AT depots occurs, but without variations in their inflammatory phenotype (Contreras et al., 2016).

In transition cows, AT remodeling may be a major mechanism driving AT specific insulin resistance as described by Zachut and et al. (2013). In their study, cows that lost more body condition during early lactation exhibited a pronounced reduction in the phosphorylation of key components of the insulin signaling pathways, including IRS-1 and AKT, compared to cows with low lipolysis and minimal weight loss. The mechanism linking AT remodeling and AT insulin resistance is the inflammatory responses of AT macrophages that once activated potent blockers of insulin signaling, including IL1-β, IL-6, resistin, and TNF-α (Martinez-Santibanez and Lumeng, 2014).

Lipolysis Products as Modulators of Inflammation and Metabolic Function

Fatty acids released during lipolysis are potent modulators of the activity of macrophages and other immune cells. AT macrophages exposed to saturated FA rapidly acquire an M1 like inflammatory phenotype through the activation of Toll-Like Receptors (**TLR**) 1, 2, 4, and 6 (Suganami et al., 2007; Grant and Stephens, 2015; Velloso et al., 2015). Saturated FA, such as lauric, myristic, and palmitic, strongly activate TLR4 and enhance the secretion of monocyte chemotactic protein-1 (**MCP-1**) (Han et al., 2010). Importantly, these saturated FA are preferentially mobilized from AT during the transition period (Douglas et al., 2007; Contreras et al., 2017a).

Polyunsaturated fatty acids released during lipolysis modulate immune function and inflammation through their oxidation products (oxylipids). For example, linoleic acid is oxidized by 15-lipoxygenase (**LOX**) and by other non-enzymatic reactions to produce hydroxyl-octadecadienoic acids (**HODE**). 13-HODE, a product of lipooxigenases and cyclooxigenases, promotes M2 polarization during lipolysis and acts as a PPAR gamma ligand that promotes adipogenesis and lipogenesis (Lee et al., 2016). In contrast, 9-HODE, promotes M1 polarization and could enhance macrophage infiltration into AT (Vangaveti et al., 2010).

In dairy cows, linoleic acid is the most abundant polyunsaturated fatty acid in plasma and in AT and it is preferentially mobilized by lipolysis during the transition period (Contreras et al., 2010). The dynamics of the plasma and AT contents of its derived oxylipids are linked with lipolysis intensity. In healthy transition cows, plasma 13-HODE increases at 1 week after parturition from its levels at 1 week before calving. In contrast, 9-HODE, an indicator of oxidative stress, remains unchanged. In AT, 9-HODE tends to increase after parturition and 13-HODE is higher than at either 1 or 4 weeks before calving. AT content of 13-HODE is positively associated with plasma beta hydroxybutyrate concentrations (Contreras et al., 2017a). It is expected that as lipolysis rate and oxidative stress status increase there will be an accumulation of 9-HODE within AT. Although more research is needed to characterize the dynamics of 9- and 13-HODE in AT and systemically, in the future, HODEs could be used as lipolysis intensity markers and disease risk or lactation performance predictors in transition dairy cows.

Lipolysis and Immune Function

Excessive lipolysis impairs the efficacy of the inflammatory responses of both the innate and the adaptive immune system cells [reviewed by Contreras et al. (2018)]. For example, cows challenged with Strep. uberis intramammary and with high lipolysis rates induced by feed restriction, exhibit an increased number of immature polymorphonuclear cells in circulation that have lower phagocytic activity compared with cows in positive energy balance (Moyes et al., 2009). In transition cows, high lipolysis rates are associated with reduced chemotactic activity and impaired phagocytosis in neutrophils (Nonnecke et al., 2003). The same population of cells has limited oxidative burst when circulating NEFA are above 500 μ*M* and its viability is drastically reduced when NEFA concentrations reach >1 m*M* (Ster et al., 2012). The inflammatory response of macrophages and polymorphonuclear cells are also affected by excessive lipolyisis during the transition period. Exposure to high NEFA concentrations reduces the mitogenic capacity of these immune cell populations and limits their secretion of IFN-γ and IgM (Ster et al., 2012). Excessive lipolysis also affects the function of cells of

the adaptive immune system. High NEFA concentrations are associated with increments of the B lymphocyte populations and reduction in the numbers of γδ T lymphocytes. Decreased numbers of γδ T lymphocytes are observed in cattle with deficient immune responses in epithelial tissues (Pollock and Welsh, 2002). In summary, lipolytic products, such as NEFA, impair the inflammatory responses of innate and adaptive immune cells and reduce their capacity to clear pathogens, leading to increased disease susceptibility in transition dairy cows.

Adipokines Modulate Systemic Immunity and Metabolism

AT modulates the immune and metabolic functions of dairy cattle through the secretion of adipocyte-derived peptides (i.e., adipokines). Of these adipokines, only adiponectin, leptin, and resistin are well characterized in transition dairy cows. Recent studies demonstrate that the synthesis of these adipokines is modulated by AT remodeling and inflammation and their secretion may be associated with changes in immune and metabolic functions around parturition.

Adiponectin enhances insulin sensitivity in adipocytes, hepatocytes, and muscle cells. At the same time, this adipokine promotes fatty acid β-oxidation in liver and the skeletal muscle. In transition dairy cows, plasma adiponectin concentrations are reduced during the first week after parturition compared to levels observed during the dry period and peak lactation (Kabara et al., 2014). In addition to metabolic effects, adiponectin modulates the inflammatory responses of human and bovine macrophages by reducing their expression and secretion of tumor necrosis factor (**TNF**) alpha and other pro-inflammatory cytokines (Kabara et al., 2014). Adiponectin is also an important modulator of adaptive immunity as it is required for dendritic cell activation and T-cell polarization (Jung et al., 2012). Excessive AT inflammation reduces the secretion of adiponectin by adipocytes, thus impairing the use of NEFA as energy substrate in liver and skeletal muscle.

Leptin modulates the inflammatory responses locally and systemically. Hypoleptinemia impairs the efficacy of T cell immune responses by reducing their capacity for pathogen clearance. Leptin is also necessary for adequate maturation and inflammatory responses in dendritic cells. In macrophages and polymorphonuclear cells, leptin signaling is required for phagocytosis in response to toll-like-receptor activation (Naylor and Petri Jr, 2016). Similar to adiponectin, leptin reaches its nadir during the first week after calving, while the highest plasma concentrations are observed early during the dry period (Chilliard et al., 2005). The effect of AT remodeling on leptin secretion during the transition period is currently unknown.

Resistin is another adipokine with the capacity to systemically modulate immune and inflammatory responses. In dairy cows, plasma resistin peaks during the first week after calving and returns to prepartum levels by 5 weeks in milk (Reverchon et al., 2014). In humans and rodents, resistin expression in adipocytes is stimulated by IL-6, hyperglycemia, and growth hormone. Resistin impairs insulin signaling in adipocytes and is characterized as a pro-inflammatory adipokine (AL-Suhaimi and Shehzad, 2013). It is unknown if AT remodeling and inflammation during the transition period can enhance resistin secretion, but this possibility should be considered as a mechanism for AT specific insulin resistance in dairy cows.

Modulating Lipid Mobilization in the Transition Period

Reduced lipogenesis and increased lipolysis are homeorhetic adaptations to negative energy balance that maintain energy availability for milk production. Although, the process of lipid mobilization is affected by physiological, nutritional, and genetic, management factors, there are different management, nutritional, and pharmacological tools that can be used to limit lipolysis and could potentially promote lipogenesis [reviewed in (Contreras et al., 2018)]

Maximizing dry matter intake (**DMI**) during the transition period reduces lipolysis and promotes lipogenesis. At the same time, it is necessary to limit the sudden drop in feed intake commonly observed during the final weeks of the dry period (Grummer et al., 2004). In addition to maintaining DMI, prepartum diets should be balanced to meet but not exceed energy requirements. This is usually accomplished by feeding high levels of fiber (Allen and Piantoni, 2014). It is important to note that overfeeding energy during the last weeks of gestation enhances lipolysis postpartum and increases the risk of fatty liver (Douglas et al., 2006). Cows that gain excessive body condition score (**BCS**) during the dry period have larger adipocytes that are more sensitive to lipolytic stimuli postpartum (De Koster et al., 2016). An additional feeding strategy is to boost the production of ruminal propionate postpartum by feeding high amounts of moderately fermentable starch (van Knegsel et al., 2007). This nutritional intervention limits AT lipolysis by enhancing insulin secretion (McCarthy et al., 2015).

To complement ration balancing strategies, the inclusion of nutritional supplements that limit lipid mobilization in the diet of transition cows can be considered. Feeding niacin (as nicotinic acid) reduces AT lipolysis by limiting the activity of hormone sensitive lipase (Kenez et al., 2014). However, niacin supplementation has shown inconsistent results (Schwab et al., 2005; Havlin et al., 2016). This may be related to timing of niacin supplementation. When fed only post-partum, niacin does not have FFA-lowering effects (Havlin et al., 2016). However, supplementing niacin throughout the entire transition period was shown to effectively reduce AT lipolysis (Schwab et al., 2005).

Methyl donors are also nutritional supplements that when fed to transition cows limit lipid mobilization. Among these, choline and methionine are reported to reduce lipolysis in AT when fed alone (Cooke et al., 2007; Li et al., 2016) or combined (Sun et al., 2016). Chromium supplementation may promote lipogenesis in AT by enhancing the activity of the insulin receptor in adipocytes (Vincent, 2004). Nevertheless, reports on the pro-lipogenic activity of chromium are inconsistent with some studies demonstrating a NEFA lowering effect (Hayirli et al., 2001; Yasui et al., 2014) and others showing no changes in plasma lipids (McNamara and Valdez, 2005; Smith et al., 2008). Currently, the pool of available pharmacological and nutritional interventions that reduce lipolysis or enhance lipogenesis is still very limited. Exploring new drug targets that enhance insulin sensitivity and block the lipolytic response in adipocytes will facilitate the management of transition dairy cows.

Evaluating Adipose Tissue Function in Dairy Cattle

Transition cow management programs often include routine measures of clinical and production parameters that can directly or indirectly evaluate adipose tissue function. BCS is a good measure of subcutaneous adiposity and the dynamics of BCS changes around

parturition subjectively describes lipolysis rates. Alternatively, the use of image biomarkers obtained during ultrasound examination of adipose tissues provides an objective evaluation of BCS, avoiding the variability associated with subjective visual measurements. Subcutaneous adipose tissue depth is strongly correlated with BCS evaluation when measured by trained personnel and is highly sensitive and specific in predicting plasma NEFA values at close-up and calving in dairy cattle (Strieder-Barboza et al., 2015). If using subjective BCS assessment, mature cows should approach calving with a BCS of 3.0 to 3.5 and heifers with 3.25 to 3.75 as excessively thin or over-conditioned cows are more susceptible to disease.

Currently, the most common direct measure of lipolysis is plasma NEFA. In preventive herd medicine, pre and post calving plasma NEFA values are used as early lactation disease predictors. Similar to plasma NEFA, post-partum plasma β-hydroxybutyrate indicate negative energy balance and predict disease risk in early lactation (Ospina et al., 2013). Lipolysis can also be evaluated at the group or individual animal level using the milk fat to milk protein percentage ratio. Milk fat increases as plasma NEFA rise. Cows with milk fat to milk protein ratio values higher than 2 during the first week after calving are at a higher risk for developing retained fetal membranes, DA, clinical endometritis, and being culled before the end of lactation (Toni et al., 2011).

Novel biomarkers of AT function are being explored. Low concentrations of the NEFA transporters albumin and fetuin-A are associated with low lipogenic activity in AT (Strieder-Barboza et al., 2018) and may indicate higher risk for developing fatty liver. HODEs and other oxylipids that are markers of inflammation in AT may provide disease risk information regarding AT function but still require large epidemiological studies to be validated. It is necessary to mention that single biomarkers do not provide enough information to support management decisions during the transition period. However, when multiple biomarkers are analyzed together and combined with health, production, nutritional, and environmental data, biomarkers become essential for identifying metabolic problems related to extended periods of intense lipolysis (Contreras et al., 2017b). The mechanisms for this cause effect relationship may include lipolysis induced AT remodeling processes, alterations in the expression of adipokines, and the development of insulin resistance.

Conclusions

Lipid mobilization modulates the inflammatory responses within AT and systemically. Lipolysis, a key component of the lipid mobilization proces, is a major trigger of inflammation within AT by driving macrophage infiltration into AT and inducing changes in the structure of the adipose organ. Systemically, lipolysis products, including NEFA and oxylipids, are inflammatory mediators that modulate immune and metabolic functions. Reducing the intensity and duraton of the periparturient lipolytic surge by management and nutritional interventions may ensure a rapid return to positive energy balance and ensure a productive lactation.

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