Symposium review: Adipose tissue endocrinology in the periparturient period of dairy cows*

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ABSTRACT

The involvement of adipose tissue (AT) in metabolism is not limited to energy storage but turned out to be much more complex. We now know that in addition to lipid metabolism, AT is important in glucose homeostasis and AA metabolism and also has a role in inflammatory processes. With the discovery of leptin in 1994, the concept of AT being able to secrete messenger molecules collectively termed as adipokines, and acting in an endo-, para-, and autocrine manner emerged. Moreover, based on its asset of receptors, many stimuli from other tissues reaching AT via the bloodstream can also elicit distinct responses and thus integrate AT as a control element in the regulatory circuits of the whole body's functions. The protein secretome of human differentiated adipocytes was described to comprise more than 400 different proteins. However, in dairy cows, the characterization of the physiological time course of adipokines in AT during the transition from pregnancy to lactation is largely limited to the mRNA level; for the protein level, the analytical methods are limited and available assays often lack sound validation. In addition to proteinaceous adipokines, small compounds such as steroids can also be secreted from AT. Due to the lipophilic nature of steroids, they are stored in AT, but during the past years, AT became also known as being able to metabolize and even to generate steroid hormones *de novo*. In high-yielding dairy cows, AT is substantially mobilized due to increased energy

requirements related to lactation. As to whether the steroidogenic system in AT is affected and may change during the common loss of body fat is largely unknown. Moreover, most research about AT in transition dairy cows is based on subcutaneous AT, whereas other depots have scarcely been investigated. This contribution aims to review the changes in adipokine mRNA and—where available—protein expression with time relative to calving in high-yielding dairy cows at different conditions, including parity, body condition, diet, specific feed supplements, and health disorders. In addition, the review provides insights into steroidogenic pathways in dairy cows AT, and addresses differences between fat depots where possible.

Key words: adipokines, adipose tissue, endocrinology, periparturient period

INTRODUCTION

Adipose tissue (AT) is not only a simple energy store, but is also considered as an endocrine organ that produces factors regulating lipid homeostasis, insulin sensitivity, glucose metabolism, fat distribution, and inflammation (Kershaw and Flier, 2004; Coelho et al., 2013). Signaling molecules produced and secreted by AT, termed adipokines, include cytokines, hormones, growth factors, chemokines, complement factors, and various other proteins. In addition to proteins, lipids, metabolites, noncoding RNAs, and extracellular vesicles are released by AT, contributing to maintaining systemic homeostasis (Funcke and Scherer, 2019). Moreover, due to their lipophilic properties, steroid hormones are stored in AT and can also be metabolized or converted to other steroids depending on the enzyme composition (Deslypere et al., 1985; Diamanti-Kandarakis, 2007), with significant metabolic effects in the early lactation of cows (Grummer et al., 1990; Bell, 1995). Trayhurn and Wood (2004) suggested describing the entirety of proteins and lipids as adipokinome, according to biological omics approaches. Adipokines play an important role in the communication of cells within AT, but also in the endocrine crosstalk with other tis-

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sues such as liver and skeletal muscle (Romacho et al., 2014). In ruminants, data on adipokines mainly focus on mRNA; thus, besides from leptin and adiponectin, protein data from adipokines in AT and in the circulation are very limited.

In high-yielding dairy cows, the period around parturition is characterized by extensive physiological and metabolic adaptations: Within a short period, energy requirements increase due to the onset of lactation compared with precalving requirements (Bell, 1995; Drackley et al., 2005). Consequently, most high-yielding dairy cows experience a negative energy balance (**NEB**) at the onset of lactation, leading to the mobilization of body reserves mainly from AT and muscle tissues (Drackley, 1999). Lipolysis results in increased blood concentrations of free fatty acids (**FFA**), which can lead to metabolic diseases such as fatty liver and ketosis (Adewuyi et al., 2005). Larger initial fat depots in late lactation lead to increased mobilization of AT in the subsequent lactation, with over-conditioned cows consuming less DM due to circulating FFA and resulting ketone bodies (Rukkwamsuk et al., 1999; Laeger et al., 2013). Increased peripartum lipolysis also affects the immune system and reproduction of dairy cows; the direct effects of increased FFA and BHB concentrations on various immune cells have been demonstrated in vitro and in vivo (Bernabucci et al., 2005; Lacetera et al., 2005; Scalia et al., 2006). Furthermore, increased hepatic triglyceride storage may lead to fatty liver in early-lactating dairy cows (Trevisi et al., 2013). The excessive lipolysis in early-lactating dairy cows might originate from various AT depots, with greater lipolytic capacity from retroperitoneal AT, compared with subcutaneous AT (Kenéz et al., 2015). Moreover, depot-specific variations of AT have been observed in homeorhetic adaptations during the periparturient period in dairy cows and should be considered when regarding endocrine responses and adipose energy metabolism at the onset of lactation (Kenéz et al., 2019).

This paper reviews the changes in adipokine mRNA and, where available, protein expression over time relative to calving in high-yielding dairy cows under a variety of conditions, such as parity, body condition, diet, specific feed supplements, and health disorders. In addition, the review highlights recent findings related to steroidogenic pathways in AT from dairy cows. Moreover, differences between fat depots are addressed where possible.

Adipose Tissue as an Endocrine Organ

Being a highly active metabolic and endocrine organ, AT is the major energy store in the body for excess

energy. However, it can also express and secrete several biologically active factors that regulate metabolic homeostasis, fat distribution, satiety, insulin sensitivity, and secretion (Rosen and Spiegelman, 2006; Coelho et al., 2013). Various adipokines, such as leptin, adiponectin, chemerin, visfatin, pigment epithelium-derived factor (**PEDF**), resistin, fibroblast growth factor 21 (**FGF21**), retinol-binding protein 4 (**RBP4**), apelin, omentin, and many others are produced and secreted by AT (Funcke and Scherer, 2019). In addition to these adipokines, AT produces and secretes inflammatory cytokines [e.g., tumor necrosis factor- α (**TNF- α**), IL-6, and monocyte chemoattractant protein-1 (**MCP-1**); Funcke and Scherer, 2019], acute phase proteins (e.g., haptoglobin, acid glycoprotein, and serum amyloid A; Cecilian et al., 2012), many lipids (e.g., endocannabinoids, prostaglandins, steroids, and FFA), complement and complement-related proteins, proteins of fibrinolytic, enzymes, and lipid transport (Kershaw and Flier, 2004; Ahima, 2006). Adipose-derived factors are involved in the regulation of metabolism by communicating within AT or between other organs and tissues involved in metabolic processes, such as liver, pancreas, skeletal muscle, heart, and brain (Kita et al., 2019). In humans and mice, receptors for the adipokines leptin, adiponectin, and resistin as well as for the cytokine TNF- α were shown to be expressed in the central nervous system (**CNS**; Parimisetty et al., 2016). To exert their function via receptors in the CNS, adipokines have to cross the blood-brain barrier or affect the CNS indirectly via pathways stimulated by cells of the blood-brain barrier. Being involved in feeding behavior, leptin could be synthesized de novo in the brain from rodents, acting directly on the CNS (Parimisetty et al., 2016). Lipolysis from AT depots during the transition period coincides with a period of induced AT remodeling (Contreras et al., 2017, 2018) and decreased insulin sensitivity in hepatocytes, adipocytes, and myocytes, redirecting energy toward milk synthesis (De Koster and Opsomer, 2013). Intense and prolonged lipolysis leads to changes in the secretion pattern of adipokines and is simultaneously modulated by these bioactive compounds (Bell and Bauman, 1997; Contreras et al., 2017). Bovine adipocytes become more sensitive to insulin as lactation progresses, resulting in decreased rates of lipolysis and increased lipogenesis (McNamara, 1994). Moderate insulin resistance in AT might ensure healthy and productive lactation during the transition period; however, when insulin resistance in AT is intense and prolonged, it predisposes dairy cows to inflammation and metabolic dysfunction by limiting the ability of AT to expand its energy buffering capacity (De Koster and Opsomer, 2013).

Adipokines: Definition, Structure, and Assessment

The collective name adipokines was recommended to describe proteins that are synthesized and secreted by AT; moreover, restricting the term to those proteins that are secreted exclusively from adipocytes (and not by the stromal vascular cells present in AT) was suggested (Trayhurn and Wood, 2004). However, the term adipokine is commonly used to refer to AT-derived proteins. With growing knowledge about far more compounds being released from AT (i.e., noncoding RNA, nonlipid metabolites, and extracellular vesicles), extended definitions comprising the entirety of signaling mediators secreted by AT were suggested (Funcke and Scherer, 2019). Overall, the term adipokinome should be used to describe the entirety of proteins and lipids, such as the secretome of AT (Trayhurn and Wood, 2004). This review focuses on the bovine AT secretome, in particular, protein, peptide, and lipid mediators secreted by adipocytes as well as the cells of the stromal vascular cell fraction in various AT depots of dairy cows in the periparturient period.

Protein Adipokines

Concerning the proteins, aside from leptin and adiponectin, the knowledge about most proteinaceous adipokines in dairy cows, and ruminants in general, is largely limited to mRNA data, whereas protein data, both for AT itself and in the circulation are scarce. One important reason for this is the lack of suitable and valid assays. Even though antisera used in western blotting and ELISA are available from commercial sources, they are hardly validated for bovine samples, and using them may result in misleading data. For western blot data, not only the antibodies but also the conditions used (linearity of signal to the amount of sample, to the dilution of the first and second antibody) should be validated and appropriate controls integrated when aiming at quantification (as recommended for example by Pillai-Kastoori et al., 2020). When using proteomics, validation of individual proteins using western blot or ELISA is often requested but can result in the dilemma of inappropriate assays that are not suitable for validation. This is certainly not limited to adipokines, and care should be taken both by authors and reviewers to support that only validated data make their way into the literature. The following section provides an overview of selected protein adipokines and cytokines. Table 1 summarizes the adipokines and their main functions discussed in this review article.

Adiponectin. Adiponectin, predominantly derived from adipocytes, is synthesized as a monomer; however, polymerization of adiponectin is essential to regulate

biological activity (Wang et al., 2006). In dairy cows, adiponectin circulates mainly as a high molecular weight isoform, regardless of lactation stage (Giesy et al., 2012; Sauerwein and Häußler, 2016). The different isoforms mediate their function via different receptors (see Table 1). Decreased circulating adiponectin levels, as well as reduced biological response to adiponectin through reduced expression of adiponectin receptors (ADIPOR1 and ADIPOR2), can reduce adiponectin sensitivity (Stojanovic et al., 2020). In obese humans, reduced *ADIPOR1* expression in AT was associated with reduced biological adiponectin response and consequently aggravate negative metabolic effects of low adiponectin concentrations (Rasmussen et al., 2006). Therefore, downregulation of adiponectin receptors (*ADIPOR1* and *ADIPOR2*) mRNA abundance in subcutaneous AT (**scAT**) in periparturient dairy cows might suggest decreased insulin sensitivity, leading to reduced glucose uptake and increased lipolysis after parturition (Lemor et al., 2009).

The anti-inflammatory properties of adiponectin have been substantiated in dairy cows during the periparturient period, where reduced adiponectin concentrations together with increased lipolysis could enhance the inflammatory response of monocytes (Kabara et al., 2014). Moreover, adiponectin treated primary bovine monocytes suppressed upregulation of TNF- α gene and protein expression after LPS administration, confirming an immune-modulatory function of adiponectin (Kabara et al., 2014). Pereira et al. (2020) reported increased plasma adiponectin concentrations at d 21 and 45 postpartum (**PP**) in dairy cows with persistent endometritis. Based on their overall results, adiponectin was suggested as a biomarker for early diagnosis of subclinical endometritis (Pereira et al., 2020). Adiponectin plays a key role in controlling energy metabolism by promoting insulin sensitivity, adipogenesis, and lipid storage in AT (Fu et al., 2005), lipogenesis in hepatocytes, and fatty acid (**FA**) β -oxidation in myocytes and hepatocytes in humans (Stern et al., 2016). For cattle, we have investigated endogenous and exogenous factors affecting the concentrations of adiponectin in various body fluids and tissues (Sauerwein and Häußler, 2016). Using an in-house developed competitive ELISA, we found that serum adiponectin concentrations exceeds those in AT (Singh et al., 2014a); however, around parturition, adiponectin concentrations in circulation as well as in various AT depots decrease in high-producing dairy cows and reach their nadir immediately after calving (Singh et al., 2014a,b). Moreover, the mRNA abundance of adiponectin receptors *ADIPOR1* and *ADIPOR2* in scAT was lesser than in liver during the transition from pregnancy to lactation in high-yielding dairy cows (Saremi et al., 2014). Different mRNA abun-

Table 1. Main adipokines in dairy cows, their main metabolic functions, and their potential to serve as biomarkers (in different species)¹

Adipokine: molecular weight and isoforms	Receptor	Main metabolic function	Potential biomarker
Adiponectin: 28–30 kDa (monomer); in circulation: trimer (~90 kDa), hexamer (~180 kDa), HMW ² (>250 kDa)	AdipoR1 (AdipoQ trimer); AdipoR2 (AdipoQ hexamer); T-cadherin (AdipoQ hexamer and HMW forms); Calreticulin (hexamer and HMW forms); (Jasinski-Bergner et al., 2017; Kita et al., 2019)	Enhance insulin sensitivity (Stern et al., 2016); anti-inflammatory (Kabara et al., 2014); anti- atherogenic; increase free fatty acid oxidation in hepatocytes and myocytes; increase glucose uptake; increase adipogenesis and lipid storage in AT (Fu et al., 2005; Stern et al., 2016)	May predict the risk of persistence of uterine inflammation in cows (together with chemerin; Pereira et al., 2020); biomarker for metabolic health in humans (Trujillo and Scherer, 2005)
Apelin: apelin-36 (preproapelin 42–7); apelin-17 (preproapelin 61–77); apelin-13 (preproapelin 65–77); pyroglutamate apelin-13 (Pry-apelin-13) (Kurowska et al., 2018)	APLNR/APJ receptor (angiotensin-1- like receptor)	Anti-inflammatory; increase glucose uptake by adipose tissue and skeletal muscle in mice (Dray et al., 2008)	May predict type 2 diabetes in men (Ma et al., 2014)
Chemerin: 18 kDa (inactive prechemerin); 16 kDa (active)	Chemokine receptor-like 1 (CMKLR1)	Regulation of the immune system, inflammation, angiogenesis, adipogenesis, and glucose metabolism in humans (Heller and Wu, 2018)	Inflammatory biomarker in the development of metabolic disorders in humans (Koelman et al., 2021); indicator for insulin sensitivity in bovine (Kopp et al., 2014) Biomarker for diabetes prediction in humans (Woo et al., 2017)
FGF21: 23 kDa	FGF receptor	Metabolic effects on energy metabolism, glucose homeostasis, and insulin sensitivity in liver and skeletal muscle (Holland et al., 2013; Lin et al., 2013)	
Leptin: 16 kDa	Leptin receptor (ObR)	Induce lipolysis (Stern et al., 2016); induce fatty acid oxidation (Stern et al., 2016); inhibit adipocyte differentiation (Zhou et al., 1999); anti-adipogenic (Gerhardt et al., 2001); mediator between nutritional status and immune system; pro-inflammatory stimulus (increased leptin levels) in obese humans (Boutari et al., 2018) Anti-angiogenic (Bouck, 2002); neurotrophic (Simonovic et al., 2001); anti-inflammatory functions in humans (Zhang et al., 2006)	Adiponectin/leptin-ratio: predictive marker for the metabolic syndrome in humans (Frühbeck et al., 2017)
PEDF: 50 kDa	Patatin-like phospholipase domain containing 2 (ATGL; adipose triglyceride lipase); ribosomal protein SA (LR1; laminin receptor 1) (Notari et al., 2006; Bernard et al., 2009)	Facilitates the transport of retinol from liver to peripheral organs (Berni et al., 1990); binds and transports FA (Perduca et al., 2018); induce insulin resistance in mice (Yang et al., 2005); inhibits adipogenesis in humans (Romacho et al., 2014)	Biomarker for insulin resistance or visceral obesity in humans (Yamagishi and Matsui, 2018)
RBP4: 21 kDa	Signaling transporter and receptor of retinol 6 (STRA6); retinol-binding protein receptor 2 (RBPR-2)		Predictive biomarker at early stages of insulin resistance in humans (Torabi and Ghourchian, 2020); marker for type 2 diabetes in human and cardiovascular risk (Klötting et al., 2007)

Continued

Table 1 (Continued). Main adipokines in dairy cows, their main metabolic functions, and their potential to serve as biomarkers (in different species)¹

Adipokine: molecular weight and isoforms	Receptor	Main metabolic function	Potential biomarker
Resistin: 12 kDa (monomer); in circulation: dimers, trimers, and hexamers (Estienne et al., 2019)	Isoform of decorin (DCN; Daquinag et al., 2011); mouse receptor tyrosine kinase-like orphan receptor 1 (ROR1; Sánchez-Solana et al., 2012); toll-like receptor 4 (TLR4; Benomar et al., 2013); adenylyl cyclase-associated protein 1 (CAP1; Lee et al., 2014)	Regulates reproductive and metabolic processes at the level of the central nervous system comparable to leptin in ruminants (Zieba et al., 2020)	Inflammatory biomarker and potential mediator of diabetes and cardiovascular disease in humans (Schwartz and Lazar, 2011); biomarker for insulin resistance in humans (Schwartz and Lazar, 2011); biomarker for tumorigenesis in humans (Tripathi et al., 2020)
Visfatin: 52 kDa; intracellular and extracellular NAMPT (Estienne et al., 2019)	Insulin receptor	Mimics insulin action (Revollo et al., 2007)	May identify cows at increased risk for metabolic diseases (Fadden and Bobe, 2016)

¹FGF21 = fibroblast growth factor 21; PEDF = pigment epithelium-derived factor; RBP4 = retinol-binding protein 4.²HMW mainly in cows.

dance of *ADIPOR1* and *ADIPOR2* in various tissues (i.e., sc and visceral fat depots, liver, muscle, and mammary gland) suggests differential local regulation of insulin sensitivity (Saremi et al., 2014). During the dry period of dairy cows, De Koster et al. (2017) observed a negative correlation between body condition and serum adiponectin concentrations, with adiponectin values decreasing at the end of the dry period. However, comparing multiparous dairy cows with high (>4.0) and normal (3.25–3.5) BCS, body condition at parturition did not affect circulating adiponectin concentrations (Mansouryar et al., 2018).

Overall, it has been suggested that lower blood adiponectin concentrations and decreased mRNA abundance in tissues around parturition contribute to increased lipolysis and decreased insulin sensitivity of peripheral tissues, both of which improve the nutritional status of dairy cows after calving (Singh et al., 2014b). Thus, the local and endocrine functions of adiponectin in dairy cows are thought to contribute to the homeorhetic adaptations in early lactation (Contreras et al., 2017).

Apelin. Apelin, another fat-derived factor, has been reported to increase glucose uptake by AT and skeletal muscle in mice (Dray et al., 2008). In addition to adipocytes, *APLN* mRNA and its receptor are also expressed in other tissues such as lung, heart, skeletal muscle, kidney, brain, and liver (De Falco et al., 2002). Four isoforms of apelin exist with different biological activities (see Table 1). Although, the isoforms are not fully understood, apelin-13 and pyroglutamate apelin-13 have greater activity than apelin-36 (Kurowska et al., 2018). The isoforms show different affinities for the G-protein-coupled apelin receptor APJ, an angiotensin-1-like receptor (i.e., apelin-13 binds more effectively than apelin-36; Hosoya et al., 2000). However, the longer apelin-36 is considered the physiologically active form in dairy cows (Alhussien and Dang, 2020). Using untargeted liquid chromatography in conjunction with high resolution and high accuracy mass spectrometry, 46 apelin peptides has been detected in bovine colostrum, with varying abundance between different colostrum samples (Mesmin et al., 2011). However, the biological relevance of the different apelin compositions in bovine colostrum is unclear, albeit an individual effect on calves has been suggested (Mesmin et al., 2011).

In dairy cows, apelin was detected in blood, milk, and colostrum (Mesmin et al., 2011; Aydin, 2013). However, both tissue and colostrum concentrations were reportedly greater (approximately 200 ng/mL; Habata et al., 1999; Mesmin et al., 2011) compared with serum concentrations (1–1.4 ng/mL) in dairy cows (Weber et al., 2016a), which might result out of different assays used for the analysis. Weber et al. (2016a) showed that total serum apelin concentrations were nearly constant from

late gestation to 100 DIM in high-yielding dairy cows and thus, did not reflect metabolic challenges around parturition.

Using an ELISA that exclusively detects apelin-36, decreased apelin-36 concentrations accompanied with decreased insulin and glucose concentrations were observed in primiparous and multiparous cows during the transition period with concomitant BCS reduction (Norvezh et al., 2019). Regarding the contradicting results to Weber et al. (2016a), Norvezh et al. (2019) suggested that the proportion of the different apelin peptides might change during the periparturient period, without affecting the overall serum apelin concentrations. Moreover, markers related to NEB in dairy cows, such as FFA, insulin, and glucose concentrations, were associated with decreasing apelin-36 serum concentrations around calving. Thus, the altered apelin-36 concentrations during the periparturient period might be involved in adaptations of dairy cows to NEB in early lactation (Norvezh et al., 2019).

Chemerin. Chemerin, encoded by the retinoic acid 2 receptor (*RARRES2*), is predominantly expressed and secreted by adipocytes (Reverchon et al., 2015; Helfer and Wu, 2018) and hepatocytes (Krautbauer et al., 2013). Chemerin is involved in the regulation of the immune system, inflammation, angiogenesis, adipogenesis, and glucose metabolism in humans (Helfer and Wu, 2018). In dairy cows, plasma concentrations of chemerin range from 3.6 to 4.8 ng/mL in early lactation and then steadily decrease until wk 20 of lactation (Mellouk et al., 2019). The mRNA abundance of *RARRES2* in bovine scAT was related to BCS and yearling weight (Lindholm-Perry et al., 2012), adipocyte differentiation (Song et al., 2010), and body fat mobilization (Elis et al., 2013, 2016; Mellouk et al., 2019). Fu et al. (2016) investigated the effects of chemerin treatment on mature adipocytes as well as de-differentiated bovine intramuscular preadipocytes in vitro. They found that chemerin and its receptor (G-protein-coupled chemerin-like receptor 1) were predominantly expressed in bovine intramuscular adipocytes and were downregulated during adipocyte lipolysis, whereas they were reversed during preadipocyte differentiation (Fu et al., 2016). Exposure to chemerin induced lipolysis in intramuscular mature adipocytes in vitro, as indicated by increased glycerol levels, FFA, and upregulated expression of the lipolysis-critical factors hormone-sensitive lipase, lipoprotein lipase (LPL), and leptin (Fu et al., 2016). Previous in vivo studies (Suzuki et al., 2012a,b) reported the metabolic and endocrine changes in response to chemerin in sheep. They found that chemerin analog regulated insulin secretion related to glucose metabolism (Suzuki et al., 2012b) and treatment with chemerin analog up-regulated *RARRES2* mRNA abundance in bovine dif-

ferentiated adipocytes (Suzuki et al., 2012a). Moreover, treatment of bovine adipocytes with nicotinic acid (10 μ M) for 24 h resulted in increased mRNA abundance of *RARRES2* compared with the untreated controls (Kopp et al., 2014). Kopp et al. (2014) assumed that niacin supplementation might improve insulin sensitivity or adipocyte metabolism, suggesting chemerin as a potential indicator for insulin sensitivity.

Fibroblast Growth Factor 21. Fibroblast growth factor 21, a member of the endocrine branch of the FGF superfamily, has important effects on energy homeostasis, glucose, and lipid metabolism, and insulin sensitivity (Kharitonov et al., 2005). The FGF21 acts through the FGF receptor (**FGFR**) with the transmembrane protein β -Klotho as an essential co-factor activating FGFR (Itoh, 2010). The liver is considered the main site of FGF21 production in mice, where production is induced by fasting or ketogenic diets (Badman et al., 2007; Inagaki et al., 2007) and by activation of peroxisome proliferator-activated receptor (**PPAR**) α , cAMP-responsive element-binding protein H, and the deacetylase sirtuin 1 (Fisher and Maratos-Flier, 2016). In addition, FGF21 is considered as an adipokine (Itoh, 2014), with the adipokine adiponectin as a downstream effector of FGF21 mediating the metabolic effects of FGF21 on energy metabolism, glucose homeostasis, and insulin sensitivity in liver and skeletal muscle (Holland et al., 2013; Lin et al., 2013). However, a bolus and chronic administration of FGF21 did not provide evidence for FGF21 stimulation of adiponectin in early-lactating dairy cows (Krumm et al., 2019). Plasma FGF21 levels increase abruptly in periparturient dairy cows at the beginning of lactation and remain elevated during the energy deficit of early lactation (Schoenberg et al., 2011). The mRNA abundance of *FGF21* was detectable in scAT on d -40 and 7 relative to calving in multiparous cows but was much lower than in the liver ($\leq 4\%$; Schoenberg et al., 2011). In prepubertal dairy heifers, *FGFR1c* was the dominant expression in scAT and perirenal AT among all FGFR transcripts, and that of *KLB* mRNA was more abundantly expressed in AT than in the liver (Schoenberg et al., 2011). The transition from late gestation to early lactation did not affect the abundance of *FGFR1c* mRNA in scAT in multiparous cows (Schoenberg et al., 2011) and in dairy cows receiving the PPAR agonist CLA (Sadri et al., 2014). However, protein data of FGF21 in bovine AT are lacking so far. Therefore, studies on the regulation of *FGF21* expression in different AT depots and a possible endocrine role of AT as a source of systemic FGF21 in cattle as well as on FGF21 protein in bovine AT may be particularly relevant.

Leptin. The protein hormone leptin is primarily known as an adipokine; however, leptin is also ex-

pressed and secreted by several other tissues, including muscle, mammary gland, placenta, and gastric mucosa (Chilliard et al., 2001). Leptin acts in an autocrine, paracrine, and endocrine manner and modulates food intake and energy expenditure, predominantly via hypothalamic signals in the CNS (Liefers et al., 2005). Leptin is ubiquitously encoded by the *LEP* gene and plays a central role in regulating body energy homeostasis, with concentrations correlating with body fat content (Chilliard et al., 2001). As known from human studies, leptin induces lipolysis and FA oxidation during periods of suppressed feed intake (Stern et al., 2016). In addition, an inhibitory effect on adipocyte differentiation has been reported for this adipokine in rats (Zhou et al., 1999), which directly contributes to the antiadipogenic effects of chemokines observed in cultured human adipocytes (Gerhardt et al., 2001). Ingvarlsen and Boisclair (2001) reviewed the effects of low leptin levels due to starvation as well as exogenous leptin administration on immune parameters in rodents. In mice, exogenous leptin administration inverted the inhibitory effects of starvation on T-cells (Lord et al., 1998). In this context, it has been suggested that leptin is a mediator between nutritional status and the immune system (Friedman and Halaas, 1998). Leptin mainly acts in a pro-inflammatory way, affecting both the immune cell development and function (Kiernan and MacIver, 2021). Because the immune system of dairy cows is prone to dysfunctions in the periparturient period (reviewed by Sordillo 2016), leptin deficit in early lactation might contribute to the development of depressed immunity (Ingvarlsen and Boisclair, 2001). A possible immunosuppressing effect of leptin therapy on immune cells, as shown in starving mice (Lord et al., 1998), may offer advantages for the strained metabolic situation in early-lactating dairy cows.

In ruminants, AT is the major supplier of plasma leptin (Chilliard et al., 2001) with varying mRNA abundance in different subcutaneous and visceral AT (Saremi et al., 2014). With the development of valid assays, both RIA (Ehrhardt et al., 2000; Delavaud et al., 2000) and ELISA (Kauter et al., 2000; Sauerwein et al., 2004), leptin concentrations were quantified in ruminants. In dairy cows, plasma leptin concentrations are greatest during the dry period (Holtenius et al., 2003), whereas they decrease around the time of parturition due to lesser leptin secretion from AT (Block et al., 2001). Both leptin concentrations in plasma and cerebrospinal fluid decreased until calving and remained low in early lactation when compared with values before calving (Laeger et al., 2013). Given that leptin reduces feed intake in ruminants when binding to its receptors located in the hypothalamus (Morrison et al., 2001), Laeger et al. (2013) assumed that reduced

circulating leptin stimulates hyperphagia during early lactation. Both primiparous and multiparous cows exhibited decreasing plasma leptin concentrations during the transition period, which was accompanied by decreasing mRNA abundance of *LEP* in scAT from the tail head region (Saremi et al., 2014). This may promote a rapid return to normal DMI within this period (Contreras et al., 2017). Moreover, Sadri et al. (2011) observed inverse leptin concentrations with the greatest NEFA concentrations in the blood of dairy cows one week after parturition, due to either NEB or increased turnover rate during lactation. A greater decrease in plasma leptin was observed in over-conditioned dairy cows during the last week before and the first week after calving compared with cows with normal body fatness, postulating that plasma leptin was closely related to body fatness in early-lactating dairy cows (Kokkonen et al., 2005). Furthermore, leptin was greater in dairy cows with a greater degree of periparturient lipomobilization than normally conditioned cows due to their over-conditioning in the antepartum (AP) period (Schuh et al., 2019). Leptin resistance during gestation prevents reduction of feed intake in dairy cows; however, after parturition, leptin sensitivity seems to increase due to an increased expression of leptin receptors (Liefers et al., 2005). Albeit the mechanisms of leptin resistance require further investigations, the reduction of plasma leptin around parturition likely contributes to the adaptive metabolism of early-lactating dairy cows (Ehrhardt et al., 2016).

Pigment Epithelium-Derived Factor. Being one of the major biological active secretion products of human adipocytes PEDF has anti-angiogenic (Bouck, 2002), neurotrophic (Simonovic et al., 2001), and anti-inflammatory functions (Zhang et al., 2006). Treatment with PEDF-induced insulin resistance in human adipocytes and skeletal muscle cells (Famulla et al., 2011). It has been suggested as a marker of body mass changes, because weight loss has been associated with decreased serum PEDF in both animal models of obesity and obese humans (Crowe et al., 2009; Sabater et al., 2010). Based on the expression profile of *SERPINF1* mRNA during 13 d of differentiation of primary bovine pre-adipocytes, adipocytes have also been shown to be a source of PEDF synthesis in AT of dairy cows (Sadri et al., 2018). Regarding the putative functional receptors of PEDF (see Table 1), ATGL is required for the PEDF-induced lipolysis and triglycerides degradation in liver and adipocytes (Chung et al., 2008; Borg et al., 2011). The lactation-induced increase in *SERPINF1* mRNA abundance in scAT was attenuated by CLA supplementation and coincided with reduced serum concentrations of PEDF in multiparous cows 21 DIM (Sadri et al., 2018). When comparing different tissues

of primiparous cows, *SERPINF1* mRNA was greatest in the liver, followed by scAT (tail head, withers, and sternum) and then visceral AT (omental, mesenteric, and retroperitoneal). However, the similarities between the time course of serum PEDF concentrations and its mRNA abundance in scAT observed in multiparous cows suggest that AT is relevant in terms of circulation and thus may indicate a regulatory role for AT rather than liver for PEDF in dairy cows (Sadri et al., 2018). The abundance of *SERPINF1* mRNA in scAT was constant between the different serum-metabotypes of periparturient over-conditioned (BCS >3.75) dairy cows (Sadri et al., 2021). Protein data of PEDF in bovine AT are lacking so far; however, the limited available (mRNA) data support a regulatory role for PEDF in dairy cows. Studies on a possible endocrine role for AT as a source of systemic PEDF and its potential contribution in lactation-driven body fat loss in periparturient dairy cows may be particularly relevant.

Retinol-Binding Protein 4. The protein RBP4 is expressed in adipocytes, myocytes, macrophages, and other tissues and cells (Yang et al., 2005; Broch et al., 2010; Kuperman et al., 2011). The RBP4 facilitates the transport of retinol from the liver to peripheral organs (Berni et al., 1990; Tsutsumi et al., 1992). Beyond retinol transport, RBP4 binds and transports FA (Perduca et al., 2018). As a member of a gene set, RBP4 is involved in intramuscular adipocyte lipid metabolism in bovine skeletal muscle (De Jager et al., 2013). In mice, RBP4 has been shown to induce insulin resistance (Yang et al., 2005), and serum concentrations of RBP4 correlated with the extent of insulin resistance in humans with impaired glucose tolerance, obesity, or type 2 diabetes (Graham et al., 2006; Kilicarslan et al., 2020). It has been shown that RBP4 plays a role in the degradation of very low-density lipoproteins and the formation of small dense low-density lipoproteins in humans (Usui et al., 2009; Wu et al., 2012). Increased RBP4 levels were associated with increased fat deposition and altered FA profiles (i.e., greater polyunsaturated and lesser saturated proportions of FA; Liu et al., 2019). In nonpregnant, nonlactating dairy cows, plasma concentrations of RBP4 measured by western blot (around 45 µg/mL) decreased immediately after calving and returned to pre-calving concentrations by 2 wk after calving (Abd Eldaim et al., 2010). The decrease in plasma RBP4 may be due to influx into the mammary gland after calving, although other factors such as protein intake and inflammatory responses may also influence RBP4 synthesis in dairy cows (Selim et al., 2015). Analyzing the dietary effect on circulating RBP4 levels, Lindberg et al. (1999) observed increasing serum RBP4 concentrations after crude protein supplementation during the dry period in dairy cows

(Lindberg et al., 1999). A recent study in crossbred bulls showed that RBP4 was expressed at the mRNA and protein levels in various AT depots (subcutaneous, omental, perirenal, and intestinal AT) as well as in the liver (Liu et al., 2019). In dairy cows, Rezamand et al. (2012) observed a positive association between the mRNA abundance of *RBP4* and the pro-inflammatory cytokine *TNF*, in a tissue-specific manner (weak relationship in AT, strong relationship in liver) during the periparturient period, suggesting a role for RBP4 in the inflammatory processes in dairy cows. Albeit RBP4 is a crucial predictor for insulin resistance in mice and humans, the mechanisms by which RBP4 induces insulin resistance are not fully understood.

Resistin. Known as an adipocyte-derived factor, resistin belongs to the family of proteins found in inflammatory zone 3 (Steppan et al., 2001), mediating insulin resistance in mice and serving as a biomarker for insulin resistance in humans (Schwartz and Lazar, 2011). Comparable to leptin, resistin regulates reproductive and metabolic processes at the level of the CNS in ruminants (Zieba et al., 2020). Although, the receptor for resistin is unknown, several potential receptors have been proposed (see Table 1). In addition, resistin activates signaling pathways in various tissues, such as phosphatidylinositol 3'-kinase/protein kinase B (Akt), mitogen-activated protein kinases (**MAPK**; ERK1/2 and p38), signal transducer and activator of transcription 3, and PPAR (Rak et al., 2017). The source of resistin is species-specific: in mice, cattle, and sheep, resistin is mainly synthesized by adipocytes, whereas in humans, monocytes and macrophages are the main sources (Mellouk et al., 2017).

In high-yielding dairy cows, resistin concentrations increased before parturition and peaked during the first week of lactation (Reverchon et al., 2014; Weber et al., 2016a). Moreover, circulating resistin concentrations were greater in cows fed low-energy diets compared with over-conditioned cows (Mellouk et al., 2017). The positive correlation of plasma resistin concentrations with circulating FA and backfat thickness in dairy cows fed different energy levels (Mellouk et al., 2017) suggests that resistin is involved in periparturient lipolytic processes (Reverchon et al., 2014; Weber et al., 2016a). Comparable to circulating concentrations, *RETN* mRNA abundance and protein concentrations were elevated in scAT of cattle one week after calving (Reverchon et al., 2014). During the periparturient period, resistin concentrations in cerebrospinal fluid in dairy cows remained unchanged, suggesting that resistin does not play a major role in the central control of feed intake around parturition (Laeger et al., 2013).

Recombinant resistin was able to modulate steroidogenesis by decreasing the secretion of progesterone

and estradiol from primary bovine granulosa cells and stimulated basal proliferation of granulosa cells in cows (Maillard et al., 2011). Thus, resistin may be a metabolic signal involved in reproductive functions in cattle (Maillard et al., 2011). Due to its effects on immune cells, such as stimulation of inflammatory cytokine synthesis, resistin was described as an inflammatory marker in humans (Schwartz and Lazar, 2011). Furthermore, in humans resistin was suggested as a potential marker for diabetes, insulin resistance, and cardiovascular diseases (Schwartz and Lazar, 2011). However, because the main sources of resistin were described to be species-specific (Mellouk et al., 2017), the potential of resistin to serve as a biomarker for metabolic or inflammatory dysfunctions as already described in humans needs to be clarified in dairy cows.

Visfatin. Visfatin, a multifunctional protein, is also known as nicotinamide phosphoribosyltransferase (**NAMPT**) or pre-B cell colony-enhancing factor in mammals (**PBEF**). In humans and mice, visfatin is highly enriched in visceral AT (Fukuhara et al., 2005) and its plasma concentrations have been positively associated with obesity (Berndt et al., 2005). Visfatin mimics insulin actions via the insulin receptor (Revollo et al., 2007). In mammals, 2 forms of visfatin exist (see Table 1). Although the intracellular form plays an important role in sirtuin activation in mitochondria and functions as an NAD^+ biosynthetic enzyme, the function of the extracellular isoform is controversial (Estienne et al., 2019).

In addition to AT, visfatin is expressed in bone marrow, liver, muscle, female reproductive organs, and various other tissues and is linked to the regulation of energy metabolism, growth, and development in humans (Shen et al., 2020). In humans, visfatin is involved in glucose homeostasis, which lowers plasma glucose (Fukuhara et al., 2005), inflammation, various metabolic and stress responses, and cellular energy metabolism (Zhang et al., 2011; Reverchon et al., 2016).

After calving, *NAMPT* mRNA abundance tends to be decreased in the scAT of dairy cows when compared with values AP (Lemor et al., 2009). Furthermore, the mRNA abundance of *NAMPT* in the scAT of these cows was negatively correlated with NEFA and BHB concentrations, which coincided with unchanged insulin receptor mRNA abundance around parturition (Lemor et al., 2009), proposing a possible role of visfatin in insulin resistance in periparturient dairy cows. In addition to decreased *NAMPT* mRNA abundance in scAT from PP to AP levels, decreasing mRNA abundance in retroperitoneal AT after parturition was suggested to reflect a tissue-dependent mechanism to decrease insulin-stimulated lipogenesis and increase lipolysis (Weber et al., 2016b). The *NAMPT* mRNA was positively cor-

related with *ADIPOR1* mRNA in the scAT of dairy cows, likely representing a local regulatory mechanism (Weber et al., 2016b). Along with other adipokines, such as adiponectin, leptin, and resistin, all of which are expressed in the placenta of cows, visfatin has been proposed to play a coordinating role in promoting intra-uterine growth in calves (Shen et al., 2020). Fadden and Bobe (2016) were the first to report circulating visfatin in dairy cows. Using a competitive enzyme immunoassay, they demonstrated that decreasing serum visfatin concentrations 3 wk before calving may contribute to homeorhetic adaptations due to parturition. Visfatin is elevated in association with retained placenta and other metabolic diseases (e.g., metritis and ketosis), therefore, it may help to identify cows at increased risk for metabolic diseases (Fadden and Bobe, 2016).

Other Adipokines. There are several other adipokines, such as lipocalin-2, vaspin, omentin, follistatin-like 1, secreted protein acidic and rich in cysteine, secreted frizzled-related protein 5, C1q/TNF-related proteins, family with sequence similarity to 19 member A5, wingless-type inducible signaling pathway protein-1, progranulin, nesfatin-1, and plasminogen activator inhibitor-1, whose role in humans has been thoroughly investigated; however, limited research has been conducted to assess the function of these adipokines in dairy cattle. Because a detailed discussion of these adipokines in other tissues is beyond the scope of this review, they are not discussed further here.

Cytokines

Tumor Necrosis Factor α . Tumor necrosis factor α (25 kDa, 233 AA), a multifunctional regulatory adipocytokine, is produced in AT, derived from resident macrophages and monocytes and possibly adipocytes (Hotamisligil et al., 1993; Olefsky and Glass, 2010). It has a central role in inflammation, production of other cytokines, lipolysis, and reduction of insulin sensitivity in animal models of obesity and insulin resistance (Uysal et al., 1997; Kushibiki et al., 2002; Wellen and Hotamisligli, 2005), whose main effects are mediated by its receptors, TNFR1 and TNFR2 (Sethi et al., 2000).

The mRNA abundance of *TNF- α* in scAT of dairy cows was found to increase from wk 8 AP to the day of calving; however, this was not reflected by greater *TNF- α* concentrations in plasma (Sadri et al., 2010), pointing that *TNF- α* of AT origin might act locally with evidence from human medicine that it acts predominantly as a local factor (Ronti et al., 2006; Frühbeck et al., 2014). The abundance of *TNF* mRNA in bovine scAT was dependent on parity (Saremi et al., 2014), remaining unchanged when considering multiparous cows from d 21 AP to 252 DIM, or increasing in

primiparous cows from 1 to 42 DIM. It is not clear to what extent TNF- α of AT origin is contributing to the inflammatory signals that are elevated in dairy cows around parturition (McNamara and Huber, 2018), though these signals are not always pathological (Bradford and Swartz, 2020). Lactating cows with a high BCS (≥ 3.5 vs. 2.5–2.7) had greater concentrations of TNF- α in plasma (O’Boyle et al., 2006), whereas its mRNA abundance in scAT did not differ in periparturient over-conditioned dairy cows (BCS > 3.75) of divergent serum-metabotype (Sadri et al., 2021). The abundance of *TNF* mRNA was positively associated with adipocyte size in dairy cows at the end of gestation and differed among the AT depot. The greater mRNA abundance of *TNF* in the subcutaneous and omental depots than in the intrapelvic depot (Depreester et al., 2018), may suggest potential differences in inflammatory characteristics depending on the anatomical location of AT depots. Adipose tissue depot-dependent differences were also found in terms of *TNFRSF1A* mRNA abundance, being greater in retroperitoneal AT than in scAT on d 42 AP and d 21 PP (Weber et al., 2016a). A continuous low dose infusion of recombinant bovine TNF- α into a scAT depot of lactating dairy cows had no measurable effect on metabolism, whereas a counter-regulatory anti-inflammatory response (increased IL-10 protein in the contralateral AT depot) was observed in the liver and the AT (Martel et al., 2014), pointing to an apparent homeostatic response in the opposite direction (Bradford and Swartz, 2020). In most studies, AT of transition cows is characterized by greater gene expression of the pro-inflammatory cytokine *TNF* (e.g., Contreras et al., 2015; Selim et al., 2014). However, it is not clear to what extent TNF- α derived from AT contributes to the inflammatory response elevated around parturition in dairy cows and whether this cytokine affects either locally or systemically the metabolism of the cows.

Interleukin-6. Interleukin-6, a pluripotent cytokine, is produced by several tissues and cells, such as macrophages, endothelial cells, adipocytes, skeletal muscle, and fibroblasts (Tanaka et al., 2014). The biological functions of IL-6 are mediated through binding to the IL-6 receptor (Garbers et al., 2012). Interleukin-6 has both pro- and anti-inflammatory effects, with a central role in the regulation of inflammation, immune responses, host defense mechanisms, multiple aspects of metabolism, including glucose disposal, lipolysis, oxidative metabolism, energy expenditure, and insulin resistance (Makki et al., 2013); though, data in the context of its role in both insulin resistance and obesity in human medicine is controversial and unresolved (Taylor, 2021). It was demonstrated in rodents that the source of IL-6 production plays a major role in

the physiological regulation of metabolism (Han et al., 2020). Adipose tissue macrophages (**ATM**) and adipocytes are regarded as the main source of IL-6 within white AT (Weisberg et al., 2003). In humans, adipose-derived IL-6 is an important source of circulating IL-6, as approximately a third of circulating IL-6 in healthy individuals is estimated to originate from AT (Makki et al., 2013). It has also been regarded as a marker for visceral adiposity because visceral AT releases greater IL-6 than scAT in humans (Fried et al., 1998). Whether AT-derived IL-6 acts in the same manner in dairy cows is currently unknown. Comparing different fat depots from primiparous cows, the abundance of *IL6* mRNA in scAT from the tail head and withers was decreased from 1 to 105 DIM, whereas that of the liver was increased (Saremi et al., 2014). Moreover, the mRNA abundance of *IL6* was upregulated in AT depots with enlarged adipocytes in dairy cows at the end of gestation and was influenced by the AT depot, with lesser abundance in scAT than in other depots (i.e., omental, mesenteric, intrapelvic, and perirenal; Depreester et al., 2018). Lopreiato et al. (2018) investigated the effect of dietary energy level in nonlactating and nonpregnant Holstein cows on the mRNA abundance of *IL6* and *NFKB1* in scAT. Together with upregulated *IL6* and *NFKB1* mRNA in scAT 2 h after TNF- α incubation in vitro, greater mRNA abundance in control than in cows receiving a higher-energy diet, suggests for a rapid inflammatory response (Lopreiato et al., 2018). However, the abundance of *IL6* mRNA was not affected by overfeeding AP in transition dairy cows (Selim et al., 2014). The mRNA abundance of *IL6* on d 21 and 42 PP in scAT of multiparous cows was positively correlated with BCS loss, being greatest in high BCS loss, intermediate in moderate BCS loss, and least in low BCS loss cows (Dirandeh et al., 2020).

Albeit levels of circulating pro-inflammatory cytokines such as IL-6 varies between different studies in the periparturient period of dairy cows, concentrations generally increased during the first week after parturition (reviewed by Kuhla, 2020). However, to what extent IL-6 from AT contributes to the peak right after calving in dairy cows, remains currently open.

Monocyte Chemoattractant Protein-1. Monocyte chemoattractant protein 1 is secreted in response to signals such as pro-inflammatory cytokines (Deshmane et al., 2009). Being a potent chemotactic factor for monocytes (Deshmane et al., 2009), MCP-1 acts as a pro-inflammatory chemokine (Christiansen et al., 2005), including in AT as reported in mice (Kanda et al., 2006). The MCP-1 is secreted by various cell types, such as macrophages and endothelial cells, but also by human preadipocytes and isolated mature adipocytes (Gerhardt et al., 2001).

In dairy cows, MCP-1 is encoded by chemokine (CC motif) ligand 2 (*CCL2*) and was upregulated in scAT after calving when compared with p.p. levels (Mann et al., 2016). Furthermore, Contreras et al. (2015) observed greater *CCL2* mRNA abundance in AT of cows with displaced abomasum compared with healthy cows. Specifically, visceral AT depots expressed more *MCP-1/CCL2* mRNA than the scAT in early-lactating dairy cows (Contreras et al., 2015; Häussler et al., 2015).

Acting as a chemokine, MCP-1 is one of the first molecules mobilized in response to inflammatory challenges (Tang and Wang, 2018). In humans, increased expression of MCP-1 in cells from the stromal vascular fraction in AT recruit macrophages infiltrating into AT leading to a low-grade inflammatory status (Capurso and Capurso, 2012). De Koster et al. (2018b) confirmed the chemoattractant role of *CCL2* for ATM in bovine scAT during the first week after calving; however, the ATM proportion was not related to the gene expression of other pro-inflammatory cytokines (*TNF* or *IL6*). Macrophages can be categorized into classically activated, M1 macrophages being involved in inflammatory processes (releasing pro-inflammatory cytokines) and alternatively activated, M2 macrophages playing a role in immunosuppressive activities (Hill et al., 2014). The results from De Koster et al. (2018b) point to an immunosuppressive role of *CCL2* in bovine scAT; however, further research is necessary to clarify the function of ATM, the processes leading to ATM infiltration, and the respective role of MCP-1 or *CCL2* in this context.

Lipid Adipokines

It is long known that AT contains and releases lipids other than FA, such as steroids (McCracken, 1964). The notion that these lipids may not only be passively incorporated and released but also partly synthesized and metabolized in AT also emerged decades ago, for example, as reviewed by Richelsen et al. (1992) for eicosanoids. In addition to eicosanoids and steroids, the current list of lipid adipokines comprises ceramides, endocannabinoids, FA esters of hydroxy FA, lysophosphatidic acids, and sphingolipids (Funcke and Scherer, 2019), as well as oxysterols (Li et al., 2014) and bile acids (Jäntti et al., 2014). In contrast to proteins, analytical methods detecting these lipid adipokines developed in other species can principally be transferred for use in bovine samples. In addition, with the rapid development of lipidomics technologies, great progress can be expected also for lipid adipokines from targeted approaches. In this review, the endocannabinoids, FA, and steroids are in focus.

Endocannabinoids. The endocannabinoid (eCB) system consists of endogenous cannabinoids, cannabi-

noid receptors (CNR1 and CNR2), and the enzymes responsible for the synthesis and degradation of eCB (Lu and Mackie, 2016). Anandamide (*N*-arachidonoyl-ethanolamine, **AEA**) and 2-arachidonoylglycerol (**2AG**) are the 2 major eCB as ligands of cannabinoid receptors (Spoto et al., 2006; De Petrocellis and Di Marzo, 2009). The eCB system is a central regulator of metabolism and energy homeostasis by regulating energy intake and expenditure (Nogueiras et al., 2009; Rakotoarivelo et al., 2021). Functions of the eCB system include immune modulation, modification of cell proliferation, and preservation of energy-storing reservoirs (reviewed by Myers et al., 2021). Inflammatory responses can be activated by the eCB system depending on the tissue, the eCB, and their receptors (Myers et al., 2021). Cannabinoid receptors are expressed in immune cells that can be affected by cannabinoid analogs (Tanasescu and Constantinescu, 2010). Although CNR1 are found in the CNS and in some peripheral tissues, including immune cells, CNR2 are mainly expressed by immune cells, such as B-cells and natural killer cells (Pertwee, 1997; Pertwee and Ross, 2002). In mammal AT, activation of the eCB system promotes lipogenesis and adipogenesis, but inhibits lipolytic activity (Myers et al., 2021). Plasma concentrations of AEA and 2AG were 2- to 2.3-fold greater during early lactation (7–28 DIM; 3.0 ± 0.94 nmol/mL) compared with d 7 AP (1.5 ± 0.94 nmol/mL) in dairy cows (Kuhla et al., 2020). Moreover, Zachut et al. (2018) reported that concentrations of AEA and 2AG in scAT were increased at the beginning of lactation in cows exhibiting high PP weight loss (>8% during the first month PP) but not in the low weight loss group. They concluded that the activation of the eCB system in AT is most likely associated with a metabolic response of greater lipolysis, BW loss, and AT inflammation in PP dairy cows, which is a part of the metabolic adaptations related to the onset of lactation (Zachut et al., 2018). There is growing evidence of the effects of eCB on the control of feed intake and energy metabolism in dairy cattle (Kuhla et al., 2020). Thus, the eCB system may play an important role in early-lactating dairy cows by increasing feed intake, decreasing adipocyte lipolysis, and alleviating acute inflammation (Kuhla et al., 2020). Due to its positive effect on appetite, adipogenesis, lipogenesis as well as the suppressive properties on lipolysis and AT inflammation, the eCB system is supposed to have beneficial effects during the periparturient period in dairy cows (Myers et al., 2021). However, further research is warranted to explore the relationship between the eCB system and metabolic adaptation in dairy cattle.

Free Fatty Acids and their Receptors. Periparturient dairy cows experience a period of energy deficit after parturition that can lead to excessive lipolysis,

releasing FFA from AT triglyceride molecules into the bloodstream where they are transported by albumin and Fetuin-A (also named α -2-Heremans-Schmid glycoprotein) for use in other tissues as fuel or excreted in milk fat (Contreras and Sordillo, 2011; De Koster et al., 2018a; Strieder-Barboza et al., 2018). Free FA are not only an important direct source of energy but also function as signaling molecules in the regulation of various physiological processes (Hara et al., 2013). Rodríguez-Carrio et al. (2017) summarized several functions of FFA, such as its effect on the macrophage, adipocyte or endothelial cell gene expression, and modulation of chemokine and cytokine production. In periparturient cows, stearic acid, palmitic acid (both SFA), and oleic acid (MUFA) were the major FA of scAT (Douglas et al., 2007).

The functions of FFA are mediated by several FFA receptors (**FFAR**), which belong to the class of G protein-coupled receptors (Ichimura et al., 2014). Short-chain FA (acetate, propionate, and butyrate), are important substrates in ruminant energy metabolism, with propionate serving as the primary gluconeogenic substrate in ruminants (Allen et al., 2005). Short-chain FFA activate FFAR2 (GPR43) and FFAR3 (GPR41), whereas medium- and long-chain FFA are ligands for FFAR1 (GPR40) and FFAR4 (GPR120), respectively; in addition, GPR84 is activated by medium-chain FFA (Hara et al., 2014; Ichimura et al., 2014). In rodent models, FFAR1 is involved in insulin (Meidute Abaraviciene et al., 2013) and glucagon (Flodgren et al., 2007) secretion in pancreatic islets, whereas FFAR2 increases lipid accretion and reduces lipolysis (Hong et al., 2005). There is evidence for the role of FFAR4 in mediating increased adipogenesis, lipogenesis as well as increased insulin sensitivity and anti-inflammatory processes (Ichimura et al., 2014). The various functions of FFAR in livestock such as pigs, chickens, and ruminants have been reviewed by Mielenz (2017). In general, FFAR has been reported to be involved in adipocyte differentiation, anti-inflammatory processes, nerve activation, and taste preferences (Hara et al., 2013).

In multiparous dairy cows, the mRNA abundance of *FFAR1*, *FFAR2*, and *FFAR3* varied in different AT depots, muscle, liver, and mammary glands during early lactation (Friedrichs et al., 2014). Comparing early and late lactation, the *FFAR3* mRNA abundance was greater in the scAT from early-lactating cows (Lemor et al., 2009). Being involved in the monitoring of energy storage and its relationship to leptin synthesis, *FFAR3* abundance has been suggested to increase after calving in response to NEB when insulin and leptin concentrations are low (Accorsi et al., 2005). However, no effect of insulin on the mRNA abundance of *FFAR3* was detected in sc and retroperitoneal AT bovine explants

(Hosseini et al., 2010). Moreover, greater *FFAR2* and *FFAR3* mRNA abundance were observed in visceral AT depots, such as mesenteric, omental, retroperitoneal AT depots (except for *FFAR2* with low mRNA abundance in retroperitoneal AT), compared to scAT from sternum, withers, and tail head region in dairy cows (Friedrichs et al., 2014). Visceral adipocytes are metabolically more active and sensitive to lipolysis than subcutaneous ones (Capurso and Capurso, 2012) and showed a greater insulin response after parturition (Kenéz et al., 2019), all of which could be related to the FFA and FFAR interaction. Although, the presence of FFAR has been studied in bovine AT, further studies are needed to reveal the function of FFAR in bovine adipocytes as well as the mechanisms behind the FFA and FFAR interaction.

Steroids. Steroid hormones, such as sex steroids, mineralocorticoids, and glucocorticoids, are derivatives of cholesterol synthesized mainly in the gonads, placenta, and adrenal cortex (Holst et al., 2004). In addition to their endocrine effects, steroids can act via paracrine, autocrine, and intracrine mechanisms (Labrie, 1991). Due to their lipophilic character, steroid hormones can be stored in AT and also metabolized depending on the local enzyme setting (Deslypere et al., 1985; Dalla Valle et al., 2006). Murine adipocytes possess all components involved in cholesterol transport and steroidogenesis, indicating de novo steroid biosynthesis in adipocytes (Li et al., 2014). Figure 1 shows the main steroid biosynthetic pathways and the relevant enzymes involved in steroid metabolism. Steroids synthesized or metabolized in AT mediate local effects that exhibit depot-specific differences but can also influence overall metabolism, as reported in humans (Bélanger et al., 2002). Furthermore, peripheral steroid metabolism in humans can be altered by either excessive AT accumulation (Bélanger et al., 2002) or lipolysis (Newell-Fugate, 2017), both playing critical roles in energy metabolism as well as inflammatory processes in dairy cows (Contreras et al., 2018). In the periparturient period of dairy cows, in addition to FA, steroids that are stored and locally metabolized in AT may be released into the circulation during mobilization of body fat reserves (Hamudikuwanda et al., 1996; Rodrigues et al., 2011). However, the role of AT in steroid metabolism in cattle during increasing lipolysis around the periparturient period is largely unknown.

Alizadeh et al. (2016a) investigated the mRNA abundance of *STAR* and *CYP11A1* in subcutaneous and visceral AT during late pregnancy and early lactation in high-yielding dairy cows. Both enzymes initiate steroidogenesis, their presence in tissue points to either local steroid metabolism (*STAR*) or de novo steroid synthesis (*CYP11A1*). The absence of *CYP11A1*

Figure 1. Biosynthetic pathway for steroid hormones. Biosynthetic pathway for (A) progestagens and gestagens, (B) mineralo- and glucocorticoids, (C) androgens, and (D) estrogens. Enzymes involved in the pathway are shown next to the arrows in bold [the figure is based on data in Figure 1 of MacKenzie et al. (2008)]. CYP11A1 = cholesterol monooxygenase; CYP11B = aldosterone synthase; CYP17 = steroid-17 α -hydroxylase; CYP19 = aromatase; CYP21 = steroid 21-hydroxylase; HSD3A = 3 α -hydroxysteroid dehydrogenase; HSD3B = 3 β -hydroxysteroid dehydrogenase; HSD11B1 = 11 β -hydroxysteroid dehydrogenase type 1; HSD11B2 = 11 β -hydroxysteroid dehydrogenase type 2; HSD17B = 17 β -hydroxysteroid dehydrogenase type 12; SR5A1 = steroid-5 α -reductase; StAR = steroidogenic acute regulatory protein; STS = steroid sulfatase; SULT = sulfotransferase.

mRNA in subcutaneous and visceral AT together with increased *STAR* mRNA abundance in both AT depots after calving indicate bovine AT plays a role in steroid metabolism but not de novo steroid synthesis, and depends on the uptake of performed steroid precursors (Alizadeh et al., 2016a). Cholesterol reaching the inner mitochondrial membrane can alternatively be metabolized to oxysterols instead of pregnenolone. The de novo synthesis of oxysterols in adipocytes was suggested to protect adipocytes against intracellular cholesterol overload and the formation of new fat cells (Li et al., 2014). For dairy cows, limited information is available on endogenous steroids and most of the studies have focused mainly on progesterone during the periparturient period (Hamudikuwanda et al., 1996; Rodrigues et al., 2011). During pregnancy, progesterone is mainly accumulated in the scAT until certain concentrations are reached (Hamudikuwanda et al., 1996). The release of progesterone from AT into circulation has been demonstrated following restrictive feeding of dairy

cows (Ferraretto et al., 2014). Decreased fertility during the PP period in dairy cows could be associated with increased lipolysis and thus increased release of steroids such as progesterone from AT into the circulation (Hatler et al. 2003; Rodrigues et al., 2011). The release of steroids into the circulation could interfere with the hypothalamus-pituitary-axis and lead to impaired fertility or embryonic development. Compared with gestagens, estrogen concentrations in AT are lesser in cyclic dairy cows (estrone: 13–20 pg/g, estradiol-17 β : 16–23 pg/g; Tsujioka et al., 1992). Plasma estrogens were shown to interact with the leptin system in prepubertal dairy heifers, regulating the abundance of the leptin receptor in some estrogen-responsive tissues but without effect on leptin synthesis (Thorn et al., 2008). Coupled to long-chain FA, estrogens can accumulate in tissues for prolonged periods and likely serve as storage that is directly hydrolyzed to AT (Xu et al., 2002). In humans, androgens exert important effects on AT biology, including fat mass expansion and distribution,

insulin signaling, as well as lipid metabolism (Schiffer et al., 2019). In addition to affecting insulin signaling, androgens can also trigger lipolysis, increasing FA in the circulation (Rojas et al., 2014). Androgens serve as precursors for estrogens depending on the enzyme aromatase (CYP19), which in humans is found primarily in the ovaries but also in AT (Perel and Killinger, 1979). In dairy cows, the mRNA of CYP19 was neither detectable in scAT nor in retroperitoneal AT on d 42 AP and d 1, 21, and 100 PP (Alizadeh et al., 2016b). However, the mRNA abundance of *HSD17B12*, which catalyzes the conversion of estrone to estradiol-17 β was detected in both AT depots and was greatest on d 42 AP with decreasing values after calving (Alizadeh et al., 2016b). Moreover, *HSD17B12* mRNA abundance in scAT before calving was greater in over-conditioned cows compared with cows with normal BCS, suggesting local conversion of estradiol in cows with greater fat depots before parturition (Schuh et al., 2022). However, the role of androgens and its metabolism in AT of dairy cows is limited.

In peripheral tissues, glucocorticoids exert their catabolic effects by stimulating the release of glucose and FA as well as promoting protein breakdown (Tronche et al., 1998; Rose et al., 2010). In addition, glucocorticoids promote adipogenesis by differentiating preadipocytes into mature adipocytes (Tomlinson et al., 2007) and play a role in inflammatory processes (Coutinho and Chapman, 2011). The enzyme 11 β -hydroxysteroid dehydrogenase (**HSD11B**) locally regulates glucocorticoid activity (Chapman et al., 1997) by either activating cortisone to cortisol via isoform 1 (**HSD11B1**) or inactivating cortisol to cortisone via isoform 2 (**HSD11B2**). In various AT depots of early postpartum lactating dairy cows, the enzyme HSD11B1 was detected semiquantitatively by western blotting and immunohistochemistry based on an in-house developed antiserum against HSD11B1, together with an enzyme activity assay for HSD11B1 (Friedauer et al., 2015). Both the glucocorticoid receptor and the enzyme HSD11B1 were localized in mature adipocytes and cells belonging to the stromal vascular fraction within different subcutaneous and visceral AT (Friedauer et al., 2015). Based on the localization of the glucocorticoid receptor in already differentiated mature adipocytes, it has been suggested that glucocorticoids promote other effects than differentiation in bovine AT (Friedauer et al., 2015). Although, glucocorticoids have been implicated in inflammatory processes (Coutinho and Chapman, 2011), neither the glucocorticoid receptor nor the enzyme HSD11B1 was associated with the mRNA abundance of the pro-inflammatory cytokines *IL6* and *TNF* measured in the same study by Saremi et al. (2014). The importance of AT in glucocorticoid

metabolism has been demonstrated in studies of obese individuals, with increased cortisol levels in abdominal AT due to increased HSD11B1 activity (Lee et al., 2011). However, in dairy cows, information on endogenous steroids is limited to a few hormones; regarding peripartum lipolysis, data are mainly available on progesterone. Albeit the role of AT in steroid hormone metabolism in dairy cows is largely unknown, great progress has to be anticipated in view of clarifying the role of the complex mechanisms being involved in the interaction of steroid metabolism and lipid adipokines in general, based on the rapid development of targeted lipidomics.

CONCLUSIONS

In addition to energy storage, AT is recognized for its ability to secrete signaling molecules collectively termed adipokines. The adipokines play important roles in the communication between cells within the AT in an autocrine or paracrine manner and are also involved in the endocrine crosstalk with other tissues such as liver and skeletal muscle, influencing many different systems and metabolic processes in the body. In this review, we summarized the current literature regarding several selected proteinaceous adipokines with potentially important roles in dairy cows, in particular during the transition from late gestation to early lactation. Adipose tissue also releases lipid adipokines, of which endocannabinoids and steroids were in the focus of this review. The knowledge about the role of AT in the metabolism of these compounds and the systemic relevance is only in its infancy. However, in contrast to protein adipokines, whose analysis is often impeded by the lack of suitable and validated assays, and thus limited to mRNA data, lipid adipokines are expected to be better accessible, in particular when considering the rapid development of targeted lipidomics approaches. However, due to sources other than AT for both protein and lipid adipokines, interpretation of systemic changes remains challenging.

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