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Does the circadian system regulate lactation?

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Environmental variables such as photoperiod, heat, stress, nutrition and other external factors have profound effects on quality and quantity of a dairy cow's milk. The way in which the environment interacts with genotype to impact milk production is unknown; however, evidence from our laboratory suggests that circadian clocks play a role. Daily and seasonal endocrine rhythms are coordinated in mammals by the master circadian clock in the hypothalamus. Peripheral clocks are distributed in every organ and coordinated by signals from the master clock. We and others have shown that there is a circadian clock in the mammary gland. Approximately 7% of the genes expressed during lactation had circadian patterns including core clock and metabolic genes. Amplitude changes occurred in the core mammary clock genes during the transition from pregnancy to lactation and were coordinated with changes in molecular clocks among multiple tissues. In vitro *studies using a bovine mammary cell line showed that external stimulation synchronized mammary clocks, and expression of the core clock gene,* BMAL1*, was induced by lactogens. Female* clock/clock *mutant mice, which have disrupted circadian rhythms, have impaired mammary development and their offspring failed to thrive suggesting that the dam's milk production was not adequate enough to nourish their young. We envision that, in mammals, during the transition from pregnancy to lactation the master clock is modified by environmental and physiological cues that it receives, including photoperiod length. In turn, the master clock coordinates changes in endocrine milieu that signals peripheral tissues. In dairy cows, it is clear that changes in photoperiod during the dry period and/or during lactation influences milk production. We believe that the photoperiod effect on milk production is mediated, in part by the 'setting' of the master clock with light, which modifies peripheral circadian clocks including the mammary core clock and subsequently impacts milk yield and may impact milk composition.*

Keywords: mammary, lactation, circadian rhythm, photoperiod, metabolism

Implications

The circadian system coordinates internal physiological processes in mammals and synchronizes these processes to the animal's environment. We review the literature and discuss recent findings from our laboratory and others that suggest the circadian system regulates lactation, including coordinating changes in the dam's physiology needed to initiate and maintain lactation and mediating the photoperiod effect on milk production. Identification of environmental and physiological inputs that affect genes that control circadian rhythms will enable development of approaches to alter gene expression to maximize production efficiency in farm animals.

Introduction

Nearly all physiological and behavioral functions of animals are rhythmic including secretion patterns of hormones, sleep–wake cycle, metabolism and core body temperature. A circadian rhythm is a roughly 24-h cycle in the biochemical, physiological or behavioral processes of organisms. Daily and seasonal endocrine rhythms are coordinated in mammals by the master circadian clock located in the hypothalamus. The master clock receives and integrates environmental (e.g. photoperiod) and physiological (e.g. nutritional status) cues that set the master clock at the molecular level. Reference time and rhythms are sent out to peripheral tissues from the master clock via hormonal and autonomic signals. Peripheral clocks located in every organ of the body receive these signals from the master clock, which coordinate and synchronize the timing of rhythms generated by peripheral clocks across the entire body.

During the transition from pregnancy to lactation homeorhetic adaptations are coordinated across almost every organ of the body and are marked by tremendous changes in hormones and metabolism to accommodate for the increased energetic demands of lactation (Bauman and Currie, 1980; Bell *et al.*, 1987; Bell and Bauman, 1997). This transition is the most stressful period of the cow's life and has a large impact on a cow's lactation production. As a result, ~80% of dairy

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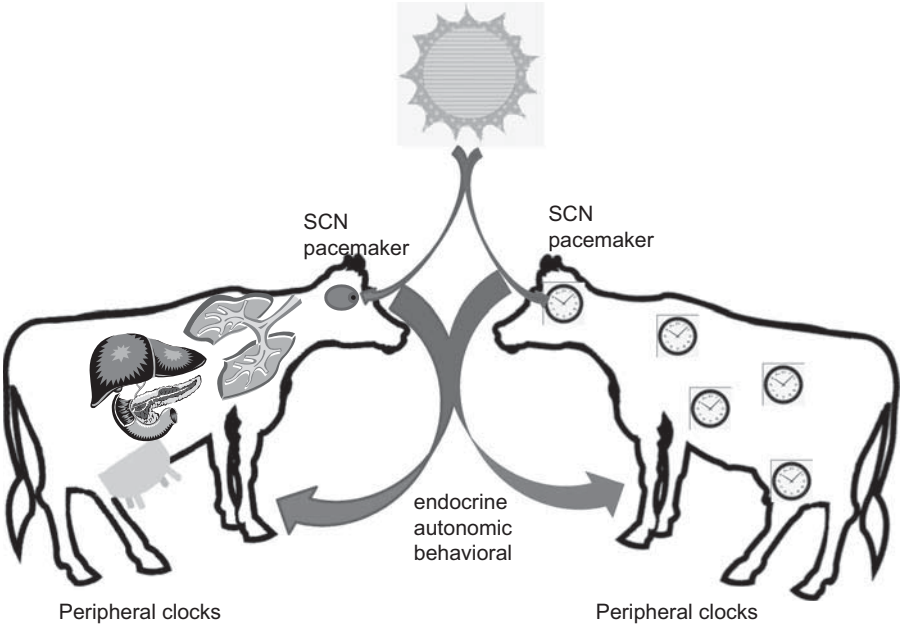

Figure 1 Schematic represents how circadian system coordinates internal physiology with the environment. The primary pacemaker, suprachiasmatic nuclei, is entrained to solar time through retinal afferents and synchronizes and maintains tissue clocks through endocrine, autonomic and behavioral (feeding-related) cues. Adapted from Hastings *et al.* (2007).

cow disease events occur in the first 3 weeks after a cow delivers a calf (Drackley, 1999; Mulligan and Doherty, 2008; Grummer *et al.*, 2010; LeBlanc, 2010).

Understanding how a cow sets her metabolic and physiological rhythms in response to changes in her physiology, nutritional status and/or environment will enable the development of simple approaches that maximize productive efficiency and minimize metabolic disturbances in dairy cows. The circadian system is a likely candidate as it is believed to have evolved to coordinate the timing of internal physiological and metabolic processes and synchronize this timing with the animal's environment. The effect of the circadian system on milk production is evident in both the variation of milk composition across the day (Kuhn *et al.*, 1980; Nielsen *et al.*, 2003; Barkova *et al.*, 2005; Lubetzky *et al.*, 2006 and 2007; Cubero *et al.*, 2007) and the photoperiod effect on milk quality and quantity in farm animals (Aharoni *et al.*, 2000; Dahl *et al.*, 2002 and 2004; Dahl and Petitclerc, 2003; Auchtung *et al.*, 2005; Wall *et al.*, 2005; Bernabucci *et al.*, 2006; Rius and Dahl, 2006; Auldist *et al.*, 2007; Oates *et al.*, 2007; Andrade *et al.*, 2008; Dahl, 2008; Mikolayunas *et al.*, 2008). In this paper, we review literature and present novel findings in support of our hypothesis that the circadian system coordinates the metabolic and endocrine changes needed to initiate and maintain lactation, and that this system also mediates the photoperiod effect on lactation.

The circadian system

The circadian system is regulated hierarchically in mammals by the master clock that lies in the suprachiasmatic nuclei (SCN; Hastings *et al.*, 2007). The intrinsic rhythmicity of the SCN is synchronized to the 24-h day by regularly occurring environmental signals or 'Zeitgebers' (Welsh *et al.*, 1995). The light–dark (LD) cycle is the most salient environmental cue for entraining circadian clocks (Reppert and Weaver, 2002). Non-photic environmental cues including exercise, food availability, temperature and stress can also directly and/or indirectly entrain the SCN. The activity of SCN neurons is also modulated by serotoninergic pathways and melatonin (Moore *et al.*, 1978; Bosler and Beaudet, 1985; Meyer-Bernstein and Morin, 1996; Jacobs *et al.*, 2002; Moore and Speh, 2004; Wirz-Justice, 2006).

The SCN signal is translated into hormonal and autonomic signals for peripheral organs through its major outputs (i) the paraventricular nucleus (PVN) of the hypothalamus; and (ii) the pineal gland, where melatonin is synthesized according to the length of the photophase. Melatonin is the biochemical transducer of photoperiodic information to all cells in the body (including SCN neurons), and changes in duration and amplitude of nocturnal secretion serves to signal seasonal variations of day/night cycle length (for review see Simonneaux and Ribelayga, 2003). Autonomic neurons of the PVN communicate time-of-day signal to different organs, and corticotrophin-releasing factor, which is secreted by PVN neurons, indirectly communicates time of day through its circadian rhythmicity entrained by the SCN. Circadian oscillations of core body temperature are also set by the master clock and serve as output signals that influence the timing of peripheral clocks (Buhr *et al.*, 2010).

Outputs from the master clock regulate and synchronize peripheral clocks that are located in every tissue of the body (Damiola, 2000; Yamazaki *et al.*, 2000; Schibler *et al.*, 2003; Sheward *et al.*, 2007). These tissue clocks in turn drive the circadian expression of local transcriptomes, thereby coordinating metabolism and physiology of the entire animal (Figure 1).

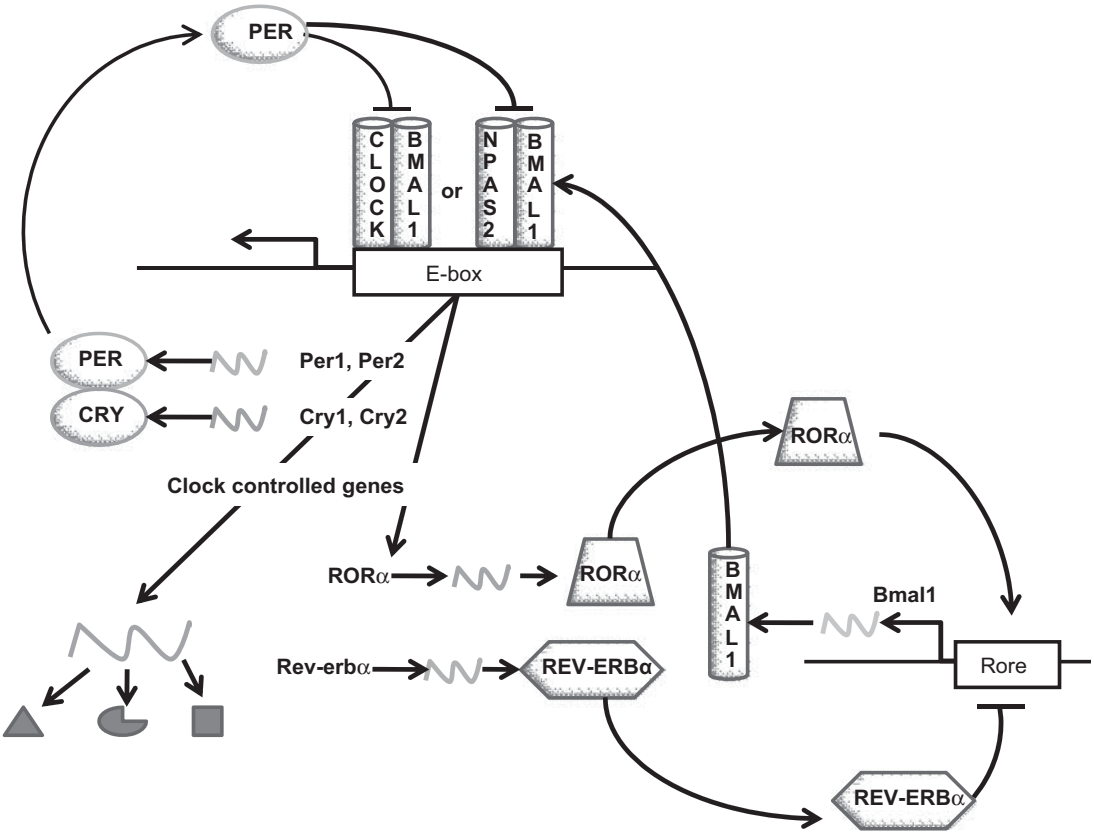

Figure 2 Transcriptional and translational autoregulatory feedback loops that regulate circadian rhythms in cells. The positive loop consists of BMAL1 and CLOCK gene products or BMAL1 and NPAS2 gene products and the negative loop consists of the *Per* and *Cry* gene products. CLOCK and BMAL1 proteins heterodimerize to activate transcription of numerous target genes, including their own repressors, PERs and CRYs thus forming a transcriptional feedback loop. BMAL1 expression is also regulated by two of its transcriptional targets, nuclear receptors *Rev-erbα* and *Rorα*, which repress or activate, respectively, BMAL1 transcription by competing for the same promoter element and forming a secondary interlocked feedback loop.

Thus, external and internal cues are integrated by pacemaker neurons within the SCN and set the master clock which in turn provides a 'reference time' for all peripheral tissue clocks. The role of SCN-synchronized peripheral clocks in coordinating xenobiotic detoxification, cell division and nutrient metabolism is important to health, and disturbances to circadian timing are recognized as factors in major systemic illness (Bass and Takahashi, 2010).

Core molecular clock genes that drive circadian rhythms contain positive and negative elements that form autoregulatory feedback loops. Control of the circadian clock consists of oscillatory feedback activities of core molecular clock genes. In mammals, the core clock genes are conserved, and the positive loop consists of *BMAL1* (aka ARNTL), CLOCK and NPAS2 gene products, whereas the negative loop consists of the Per and Cry gene products (Darlington, 1998; Gekakis, 1998; Kume, 1999; Yagita, 2000). CLOCK and BMAL1 (or NPAS2 and BMAL1) proteins activate transcription of numerous target genes, including their own repressors, Pers and Crys thus forming a transcriptional feedback loop. *BMAL1* expression is also regulated by two of its transcriptional targets, nuclear receptors Rev-erbα (NR1D1) and Rorα (RORA/NR1F1), which repress or activate, respectively, *BMAL1* transcription (Preitner *et al*., 2002; Guillaumond *et al*., 2005). The CLOCK/BMAL1 (NPAS2/CLOCK) complex also drives rhythmic expression of numerous other genes (Figure 2; Brown and Schibler, 1999; Noshiro *et al*., 2007). Both external and internal cues can directly or indirectly affect the expression of core clocks genes in the SCN and peripheral clocks, and thus the molecular components of circadian control systems provide novel avenues for therapeutic intervention (Hastings *et al*., 2007).

Global temporal expression profiles of SCN, liver, adipose and heart tissues in mammals revealed that ~3% to 10% of expressed transcripts in the genome are under circadian control (Akhtar *et al*., 2002; Panda, 2002; Storch *et al*., 2002; Ando *et al*., 2005). Many of the tissue-specific clock-regulated genes were involved in rate-limiting steps critical for organ function. In the rodent liver, 35% of clock-regulated genes direct biosynthesis and metabolism and 10% regulate gene transcription (Akhtar *et al*., 2002). These include transcription factors and nuclear hormone receptors that regulate carbohydrate and lipid homeostasis (Brewer *et al*., 2005; Yang *et al*., 2006). Thus, many rate-limiting hepatic enzymes controlling glycolysis, gluconeogenesis, fatty acid metabolism and amino acid metabolism are regulated by the circadian system (Oishi *et al*., 2000; Froy, 2007).

Recent studies in our laboratory and others have shown the existence of a circadian clock in the mammary gland (Metz *et al*., 2006; Casey *et al*., 2009; Maningat *et al*., 2009). Using transcriptome analysis we investigated coordinated gene expression changes in mammary, liver and adipose during the transition from pregnancy to lactation (Casey *et al*., 2009). For this study total RNA was isolated from mammary, liver and adipose tissues that were collected from rat dams on day 20 of pregnancy (P20; $n = 5$) and day 1 of lactation (L1; $n = 5$). We found that multiple pathways and gene sets related to energy homeostasis were changed in peripheral tissues at the onset of lactation. Molecular signatures of mammary, liver and adipose were enriched with gene sets associated with central nervous system reception, integration and response to environmental and internal stimuli. To gain insight into what was stimulating these changes, we examined genes commonly *upregulated* at the onset of lactation clustered in the gene ontology *transcription regulator activity.* There were 112 genes commonly upregulated among mammary, liver and adipose during the transition from pregnancy to lactation in this ontology, including the core clock genes *ARNTL* (aka *BMAL1*), *NPAS2* and *CLOCK*, the clock regulator *RORA*, as well as *SREBF2*. SREBF2 is a sterol receptor-binding protein transcription factor that activates enzymes important to *de novo* lipid synthesis. When we examined genes commonly downregulated in mammary, liver and adipose tissues during the pregnancy to lactation transition, we found that rhythmic process was significantly enriched with downregulated genes including *NR1D1*, *DBP* and *BHLHB2* (all three are well-characterized transcriptional targets of CLOCK/BMAL1). In summary, during the transition from pregnancy to lactation there was a coordinated induction in expression of the positive limb core clock genes and their regulators (*BMAL1*(*ARNTL*), *NPAS2, CLOCK* and *RORA*) and a suppression in expression of regulators of the negative limb of core clock genes (*BHLHB2, NR1D1, CSNK1E*) across all three tissues (Casey *et al*., 2009). These data suggest that coordinated changes in the circadian system occur during the transition from pregnancy to lactation. Circadian sampling (collecting tissues every 4 h over a 24-h period) to describe temporal changes in gene expression showed that expression rhythms for BMAL1 (Arntl) and PER1 increased in amplitude during the transition from pregnancy to lactation in mice (Metz *et al*., 2006). Changes in amplitude reflect the relative strength of the underlying pacemaker (Bass and Takahashi, 2010), and thus suggest that changes in the mammary core clock reflect the increase in metabolic capacity of this tissue. Global expression analysis of RNA isolated from milk fat globules of human breast milk revealed that $\sim 7\%$ of the genes expressed in lactating breast show circadian patterns including core clock and metabolic genes (Maningat *et al*., 2009), suggesting that the mammary core clock, directly or indirectly, regulates a set of genes important to its metabolic output, milk.

Preliminary studies in our laboratory suggest that cows also have functional mammary clocks. Using an approach pioneered by Balsalobre (Balsalobre *et al*., 1998), we found that treating bovine mammary cells (MAC-T) with media supplemented with 50% serum for 2 h resulted in a synchronized circadian pattern of expression of the core clock gene *BMAL1* (Casey, T. and Plaut K, unpublished results). Second, we found that expression of *BMAL1* was significantly induced when prolactin was added to bovine mammary explant culture (unpublished results), suggesting that the mammary clock is responsive to lactogens. Third, expression of core clock genes *BMAL1* and *PER2* showed circadian patterns of expression in RNA isolated from milk fat globule crescents of mid-lactation cows (unpublished results), which correlated with circadian changes in expression of acetyl-CoA carboxylase (*ACACA*) as well as percent milk fat (unpublished results). These findings suggest that the mammary clock in cows may be responsible for the diurnal variation in milk composition (Kuhn *et al*., 1980; Nielsen *et al*., 2003; Barkova *et al*., 2005; Lubetzky *et al*., 2006; Cubero *et al*., 2007; Lubetzky *et al*., 2007).

The mammary circadian clock may not only respond to systemic cues, but may also be regulated by local signals. Serotonin (5-HT), which acts as both a neurotransmitter and hormone that entrains circadian clocks, has been proposed to be a feedback inhibitor of lactation (Stull *et al*., 2007). The gene coding for tryptophan hydroxylase 1, the rate-limiting enzyme for serotonin synthesis, is expressed in bovine mammary epithelial cells and is upregulated by prolactin *in vitro* (Matsuda *et al*., 2004). Addition of serotonin to mammosphere cultures reduced the expression of α-lactalbumin and casein genes. In contrast, inhibiting serotonin synthesis or blocking its receptor increased milk protein gene expression (Hernandez *et al*., 2008). Further, intramammary infusion of serotonin reduced milk synthesis, whereas blocking the receptor increased milk synthesis in multiparous Holstein cows (Hernandez *et al*., 2008). Somatotropin treatment of mice decreased mammary expression of tryptophan hydroxylase 1 (Hadsell *et al*., 2008). Further studies will be needed to definitively link the mammary clock with serotonin's effect on milk protein synthesis and mammary involution.

Metabolic function and circadian clocks are tightly interwoven such that clocks drive metabolic processes and various metabolic parameters affect clocks (Green *et al*., 2008). In rodents, peripheral liver clocks are synchronized by hormones reflecting the integrated nature of the circadian system (i.e. melatonin and glucocorticoids) and nutrient status (i.e. glucagon and insulin) (Ruiter *et al*., 2003; Kennaway *et al*., 2006; Kohsaka and Bass, 2007; Kohsaka *et al*., 2007; Stokkan *et al*., 2001). This hormonal pattern coordinates liver metabolism to the appropriate time of day and nutritional status of the animal. Rodents with clock gene mutations have dysfunctional glucose homeostasis, insulin secretion and sensitivity and fat and cholesterol metabolism (Rudic *et al*., 2004; Turek *et al*., 2005). Similarly, single nucleotide polymorphisms in *Clock* and *Bmal1* genes in humans are associated with abnormal hepatic fat and glucose metabolism (Sookoian *et al*., 2007; Woon *et al*., 2007).

Similar to other organisms the circadian system appears to play a role in ruminant metabolism. Cows display distinct circadian patterns of intake (DeVries *et al*., 2003) and plasma concentrations of metabolic hormones including insulin, somatotropin, cortisol, melatonin, and triiodothyronine show diurnal patterns of secretion (Hedlund *et al*., 1977a and 1977b; Bitman *et al*., 1994; Lefcourt *et al*., 1993, 1994, 1995 and 1999). Circadian oscillation in plasma glucose, nonesterified fatty acids, β-hydroxybutyrate and urea nitrogen have also been observed in cows (Bitman *et al*., 1990; Lefcourt *et al*., 1999). Studies carried out at the molecular level revealed that DBP mRNA expression, a clock-regulated transcription factor that directs hepatocyte metabolism (Oishi *et al*., 2000; Noshiro *et al*., 2007), showed a circadian pattern that was altered when cattle were injected with somatotropin (Eleswarapu and Jiang, 2005). These daily cycles in hormones and metabolites likely help coordinate timing of intake with metabolism.

Feed availability is a peripheral clock Zeitgeber. Although the LD cycle is the most reliable and strongest external signal that synchronizes (entrains) biological rhythms with the environment, food availability has also been shown to entrain biological rhythms of the peripheral clock in the liver (Stokkan *et al*., 2001). When food is available only for a limited time each day, rats increase their locomotor activity 2 to 4 h before the onset of food availability (Stokkan *et al*., 2001). This food anticipatory behavior occurs in other mammals, including goats, and is often accompanied by increases in body temperature, secretion of corticosterone, gastrointestinal motility and activity of digestive enzymes (Stokkan *et al*., 2001; Piccione *et al*., 2003; Mendoza, 2007; Bass and Takahashi, 2010).

Microarray analysis of the impact of two acute restricted feeding regimens (4 *v.* 10 days) with identical body weight (BW) loss (19%) on hepatic gene expression in rats showed that the two regimens led to distinct patterns of differentially expressed genes in liver. Transcription profiles of 4-day restricted rats suggested that they were in an early phase of metabolic adaptation to feed restriction. Ten days of feed-restricting rats induced changes in gene expression associated with long-term metabolic adaptation to nutrient restriction as well as changes in the core clock genes *PER1*, *PER2* and *ARNTL* (BMAL1; Pohjanvirta *et al*., 2008). These findings suggest that molecular clocks in the liver are reset to the animal's nutrient status as well nutrient availability in their environment.

To systematically dissect the role that food, feeding pattern and the circadian oscillator play in determining rhythmic gene expression in liver, global transcriptional changes in response to fasting and re-feeding were measured in wild-type (WT) C57Bl6 mice and oscillator-deficient mice (*cry1*$^{-/-}$; *cry2*$^{-/-}$; *Cry* mutant). Circadian gene expression profiles of these mice were examined under three different conditions: *ad libitum*, daytime-restricted feeding and prolonged fasting. In oscillator-deficient *Cry* mutant mice, restricted feeding restored 24-h rhythms in gene expression in 617 transcripts, which were identified as the 'food-only' oscillating transcripts. A total of 368 circadian clock-driven transcripts were identified under fasting conditions in WT mice. When WT mice were restricted to daytime feeding, 4960 transcripts displayed rhythmic expression (Vollmers *et al*., 2009), showing that there is a clear synergy between the circadian and metabolic systems in the regulation of rhythmic transcription in the liver. These studies also suggest that there is an independent but interactive organization that links metabolic controls with circadian clocks. This organization likely allows organisms to coordinate tissue responses to predictable changes in their energy state (i.e. diurnal variation in fasting-feeding) through peripheral clocks. In addition, thousands of transcripts can be altered in response to unpredictable changes in the energy state through the uncoupling of metabolic and circadian timers.

Photoperiod manipulation has clear physiological and production effects in cattle. A long-day photoperiod (LDPP), characterized as 16 h light (L) and 8 h dark (D), has been shown to hasten puberty and increase BW gain, feed efficiency, mammary parenchyma and prolactin concentration relative to animals exposed to short-day photoperiod (SDPP; 8L : 16D; Peters *et al*., 1981; Petitclerc *et al*., 1984; Zinn *et al*., 1986). LDPP also increases milk yield without increased consumption of feed (Peters *et al*., 1978), and exposure to SDPP during the dry period enhances subsequent lactation performance (Dahl, 2008). Photoperiod effects on lactation are due in part to changes in mammary cell proliferation as well as immune and metabolic capacity of the animal (Dahl *et al*., 2002; Auchtung *et al*., 2003 and 2005).

Soay sheep, which maintain many WT characteristics, show circadian patterns of hepatic *BMAL1* and *PER2* mRNA expression, and photoperiod manipulation resulted in changes in amplitude of *BMAL1* expression and phase of *PER2* expression (Andersson *et al*., 2005). The shifting pattern of *PER2* mRNA correlated with daily rhythms in plasma cortisol secretion, suggesting that cortisol regulates timing of *PER2* expression in the ovine liver (Andersson *et al*., 2005). Photoperiodic treatment of cattle altered liver mRNA levels of multiple metabolic enzymes known to show circadian patterns, including *ACACA*, phosphoenolpyruvate carboxykinase and fatty acid synthase (Dahl, 2008).

Studies focused on understanding the endocrine effects of altering photoperiod have shown that circulating levels of prolactin increased when heifers and dairy cows were exposed to LDPP, melatonin decreased, but levels of growth hormone and glucocorticoids did not change (Peters and Tucker, 1978; Peters *et al*., 1981). The increased prolactin concentrations are believed to account in part for the increased mammary parenchymal weight in prepubertal and post-pubertal heifers exposed to LDPP compared to heifers exposed to SDPP, and these effects carried through to production, as heifers exposed to LDPP produced more milk during their first lactation than SDPP (Petitclerc *et al*., 1985; Rius and Dahl, 2006). However, and importantly, when prolactin was administered exogenously to dairy cows there was no effect on their milk production (Plaut *et al*., 1987) suggesting that other mechanisms are stimulating the increase in milk yield in lactating cows exposed to LDPP. Slow-release melatonin implants

administered during LDPP for 12 weeks decreased plasma prolactin levels and reduced milk yield by 23%. Melatonin also reduced concentrations of lactose in milk, but increased concentrations of fat, protein and casein (Auldist *et al.*, 2007). These results suggest that seasonal variation in milk quality and quantity may be due to changes in photoperiod mediated by increased concentrations of plasma melatonin in association with decreased concentrations of plasma prolactin.

Increasing exposure to light reduces the duration of melatonin secretion, and thus the duration of melatonin secretion is shorter during the LDPP. In several species, including sheep and deer, pinealectomy abolishes the photoperiod effect on prolactin concentrations, suggesting that there is a regulatory relationship of melatonin on prolactin levels. However, this regulatory relationship is not as clear cut in cattle. Pinealectomy or melatonin fed/infusion did not affect prolactin plasma concentrations in bull calves (Stanisiewski *et al.*, 1988a and 1988b). In contrast, melatonin fed to prepubertal heifers in the middle of LDPP lowered mean serum prolactin by 27%, and decreased DNA content and concentration in mammary parenchyma (Sanchez-Barcelo *et al.*, 1991). When melatonin was fed to heifers to mimic an SDPP, Insulin-like growth factor-I (IGF-I) induction by long days was suppressed, but there was no effect on milk yield in cows (Dahl *et al.*, 2000). Slow-release melatonin decreased mean concentrations of plasma prolactin by 23%, but did not affect IGF-1 concentrations (Auldist *et al.*, 2007). Immediate effects of exogenous melatonin (1 to 4 h) on dairy cows caused a significant increase in the levels of total cholesterol and triglycerides, slight increases in glucose and insulin levels, and a significant decrease in the concentration of free fatty acids, but had no effect on the activity of liver enzymes (Darul and Kruczynska, 2004).

IGF-I may also mediate the galactopoietic response to LDPP. Relative to SDPP, there are higher plasma IGF-I concentrations occur during LDPP (Dahl *et al.*, 1997). Higher basal and rbST-stimulated plasma IGF-I concentrations occurred in LDPP (i.e. summer months). These increases in plasma IGF-1 occurred despite large decreases in feed intake and energy balance due to thermal stress (Collier *et al.*, 2008). Collier *et al.* (2008) suggested that the observed seasonal patterns in plasma IGF-I may be indicative of seasonal differences in the coupling of the somatotropin-IGF axis, as there was no evidence for an uncoupling of the somatotropin-IGF-I axis in summer despite an induced negative energy balance during thermal stress.

The increase in mammary parenchyma due to LDPP may also be mediated in part by changes in the mammary clock. In rodents, expression of core clock genes and c-Myc and Cyclin D1, which regulate cell division and show circadian patterns of expression, change with mammary development and differentiation. Expression of the clock genes *PER1* and *BMAL1* were elevated in differentiated HC-11 cells, whereas *PER2* mRNA levels were higher in undifferentiated cells (Metz *et al.*, 2006). Similarly, *in vivo PER1* and *BMAL1* mRNA levels were elevated in late pregnant and lactating mammary tissues from mice, whereas *PER2* expression was higher in proliferating virgin and early pregnant glands. In both HC-11 cells and mammary glands, elevated Per2 expression was positively correlated with c-Myc and Cyclin D1 mRNA levels, whereas Per1 and Bmal1 expression changed in conjunction with β-casein mRNA levels (Metz *et al.*, 2006). These data suggest that circadian clock genes may play a role in mammary gland development and differentiation.

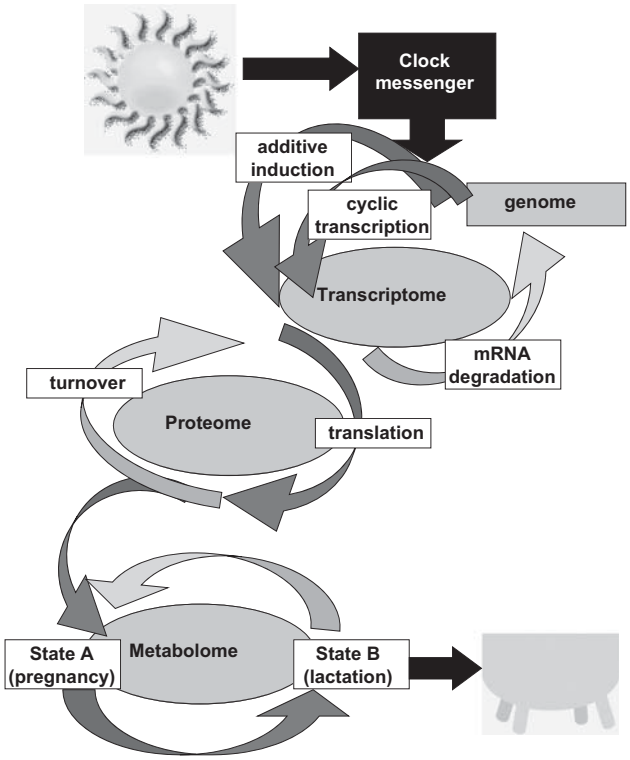

Figure 3 Illustration of how molecular clocks affect metabolic output, as modified from (Casey *et al.*, 2009). We envision that the master clock receives physiological cues during the transition from pregnancy to lactation. These cues are integrated and the master clock responds by sending out signals to peripheral tissues which result in coordinated changes in hormonal milieu and metabolic rhythms to accommodate for the increased metabolic demand of lactation. Photoperiod length and nutrient status of dam serve as inputs to the circadian system as well, and thus influence the outputs, that is, metabolic capacity of the dam. As long-day photoperiod (LDPP) is usually coincident with greater feed availability in nature, ruminants likely evolved with a circadian system pre-programmed to take advantage of these seasonal changes. Thus, a pre-set mechanism (that includes seasonal changes in melatonin levels) adjusts circadian rhythms in a manner that increases mammary metabolic output during LDPP.

Endocrine and autonomic changes due to altering photoperiod clearly play a part in the production changes evident in cattle. These changes in the endocrine system are likely regulated hierarchically by changes in the master clock of the circadian system that elicits both endocrine changes and autonomic outputs that set and synchronize peripheral clocks to the environment (Figure 3). In turn, peripheral clocks likely play a key role in setting the metabolic output of the organ, including mammary, liver and adipose tissue. Inputs and outputs of the circadian system need to be identified so that a clear understanding of environment–gene

interaction can be understood to maximize dairy production in varying environments.

Conclusion

The circadian system functions to coordinate metabolism and physiological processes and receive and respond to environmental cues. In order to initiate lactation coordinated changes in metabolism and hormonal milieu must occur. We envision that the master clock receives and responds to physiological cues during the transition from pregnancy to lactation to coordinate changes in metabolism and hormonal milieu necessary to initiate milk synthesis. Altering photoperiod causes changes in feed efficiency, cell proliferation and endocrine milieu that are indicative of homeostatic adjustments in response to the animal's environment. The SCN functions as a key site for environment–gene interactions in the cow. Changes in photoperiod induces changes in clock genes, which in turn alters autonomic signals and the endocrine milieu to prepare the animal for seasonal changes in feed availability or night/day patterns of nutrient use. By identifying environmental, physiological and nervous inputs that affect changes in expression of core clock genes centrally and/or peripherally we will be able to effectively alter the clock genes to maximize productive efficiency in the dairy cow (Figure 3).

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