Animal (2012), **6:3**, pp 394–402 © The Animal Consortium 2011
doi:10.1017/S1751731111002187

animal

Does the circadian system regulate lactation?

K. Plaut† and T. Casey

Department of Animal Science, Purdue University, West Lafayette, IN 47907, USA

(Received 15 January 2011; Accepted 5 October 2011; First published online 11 November 2011)

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

† E-mail: kplaut@purdue.edu

https://doi.org/10.1017/S1751731111002187 Published online by Cambridge University Press

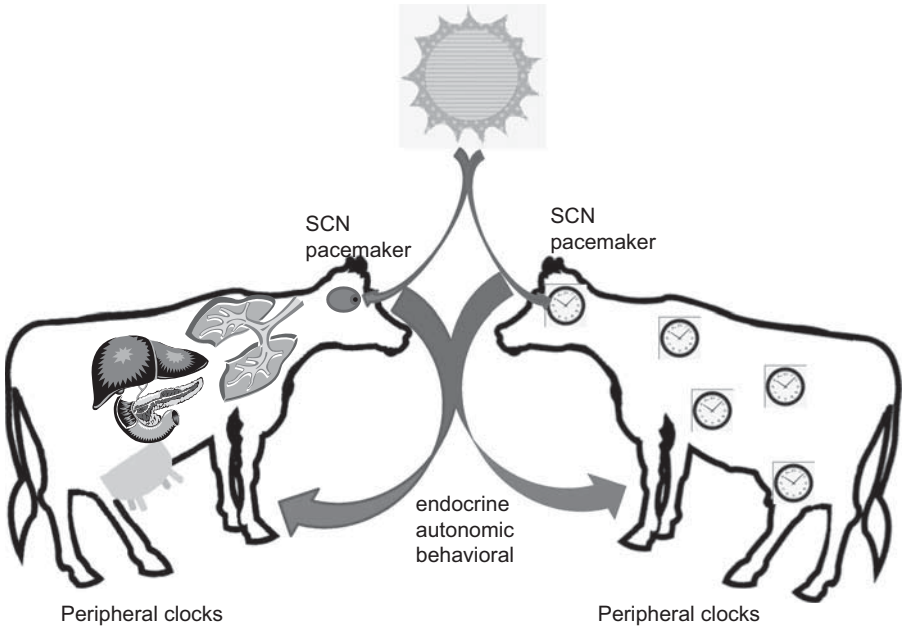


Figure 1 Schematic represents how circadian system coordinates internal physiology with the environment. The primary pacemaker, suprachiasmatic nuclei, is entrained to solar time through retinal afferents and synchronizes and maintains tissue clocks through endocrine, autonomic and behavioral (feeding-related)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

https://doi.org/10.1017/S1751731111002187 Published online by Cambridge University Press

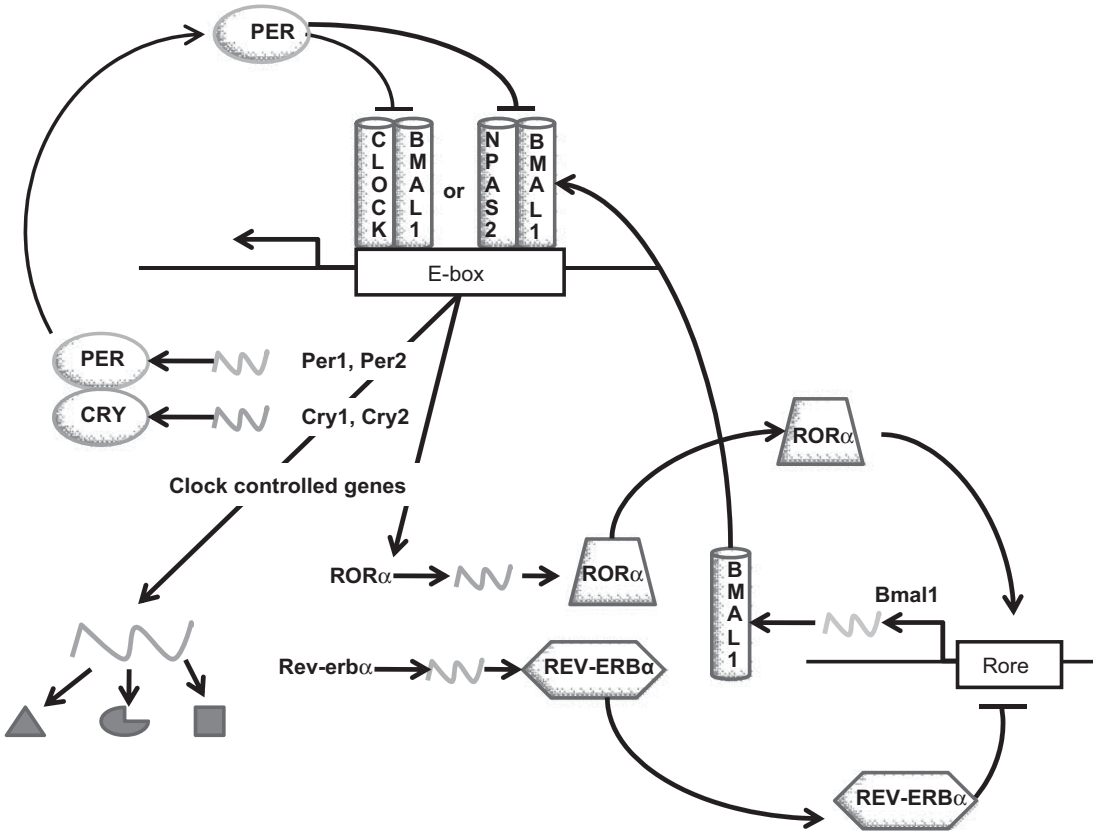


Figure 2 Transcriptional and translational autoregulatory feedback loops that regulate circadian rhythms in cells. The positive loop consists of BMAL1 and CLOCK gene products or BMAL1 and NPAS2 gene products and the negative loop consists of the *Per* and *Cry* gene products. CLOCK and BMAL1 proteins 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 auto-regulatory 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 $\sim$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).

https://doi.org/10.1017/S1751731111002187 Published online by Cambridge University Press

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).

https://doi.org/10.1017/S1751731111002187 Published online by Cambridge University Press

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 postpubertal 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

https://doi.org/10.1017/S1751731111002187 Published online by Cambridge University Press

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

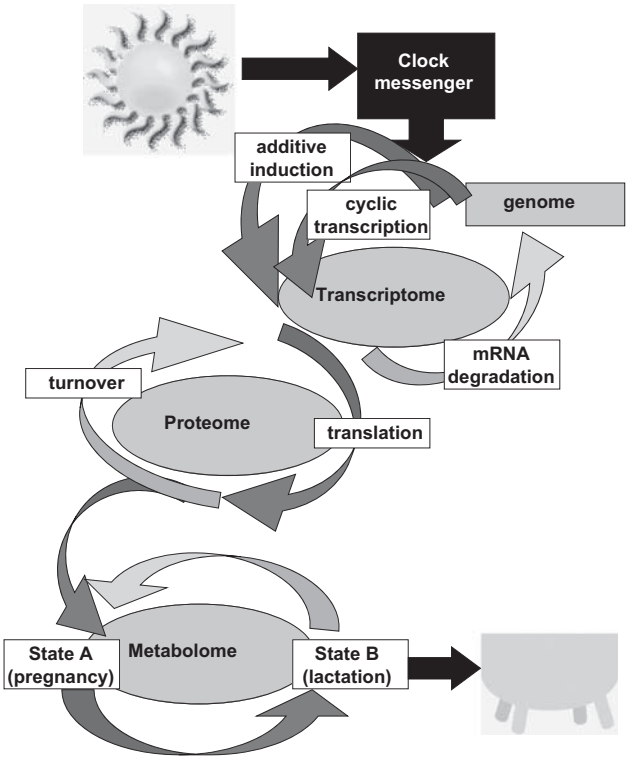


Figure 3 Illustration of how molecular clocks affect metabolic output, as modified from (Casey *et al.*, 2009). We envision that the master clock receives physiological cues during the transition from pregnancy to lactation. These cues are integrated and the master clock responds by sending out signals 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.

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.

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

https://doi.org/10.1017/S1751731111002187 Published online by Cambridge University Press

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).

Acknowledgments

We would like to acknowledge the financial support or NASA Competitive Grant: NCC2-1373.

References

Aharoni Y, Brosh A and Ezra E 2000. Short communication: prepartum photoperiod effect on milk yield and composition in dairy cows. Journal of Dairy Science 83, 2779–2781.

Akhtar RA, Reddy AB, Maywood ES, Clayton JD, King VM, Smith AG, Gant TW, Hastings MH and Kyriacou CP 2002. Circadian cycling of the mouse liver transcriptome, as revealed by cDNA microarray, is driven by the suprachiasmatic nucleus. Current Biology 12, 540–550.

Andersson H, Johnston JD, Messager S, Hazlerigg D and Lincoln G 2005. Photoperiod regulates clock gene rhythms in the ovine liver. General and Comparative Endocrinology 142, 357–363.

Ando H, Yanagihara H, Hayashi Y, Obi Y, Tsuruoka S, Takamura T, Kaneko S and Fujimura A 2005. Rhythmic messenger ribonucleic acid expression of clock genes and adipocytokines in mouse visceral adipose tissue. Endocrinology 146, 5631–5636.

Andrade BR, Salama AA, Caja G, Castillo V, Albanell E and Such X 2008. Response to lactation induction differs by season of year and breed of dairy ewes. Journal of Dairy Science 91, 2299–2306.

Auchtung TL, Kendall PE, Salak-Johnson JL, McFadden TB and Dahl GE 2003. Photoperiod and bromocriptine treatment effects on expression of prolactin receptor mRNA in bovine liver, mammary gland and peripheral blood lymphocytes. Journal of Endocrinology 179, 347–356.

Auchtung TL, Rius AG, Kendall PE, McFadden TB and Dahl GE 2005. Effects of photoperiod during the dry period on prolactin, prolactin receptor, and milk production of dairy cows. Journal of Dairy Science 88, 121–127.

Auldist MJ, Turner SA, McMahon CD and Prosser CG 2007. Effects of melatonin on the yield and composition of milk from grazing dairy cows in New Zealand. Journal of Dairy Research 74, 52–57.

Balsalobre A, Damiola F and Schibler U 1998. A serum shock induces circadian gene expression in mammalian tissue culture cells. Cell 93, 929–937.

Barkova EN, Nazarenko EV and Zhdanova EV 2005. Diurnal variations in qualitative composition of breast milk in women with iron deficiency. Bulletin of Experimental Biology and Medicine 140, 394–396.

Bass J and Takahashi JS 2010. Circadian integration of metabolism and energetics. Science 330, 1349–1354.

Bauman DE and Currie WB 1980. Partitioning of nutrients during pregnancy and lactation: a review of mechanisms involving homeostasis and homeorhesis. Journal of Dairy Science 63, 1514–1529.

Bell A and Bauman D 1997. Adaptations of glucose metabolism during pregnancy and lactation. Journal of Mammary Gland Biology and Neoplasia 2, 265–278.

Bell AW, Bauman DE and Currie WB 1987. Regulation of nutrient partitioning and metabolism during pre- and postnatal growth. Journal of Animal Science 65, 186–212.

Bernabucci U, Basirico L, Lacetera N, Morera P, Ronchi B, Accorsi PA, Seren E and Nardone A 2006. Photoperiod affects gene expression of leptin and leptin receptors in adipose tissue from lactating dairy cows. Journal of Dairy Science 89, 4678–4686.

Bitman J, Wood DL and Lefcourt AM 1990. Rhythms in cholesterol, cholesteryl esters, free fatty acids, and triglycerides in blood of lactating dairy cows. Journal of Dairy Science 73, 948–955.

Bitman J, Kahl S, Wood DL and Lefcourt AM 1994. Circadian and ultradian rhythms of plasma thyroid hormone concentrations in lactating dairy cows. American Journal of Physiology 266, R1797–R1803.

Bosler O and Beaudet A 1985. VIP neurons as prime synaptic targets for serotonin afferents in rat suprachiasmatic nucleus: a combined radioautographic and immunocytochemical study. Journal of Neurocytology 14, 749–763.

Brewer M, Lange D, Baler R and Anzulovich A 2005. SREBP-1 as a transcriptional integrator of circadian and nutritional cues in the liver. Journal of Biological Rhythms 20, 195–205.

Brown SA and Schibler U 1999. The ins and outs of circadian timekeeping. Current Opinion in Genetics & Development 9, 588–594.

Buhr ED, Yoo S-H and Takahashi JS 2010. Temperature as a universal resetting cue for mammalian circadian oscillators. Science 330, 379–385.

Casey T, Patel O, Dykema K, Dover H, Furge K and Plaut K 2009. Molecular signatures reveal the homeorhetic response to lactation may be orchestrated by circadian clocks. PLoS One 4, e7395.

Collier RJ, Miller MA, McLaughlin CL, Johnson HD and Baile CA 2008. Effects of recombinant bovine somatotropin (rbST) and season on plasma and milk insulin-like growth factors I (IGF-I) and II (IGF-II) in lactating dairy cows. Domestic Animal Endocrinology 35, 16–23.

Cubero J, Narciso D, Terron P, Rial R, Esteban S, Rivero M, Parvez H, Rodriguez AB and Barriga C 2007. Chrononutrition applied to formula milks to consolidate infants' sleep/wake cycle. Neuro Endocrinology Letters 28, 360–366.

Dahl GE 2008. Effects of short day photoperiod on prolactin signaling in dry cows: a common mechanism among tissues and environments?. Journal of Animal Science 86, 10–14.

Dahl GE and Petitclerc D 2003. Management of photoperiod in the dairy herd for improved production and health. Journal of Animal Science 81 (suppl. 3), 11–17.

Dahl GE, Buchanan BA and Tucker HA 2000. Photoperiodic effects on dairy cattle: a review. Journal of Dairy Science 83, 885–893.

Dahl GE, Auchtung TL and Kendall PE 2002. Photoperiodic effects on endocrine and immune function in cattle. Reproduction Supplement 59, 191–201.

Dahl GE, Auchtung TL and Reid ED 2004. Manipulating milk production in early lactation through photoperiod changes and milking frequency. Veterinary Clinics of North America: Food Animal Practice 20, 675–685.

Dahl GE, Elsasser TH, Capuco AV, Erdman RA and Peters RR 1997. Effects of a long daily photoperiod on milk yield and circulating concentrations of insulin-like growth factor-I. Journal of Dairy Science 80, 2784–2789.

Damiola F 2000. Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. Genes and Developement 14, 2950–2961.

Darlington TK 1998. Closing the circadian loop: CLOCK-induced transcription of its own inhibitors per and tim. Science 280, 1599–1600.

Darul K and Kruczynska H 2004. Effect of melatonin on biochemical variables of the blood in dairy cows. Acta Veterinaria Hungarica 52, 361–367.

https://doi.org/10.1017/S1751731111002187 Published online by Cambridge University Press

DeVries TJ, von Keyserlingk MA and Beauchemin KA 2003. Short communication: diurnal feeding pattern of lactating dairy cows. Journal of Dairy Science 86, 4079–4082.

Drackley JK 1999. ADSA Foundation Scholar Award. Biology of dairy cows during the transition period: the final frontier?. Journal of Dairy Science 82, 2259–2273.

Eleswarapu S and Jiang H 2005. Growth hormone regulates the expression of hepatocyte nuclear factor-3 gamma and other liver-enriched transcription factors in the bovine liver. Journal of Endocrinology 184, 95–105.

Froy O 2007. The relationship between nutrition and circadian rhythms in mammals. Frontiers in Neuroendocrinology 28, 61–71.

Gekakis N 1998. Role of the CLOCK protein in the mammalian circadian mechanism. Science 280, 1564–1569.

Green CB, Takahashi JS and Bass J 2008. The meter of metabolism. Cell 134, 728–742.

Grummer RR, Wiltbank MC, Fricke PM, Watters RD and Silva-Del-Rio N 2010. Management of dry and transition cows to improve energy balance and reproduction. The Journal of Reproduction and Development 56 (suppl.), S22–S28.

Guillaumond F, Dardente H, Giguère V and Cermakian N 2005. Differential control of Bmal1 circadian transcription by REV–ERB and ROR nuclear receptors. Journal Biological Rhythms 20, 391–403.

Hadsell DL, Parlow AF, Torres D, George J and Olea W 2008. Enhancement of maternal lactation performance during prolonged lactation in the mouse by mouse GH and long-R3-IGF-I is linked to changes in mammary signaling and gene expression. Journal of Endocrinology 198, 61–70.

Hastings M, O'Neill JS and Maywood ES 2007. Circadian clocks: regulators of endocrine and metabolic rhythms. Journal of Endocrinology 195, 187–198.

Hedlund L, Lischko MM, Rollag MD and Niswender GD 1977a. Melatonin: daily cycle in plasma and cerebrospinal fluid of calves. Science 195, 686–687.

Hedlund L, Doelger SG, Tollerton AJ, Lischko MM and Johnson HD 1977b. Plasma growth hormone concentrations after cerebroventricular and jugular injection of thyrotropin-releasing hormone. Proceedings of the Society for Experimental Biology and Medicine 156, 422–425.

Hernandez LL, Stiening CM, Wheelock JB, Baumgard LH, Parkhurst AM and Collier RJ 2008. Evaluation of serotonin as a feedback inhibitor of lactation in the bovine. Journal of Dairy Science 91, 1834–1844.

Jacobs B, Martin-Cora F and Fornal C 2002. Activity of medullary serotonergic neurons in freely moving animals. Brain Research Reviews 40, 45–52.

Kennaway DJ, Owens JA, Voultsios A and Varcoe TJ 2006. Functional central rhythmicity and light entrainment, but not liver and muscle rhythmicity, are clock independent. American Journal of Physiology Regulation, Integration, and Comparative Physiology 291, R1172–R1180.

Kohsaka A and Bass J 2007. A sense of time: how molecular clocks organize metabolism. Trends in Endocrinology and Metabolism 18, 4–11.

Kohsaka A, Laposky AD, Ramsey KM, Estrada C, Joshu C, Kobayashi Y, Turek FW and Bass J 2007. High-fat diet disrupts behavioral and molecular circadian rhythms in mice. Cell Metabolism 6, 414–421.

Kuhn NJ, Carrick DT and Wilde CJ 1980. Symposium: milk synthesis : lactose synthesis: The possibilities of regulation. Journal of Dairy Science 63, 328–336.

Kume K 1999. mCRY1 and mCRY2 are essential components of the negative limb of the circadian clock feedback loop. Cell 98, 193–205.

LeBlanc S 2010. Monitoring metabolic health of dairy cattle in the transition period. The Journal of Reproduction and Development 56 (suppl.), S29–S35.

Lefcourt AM, Bitman J, Kahl S and Wood DL 1993. Circadian and ultradian rhythms of peripheral cortisol concentrations in lactating dairy cows. Journal of Dairy Science 76, 2607–2612.

Lefcourt AM, Akers RM, Wood DL and Bitman J 1994. Circadian and ultradian rhythms of peripheral prolactin concentrations in lactating dairy cows. American Journal of Physiology 267, R1461–R1466.

Lefcourt AM, Bitman J, Wood DL and Akers RM 1995. Circadian and ultradian rhythms of peripheral growth hormone concentrations in lactating dairy cows. Domestic Animal Endocrinology 12, 247–256.

Lefcourt AM, Huntington JB, Akers RM, Wood DL and Bitman J 1999. Circadian and ultradian rhythms of body temperature and peripheral concentrations of insulin and nitrogen in lactating dairy cows. Domestic Animal Endocrinology 16, 41–55.

Lubetzky R, Littner Y, Mimouni FB, Dollberg S and Mandel D 2006. Circadian variations in fat content of expressed breast milk from mothers of preterm infants. Journal of the American College of Nutrition 25, 151–154.

Lubetzky R, Mimouni FB, Dollberg S, Salomon M and Mandel D 2007. Consistent circadian variations in creamatocrit over the first 7 weeks of lactation: a longitudinal study. Breastfeeding Medicine 2, 15–18.

Maningat PD, Sen P, Rijnkels M, Sunehag AL, Hadsell DL, Bray M and Haymond MW 2009. Gene expression in the human mammary epithelium during lactation: the milk fat globule transcriptome. Physiological Genomics 37, 12–22.

Matsuda M, Imaoka T, Vomachka AJ, Gudelsky GA, Hou Z, Mistry M, Bailey JP, Nieport KM, Walther DJ, Bader M and Horseman ND 2004. Serotonin regulates mammary gland development via an autocrine–paracrine loop. Developmental Cell 6, 193–203.

Mendoza J 2007. Circadian clocks: setting time by food. Journal of Neuroendocrinology 19, 127–137.

Metz R, Qu X, Laffin B, Earnest DJ and Porter W 2006. Circadian clock and cell cycle gene expression in mouse mammary epithelial cells and in the developing mouse mammary gland. Developmental Dynamics 235, 263–271.

Meyer-Bernstein E and Morin L 1996. Differential serotonergic innervation of the suprachiasmatic nucleus and the intergeniculate leaflet and its role in circadian rhythm modulation. Journal of Neuroscience 16, 2097–2111.

Mikolayunas CM, Thomas DL, Dahl GE, Gressley TF and Berger YM 2008. Effect of prepartum photoperiod on milk production and prolactin concentration of dairy ewes. Journal of Dairy Science 91, 85–90.

Moore RY and Speh JC 2004. Serotonin innervation of the primate suprachiasmatic nucleus. Brain Research 1010, 169–173.

Moore R, Halaris A and Jones B 1978. Serotonin neurons of the midbrain raphe: ascending projections. Journal of Comparative Neurology 180, 417–438.

Mulligan FJ and Doherty ML 2008. Production diseases of the transition cow. The Veterinary Journal 176, 3–9.

Nielsen NI, Ingvartsen KL and Larsen T 2003. Diurnal variation and the effect of feed restriction on plasma and milk metabolites in TMR-fed dairy cows. Journal of Veterinary Medicine Series A – Physiology Pathology Clinical Medicine 50, 88–97.

Noshiro M, Usui E, Kawamoto T, Kubo H, Fujimoto K, Furukawa M, Honma S, Makishima M, Honma K and Kato Y 2007. Multiple mechanisms regulate circadian expression of the gene for cholesterol 7alpha-hydroxylase (Cyp7a), a key enzyme in hepatic bile acid biosynthesis. Journal of Biological Rhythms 22, 299–311.

Oates JE, Bradshaw FJ, Bradshaw SD, Stead-Richardson EJ and Philippe DL 2007. Reproduction and embryonic diapause in a marsupial: insights from captive female Honey possums, Tarsipes rostratus (Tarsipedidae). General and Comparative Endocrinology 150, 445–461.

Oishi K, Fukui H and Ishida N 2000. Rhythmic expression of BMAL1 mRNA is altered in clock mutant mice: differential regulation in the suprachiasmatic nucleus and peripheral tissues. Biochemical and Biophysical Research Communications 268, 164–171.

Panda S 2002. Coordinated transcription of key pathways in the mouse by the circadian clock. Cell 109, 307–320.

Peters RR and Tucker HA 1978. Prolactin and growth hormone responses to photoperiod in heifers. Endocrinology 103, 229–234.

Peters RR, Chapin LT, Leining KB and Tucker HA 1978. Supplemental lighting stimulates growth and lactation in cattle. Science 199, 911–912.

Peters RR, Chapin LT, Emery RS and Tucker HA 1981. Milk yield, feed intake, prolactin, growth hormone, and glucocorticoid response of cows to supplemented light. Journal of Dairy Science 64, 1671–1678.

Petitclerc D, Chapin LT and Tucker HA 1984. Carcass composition and mammary development responses to photoperiod and plane of nutrition in holstein heifers. Journal of Animal Science 58, 913–919.

Petitclerc D, Kineman RD, Zinn SA and Tucker HA 1985. Mammary growth response of Holstein heifers to photoperiod. Journal of Dairy Science 68, 86–90.

Piccione G, Caolaa G and Refinetti R 2003. Circadian rhythms of body temperature and liver function in fed and food-deprived goats. Comparative Biochemistry and Physiology 134, 563–572.

Plaut K, Bauman DE, Agergaard N and Akers RM 1987. Effect of exogenous prolactin administration on lactational performance of dairy cows. Domestic Animal Endocrinology 4, 279–290.

https://doi.org/10.1017/S1751731111002187 Published online by Cambridge University Press

Pohjanvirta R, Boutros PC, Moffat ID, Linden J, Wendelin D and Okey AB 2008. Genome-wide effects of acute progressive feed restriction in liver and white adipose tissue. Toxicology and Applied Pharmacology 230, 41–56.

Preitner N, Damiola F, Luis Lopez M, Zakany J, Duboule D, Albrecht U and Schibler U 2002. The orphan nuclear receptor REV–ERB[alpha] controls circadian transcription within the positive limb of the mammalian circadian oscillator. Cell 110, 251–260.

Reppert SM and Weaver DR 2002. Coordination of circadian timing in mammals. Nature 418, 935–941.

Rius AG and Dahl GE 2006. Exposure to long-day photoperiod prepubertally may increase milk yield in first-lactation cows. Journal of Dairy Science 89, 2080–2083.

Rudic RD, McNamara P, Curtis AM, Boston RC, Panda S, Hogenesch JB and Fitzgerald GA 2004. BMAL1 and CLOCK, two essential components of the circadian clock, are involved in glucose homeostasis. PLoS Biology 2, e377.

Ruiter M, La Fleur SE, van Heijningen C, van der Vliet J, Kalsbeek A and Buijs RM 2003. The daily rhythm in plasma glucagon concentrations in the rat is modulated by the biological clock and by feeding behavior. Diabetes 52, 1709–1715.

Sanchez-Barcelo EJ, Mediavilla MD, Zinn SA, Buchanan BA, Chapin LT and Tucker HA 1991. Melatonin suppression of mammary growth in heifers. Biology of Reproduction 44, 875–879.

Schibler U, Ripperger J and Brown SA 2003. Peripheral circadian oscillators in mammals: time and food. Journal of Biological Rhythms 18, 250–260.

Sheward WJ, Maywood ES, French KL, Horn JM, Hastings MH, Seckl JR, Holmes MC and Harmar AJ 2007. Entrainment to feeding but not to light: circadian phenotype of VPAC2 receptor-null mice. Journal of Neuroscience 27, 4351–4358.

Simonneaux V and Ribelayga C 2003. Generation of the melatonin endocrine message in mammals: a review of the complex regulation of melatonin synthesis by norepinephrine, peptides, and other pineal transmitters. Pharmacologic Reviews 55, 325–395.

Sookoian S, Castano G, Gemma C, Gianotti TF and Pirola CJ 2007. Common genetic variations in CLOCK transcription factor are associated with nonalcoholic fatty liver disease. World Journal of Gastroenterology 13, 4242–4248.

Stanisiewski EP, Ames NK, Chapin LT, Blaze CA and Tucker HA 1988a. Effect of pinealectomy on prolactin, testosterone and luteinizing hormone concentration in plasma of bull calves exposed to 8 or 16 hours of light per day. Journal of Animal Science 66, 464–469.

Stanisiewski EP, Chapin LT, Ames NK, Zinn SA and Tucker HA 1988b. Melatonin and prolactin concentrations in blood of cattle exposed to 8, 16 or 24 hours of daily light. Journal of Animal Science 66, 727–734.

Stokkan K-A, Yamazaki S, Tei H, Sakaki Y and Menaker M 2001. Entrainment of the circadian clock in the liver by feeding. Science 291, 490–493.

Storch K, Lipan O, Leykin I, Viswanathan N, Davis F, Wong W and Weitz C 2002. Extensive and divergent circadian gene expression in liver and heart. Nature 417, 78–83.

Stull MA, Pai V, Vomachka AJ, Marshall AM, Jacob GA and Horseman ND 2007. Mammary gland homeostasis employs serotonergic regulation of epithelial tight junctions. Proceedings Of The National Academy Of Sciences of The United States Of America 104, 16708–16713.

Turek FW, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, Laposky A, Losee-Olson S, Easton A, Jensen DR, Eckel RH, Takahashi JS and Bass J 2005. Obesity and metabolic syndrome in circadian clock mutant mice. Science 308, 1043–1045.

Vollmers C, Gill S, DiTacchio L, Pulivarthy SR, Le HD and Panda S 2009. Time of feeding and the intrinsic circadian clock drive rhythms in hepatic gene expression. Proceedings of the National Academy of Sciences 106, 21453–21458.

Wall EH, Auchtung-Montgomery TL, Dahl GE and McFadden TB 2005. Short communication: Short-day photoperiod during the dry period decreases expression of suppressors of cytokine signaling in mammary gland of dairy cows. Journal of Dairy Science 88, 3145–3148.

Welsh DK, Logothetis DE, Meister M and Reppert SM 1995. Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms. Neuron 14, 697–706.

Wirz-Justice A 2006. Biological rhythm disturbances in mood disorders. International Clinical Psychopharmacology 21 (suppl. 1), S11–S15.

Woon PY, Kaisaki PJ, Braganca J, Bihoreau MT, Levy JC, Farrall M and Gauguier D 2007. Aryl hydrocarbon receptor nuclear translocator-like (BMAL1) is associated with susceptibility to hypertension and type 2 diabetes. Proceedings of the National Academy of Science of the United States of America 104, 14412–14417.

Yagita K 2000. Dimerization and nuclear entry of mPER proteins in mammalian cells. Genes and Development 14, 1353–1363.

Yamazaki S, Numano R, Abe M, Hida A, Takahashi R, Ueda M, Block G, Sakaki Y, Menaker M and Tei H 2000. Resetting central and peripheral circadian oscillators in transgenic rats. Science 288, 682–685.

Yang Q, Kurotani R, Yamada A, Kimura S and Gonzalez FJ 2006. Peroxisome proliferator-activated receptor alpha activation during pregnancy severely impairs mammary lobuloalveolar development in mice. Endocrinology 147, 4772–4780.

Zinn SA, Chapin LT and Tucker HA 1986. Response of body weight and clearance and secretion rates of growth hormone to photoperiod in holstein heifers. Journal of Animal Science 62, 1273–1278.

https://doi.org/10.1017/S1751731111002187 Published online by Cambridge University Press