Lactation Biology Symposium: Circadian Clocks and Photoperiod in Mammary Development and Lactation

88 Circadian timekeeping mechanisms. P. Hardin*, *Texas A&M University, College Station.*

Animals, plants, fungi and even some prokaryotic organisms display daily rhythms in physiology, metabolism and behavior. These rhythms are not passively driven by environmental cycles (e.g., light) but are controlled by endogenous circadian clocks that keep time even in the absence of environmental time cues. Environmental cycles are nevertheless required to entrain these clocks so that they activate rhythmic processes at the appropriate time of day. Circadian clocks are comprised of an input pathway that receives environmental cues and transmits them to the circadian oscillator, a circadian oscillator that keeps circadian time and activates output pathways, and output pathways that control various metabolic, physiological and behavioral processes. Considerable effort has been focused on determining how the circadian oscillator keeps time. Genetic and molecular studies in the fruit fly, *Drosophila melanogaster*, have contributed significantly to our understanding of the circadian oscillator. Identification and isolation of the first clock gene from Drosophila, period, and subsequent analysis of its expression led to the first molecular model of the circadian oscillator - an autoregulatory feedback loop in gene expression. Discovery of additional clock genes in Drosophila not only support the feedback loop model, but add to its mechanistic detail and complexity. Importantly, many components of the Drosophila circadian feedback loop have orthologs and/or functional equivalents in mammals, thus making Drosophila a useful model for circadian oscillators in higher organisms. New methods of identifying clock genes in Drosophila promise to uncover novel oscillator components that may be amenable to pharmacological manipulation. In animals, circadian oscillators reside in a variety of tissues, including the brain and numerous internal organs. Although these oscillators are largely photoreceptive and directly light-entrainable in Drosophila, oscillators in peripheral tissues of mammals are synchronized by systemic cues from the light-entrained central clock in the brain. Consequently, local oscillators and systemic cues control rhythms in mammalian physiology and metabolism.

Key words: circadian clock, molecular mechanisms, peripheral tissues

89 Circadian clocks in mammary gland development and differentiation. W. Porter*, *Texas A&M University, College Station.*

Biological clocks play a key role in how an organism adapts to daily and annual changes in the environment by regulating rhythmic fluctuations in metabolism, hormone and neurotransmitter release, sensory capabilities and a variety of behaviors. In vertebrates, these physiological responses are controlled by the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. In addition, peripheral tissues including the liver, heart, kidney and mammary gland contain functional endogenous clocks. These peripheral clocks, which regulate numerous physiological processes including proliferation and apoptosis, are similar to the central clock and are influenced by the SCN via a combination of neural and hormonal signals. We have recently shown that members of the molecular clock are differentially regulated during mammary gland development and present new data demonstrating their involvement in normal virgin ductal morphogenesis and functional differentiation during lactation. Moreover, these responses are intrinsic to the mammary gland and not dependent upon the central clock. Furthermore, we have also found that the molecular clock cross-talks with other transcription factor pathways to regulate lactation-dependent gene expression. Together, these results suggest that the peripheral mammary clock is required for normal mammary gland development and function.

Key words: mammary gland, circadian rhythms

90 Circadian clocks as mediators of the homeorhetic response to lactation. T. Casey* and K. Plaut, *Purdue University, West Lafayette, IN.*

The transition from pregnancy to lactation is the most stressful period of a cow's life. During this transition, homeorhetic adaptations are coordinated across almost every organ and are marked by tremendous changes in hormones and metabolism to accommodate for the increased energetic demands of lactation. Recent data from our lab showed that changes in circadian clocks occur in multiple tissues during the transition period in rats and suggest that the circadian system regulates the coordinated changes in the dam's physiology needed to support lactation. Circadian rhythms coordinate the timing of physiological processes and synchronize these processes with the animal's environment. Circadian rhythms are generated by molecular circadian clocks located in the master clock of the hypothalamus and peripherally in every organ of the body. The master clock receives environmental and physiological cues and in turn synchronizes internal physiology by coordinating endocrine rhythms and metabolism through peripheral clocks. The effect of the circadian clock on lactation may be inferred by the photoperiod effect on milk production, which is accompanied by coordinated changes in the dam's endocrine system and metabolic capacity in response to changes in day length. We have shown that bovine mammary epithelial cells possess a functional clock that can be synchronized by external stimuli, and the expression of ARNTL, a positive limb of the core clock, is responsive to prolactin in bovine mammary explants. Others showed that 7% of genes expressed in breasts of lactating women had circadian patterns of expression, and we report that the diurnal variation of composition of cow's milk is associated with changes in expression of mammary core clock genes. Together these studies suggest that the circadian system coordinates the metabolic and hormonal changes needed to initiate and sustain lactation, and that the dam's capacity to produce milk and cope with metabolic stresses in early lactation is related to her ability to set circadian rhythms during the transition period.

Key words: homeorhesis, lactation, circadian

91 Effects of photoperiod on mammary gland development and lactation. G. E. Dahl*, S. Tao, and I. M. Thompson, *University of Florida, Gainesville.*

Photoperiod, or the daily sequence of light and dark, has dramatic effects on many physiological systems across animal species. Light patterns alter melatonin secretion profiles and subsequently the release profiles and circulating concentrations of several hormones that influence a variety of physiological responses. Although the impact of photoperiod on reproductive processes is perhaps the most common example, it is often the seasonal aspects of ovulation and anestrus that

are considered. However, in cattle, the final phase of reproduction, i.e., lactation, is significantly influenced by photoperiod. In contrast to short days (SD; 8h light:16 h dark), exposure to long days (LD) of 16 to 18 h of light and 6–8 h of darkness increase milk yield 2–3 kg/d, regardless of the stage of lactation. There is evidence that this LD effect is due to increased circulating insulin-like growth factor-I independent of any effect on growth hormone concentrations. Cows that are housed under SD during the dry period have increased mammary growth and produce 3–4 kg/d more milk in the subsequent lactation compared with cows on LD when dry. While on SD, circulating prolactin (PRL) diminishes but expression of PRL-receptor increases in mammary, liver and immune cells. Moreover, PRL signaling pathways within those tissues are affected by photoperiod. Further, replacement of PRL to cows on SD partially reverses the effects of SD on production in the next lactation. Thus, effects on dry cows are mediated through a PRL dependent pathway. Before maturity, LD improve mammary parenchymal accumulation and lean body growth which lead to greater yields in the first lactation. The accumulated evidence supports the concept that photoperiod manipulation can be harnessed to improve the efficiency of production across the life cycle of the dairy cow.

Key words: prolactin, insulin-like growth factor I, milk yield