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ADSA Foundation Scholar Award: A role for serotonin in lactation physiology—Where do we go from here?

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ABSTRACT

Lactation is a physiological event that is exclusive to mammals. Lactation evolved as a strategy to improve the survival of the young by providing them with the complete nutrition that is required for survival upon birth as well as maternal–offspring bonding. Typically, milk production by the dam matches the demand of the young. The dairy cow is a unique exception in which the discoveries and genetic selection related to lactation physiology have been applied and resulted in a dramatic increase in milk yield of dairy cows. Studies on the role of mammary-derived serotonin and the coordination of various aspects of milk production and maternal metabolism have revealed novel mechanisms by which milk production and maternal metabolism can be improved. Furthermore, the investigation into molecular and cellular mechanisms regulating mammary gland function has revealed the importance of epigenetics on mammary gland function. Understanding mammary gland function at the cellular and physiological levels will be important for improving mammary gland control of maternal metabolism during early lactation. The early lactation period is a critical time for a dairy cow as that is when she is most susceptible to disease and metabolic disorders that can lead to negative effects on her productive capacity and overall health. Our research in the area of serotonin physiology has illustrated the importance of serotonin on the regulation of lactation and maternal homeostasis. Future research in the area of lactation physiology should be targeted at improving maternal health and longevity in the herd through manipulation of the signals the mammary gland sends to coordinate maternal metabolism and synthesize milk. Specifically, we believe that serotonin will play a central role in understanding the communication between the mammary gland and the maternal physiology during lactation.

Key words: lactation, mammary gland, serotonin

INTRODUCTION

As recently reviewed by Collier and Bauman (2017), the latter half of the 20th century and early portion of the 21st century represents a "golden age" of lactation biology. Numerous recent studies have focused on a variety of new biological influences, such as serotonin and epigenetic effects of heat stress, on the mammary gland, and subsequent effects on milk yield and maternal health. The mammary gland produces bioactive factors critical for autocrine-paracrine regulation of milk synthesis (Wall and McFadden, 2012; Weaver and Hernandez, 2016). Beyond understanding genetic influences on mammary gland physiology, delineation of the endocrine and autocrine-paracrine regulation of mammary gland development and function is critical. This is of particular importance because milk synthesis and secretion varies between species, particularly in relation to their reproductive strategy (e.g., tammar wallaby, fur seal, bovine). It is widely accepted that the amount of milk produced by a mammary gland is affected by the nursing frequency of the gland, and this is largely governed by autocrine or paracrine regulation (Tucker, 1966; Neville et al., 1988; Wall et al., 2012). Nursing frequency and increased milking frequency are strategies that are widely applied in both humans and dairy cattle to increase milk synthesis and secretion during established lactation (Hill et al., 2001; Wall et al., 2012). Furthermore, it has been clearly established that nutrients are partitioned during lactation to support milk synthesis due to various homeorhetic mechanisms (Bauman and Currie, 1980). Therefore, research on factors produced by the mammary gland that control maternal metabolism (i.e., energy homeostasis, calcium homeostasis, endocrine status) to regulate milk production is of great interest. Although milk production is an important focus, research on factors that improve maternal health and metabolism during lactation will be critical to the success of the lactation. The rate-limiting enzyme required for peripheral serotonin synthesis, tryptophan hydroxylase 1, was initially discovered to be expressed in the mammary gland when milk filled the mammary gland (Matsuda et al., 2004). This discovery

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was instrumental in the investigation of how serotonin affects the mammary gland and lactation. My career thus far has focused on understanding how the monoamine serotonin plays a role in the regulation of maternal and mammary gland metabolism during lactation.

THE TRANSITION PERIOD

The greatest risk for cows leaving the herd (dead or sold) occurs in early lactation (Fetrow et al., 2006; De Vries et al., 2010), particularly around calving (Thomsen et al., 2004; Dechow and Goodling, 2008; McConnel et al., 2009). Approximately 45% of mortality in herds occurs in the first 60 d postpartum, and up to 52% occurs from 21 d prepartum to 60 d postpartum (Hadley et al., 2006; McConnel et al., 2009). Production diseases such as milk fever or hypocalcemia, ketosis, fatty liver, metritis, retained placenta, displaced abomasum, and mastitis have all been shown to have a negative effect on potential production and to increase the risk of involuntary culling. Chamberlin et al. (2013) found that hypocalcemic cows had significantly higher mean plasma nonesterified fatty acid concentrations on the day of calving as well as a higher liver lipid percentage on d 7 postcalving. Several studies have indicated that cows with subclinical hypocalcemia (**SCH**) do in fact have a greater risk of developing a displaced abomasum and consequently being culled within the first 60 DIM (Seifi et al., 2011; Chapinal et al., 2012).

In addition to the effects of hypocalcemia on energy metabolism, Ca has a critical role in muscle function. Hypocalcemia leads to a reduction in all muscle contractions, which can decrease rumen and abomasal motility, therefore further increasing the risk of a displaced abomasum. Likewise, insufficient contraction of the teat sphincter muscle consequently increases the risk of mastitis (Goff, 2008). Martinez et al. (2012) showed a compromised innate immune system in SCH cows compared with normocalcemic cows. Neutrophils in the blood of SCH cows were less capable of phagocytizing and killing pathogenic bacteria in vitro. The SCH cows were further compromised by an overall smaller leukocyte population, and they had a 3.2-fold increase in the incidence of metritis. Although it is recognized that cows experience immunosuppression during the periparturient period, the study of Martinez et al. (2012) suggests that immunosuppression is further exacerbated by low blood Ca levels. Kimura et al. (2006) offered data suggesting that periparturient immunosuppression in dairy cows is due, in part, to the depletion of intracellular Ca stores. A recent study using an EGTA challenge model demonstrated that cows with SCH had fewer neutrophils undergoing phagocytosis and a lower oxidative burst response after incubation with pathogenic bacteria (Martinez et al., 2014). This further supports the idea that a reduction in Ca could lead to immunosuppression in a periparturient cow.

Although dietary changes have reduced clinical hypocalcemia in the United States dairy herd from as high as 50% to approximately 5% (Block, 1984; USDA, 2010), the impact of SCH is still of great concern. In 2011, the incidence of SCH in cows of second lactation or greater was estimated to be approximately 47%, with 25% of all first-lactation cows being affected (Reinhardt et al., 2011). It is estimated that each case of hypocalcemia results in a loss of at least $300 (Guard, 1996), whereas every case of SCH costs, on average, $125 (Oetzel, 2013). In an effort to reduce SCH in periparturient cows, several groups have focused on novel ways to utilize prepartum DCAD diets to improve postpartum calcium status, including use of DCAD diets in combination with vitamin D supplementation, varying levels of DCAD in combination with low energy diets, or feeding DCAD in combination with 5-hydroxy-L-tryptophan supplementation (Leno et al., 2017; Martinez et al., 2018; Rodney et al., 2018; Slater et al., 2018). Research targeted at improving Ca homeostasis during the periparturient period will be critical for improving cow health and longevity. Our research on how serotonin coordinates Ca metabolism during lactation is a novel area in which we have demonstrated the presence of a physiological axis during lactation that can be manipulated to improve cow health and productivity.

SEROTONIN

Serotonin is a biogenic amine that has been preserved over the last 2 billion years of evolution from protozoa to mammals and has been demonstrated to influence development and plasticity of various tissues in different species (Turlejski, 1996; Raymond et al., 2001). Serotonin is one of the most ancient signaling molecules, and it is found in many animals, plants, and unicellular organisms, with the first receptor subtype appearing 750 million years ago (Turlejski, 1996; Raymond et al., 2001). The early appearance of serotonin in the evolutionary record has resulted in the regulation of a variety of physiological functions, including fundamental mechanisms such as homeostasis, feeding, immunity, glucose regulation, cardiovascular function, behavior, gut motility, and reproduction (Gershon and Tack, 2007; Horseman and Collier, 2014; Wyler et al., 2017). Additionally, serotonin receptors are thought to be one of the oldest rhodopsin-like receptors in existence (Garattini and Valzelli, 1965; Nichols and Nichols, 2008). Serotonin is synthesized from the amino acid L-tryptophan. L-Tryptophan is converted to 5-hydroxy-L-tryptophan (**5-HTP**) via tryptophan