J. Dairy Sci. 98:1–12
http://dx.doi.org/10.3168/jds.2015-9828

Autocrine-paracrine regulation of the mammary gland[1]

S. R. Weaver and L. L. Hernandez[2]
University of Wisconsin-Madison, 1675 Observatory Drive, Madison 53706

ABSTRACT

The mammary gland has a remarkable capacity for regulation at a local level, particularly with respect to its main function: milk secretion. Regulation of milk synthesis has significant effects on animal and human health, at the level of both the mother and the neonate. Control by the mammary gland of its essential function, milk synthesis, is an evolutionary necessity and is therefore tightly regulated at a local level. For at least the last 60 yr, researchers have been interested in elucidating the mechanisms underpinning the mammary gland's ability to self-regulate, largely without the influence from systemic hormones or signals. By the 1960s, scientists realized the importance of milk removal in the capacity of the gland to produce milk and that the dynamics of this removal, including emptying of the alveolar spaces and frequency of milking, were controlled locally as opposed to traditional systemic hormonal regulation. Using both in vitro systems and various mammalian species, including goats, marsupials, humans, and dairy cows, it has been demonstrated that the mammary gland is largely self-regulating in its capacity to support the young, which is the evolutionary basis for milk production. Local control occurs at the level of the mammary epithelial cell through pressure and stretching negative-feedback mechanisms, and also in an autocrine fashion through bioactive factors within the milk which act as inhibitors, regulating milk secretion within the alveoli themselves. It is only within the last 20 to 30 yr that potential candidates for these bioactive factors have been examined at a molecular level. Several, including parathyroid hormone-related protein, growth factors (transforming growth factor, insulin-like growth factor, epidermal growth factor), and serotonin, are synthesized within and act upon the gland and possess dynamic receptor activity resulting in diverse effects on growth, calcium homeostasis, and milk composition. This review will focus on the autocrine-paracrine regulation of the mammary gland, with an examination of both foundational work and the progress made within the last 10 to 20 yr of research.
Key words: lactation, milk, secretion, autocrine-paracrine

INTRODUCTION

The mammary gland has an incredible capacity for self-regulation through autocrine-paracrine signaling. From an evolutionary standpoint, the mammary gland has to balance the energy and health status of the mother while simultaneously performing its essential function of supporting the neonate by producing milk. Although autocrine-paracrine signaling is of essential importance in development and growth, the current paper will focus on the process of milk secretion and synthesis (Oka and Yoshimura, 1986). Given the challenge of balancing maternal homeostasis while producing adequate quantities of milk, it is unsurprising that milk synthesis and secretion are tightly regulated and that this regulation can take place at a local level that is largely independent of systemic influences. Peaker et al. (1998) established that the mammary gland is a unique exocrine gland in 2 respects: (1) that secretion is continuous during lactation, unlike various other exocrine glands that only secrete in response to a stimulus; and (2) the secreted substance (milk) is stored in the mammary gland in the lumen of secretory alveoli and ductal system until removal, either by suckling of the young or, in dairy animals, by milking. Mammary gland regulation of milk synthesis varies across species in accordance with that animal's evolutionary demands: the tammar wallaby (*Macropus eugenii*) and fur seal both exemplify this concept as rather extreme cases, but this differential regulation is also evident in the literature in rodents, humans, pigs, and ruminants, to name a few (Brennan et al., 2007; Neville et al., 2002). Whereas all these species will be discussed, our paper will focus on ruminants, and particularly on dairy cows, as knowledge of their mammary gland local control

Received May 18, 2015.
Accepted June 29, 2015.
[1]Presented as part of the Lactation Biology Revisited Symposium at the ADSA-ASAS Joint Annual Meeting, Orlando, Florida, July 2015.
[2]Corresponding author: llhernandez@wisc.edu

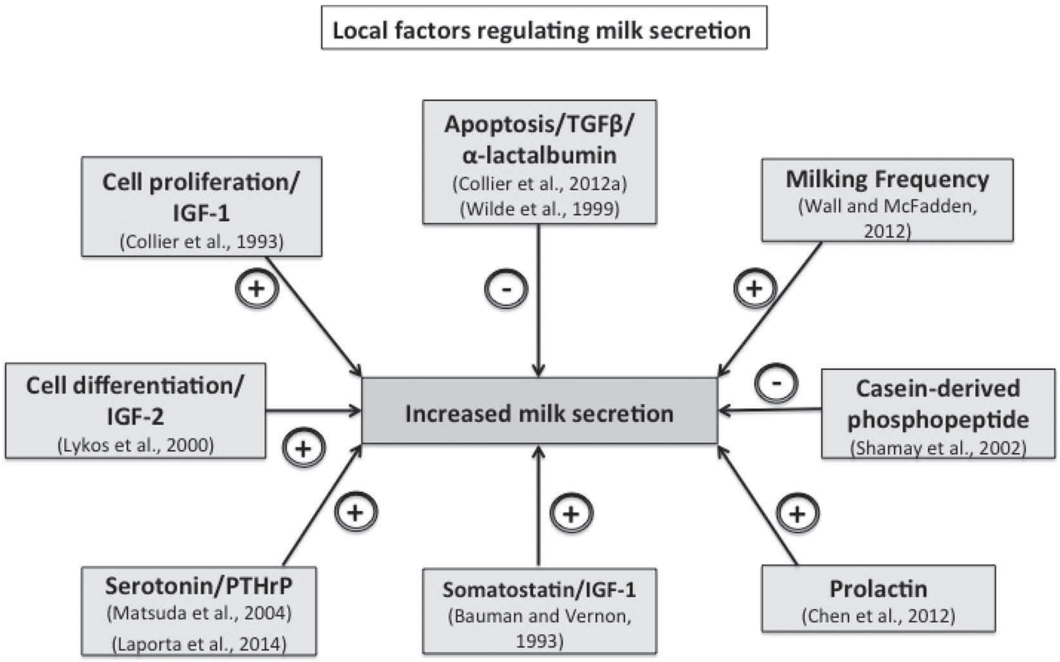

Figure 1. Local factors responsible for regulating milk secretion. A combination of bioactive factors and management practices influence the local environment of the mammary gland to regulate milk secretion. Greater milk secretion can be provoked by increasing the frequency of daily milking, increased cell proliferation through IGF-1, increased cell differentiation through IGF-2, the action of serotonin and parathyroid hormone related protein (PTHrP), somatostatin and IGF-1, and prolactin. Milk secretion is negatively regulated by apoptosis with apoptotic factors such as transforming growth factor β (TGFβ) and α-LA as well as by casein-derived phosphopeptides.

mechanisms has the most tangible effect on a production and animal welfare level. Given the mammary gland's ability to regulate the demands of mother and neonate, uniqueness in terms of exocrine function, and enormous adaptability across species, it is no wonder that the mammary gland has developed complex and comprehensive mechanisms for control at a local level.

LOCAL CONTROL—WHAT DOES IT MEAN?

Local control is a rather ambiguous term that encompasses a wide range of processes that occur at the level of the mammary gland, largely by autocrine-paracrine signaling (Figure 1). Perhaps the most extreme example of mammary gland local control comes from the tammar wallaby (*Macropus eugenii*), which is capable of asynchronous concurrent lactation (**ACL**; Nicholas et al., 1995). Through modulation of the mammary gland at the local level, tammar wallabies are able to support multiple young at different stages of development throughout 4 distinct phases of lactation. Stage 1 is defined by mammary gland development up until parturition. The first 100 d of lactation when the young is in the pouch and permanently attached to the teat define stage 2a, whereas the subsequent 100 d with less frequent suckling characterize stage 2b. Milk is largely diluted in stage 2, with high concentrations of carbohydrates. Finally, stage 3 takes place when the young is intermittently leaving the pouch up until it stops suckling, with a shift in milk composition to higher fat and protein content and decreased carbohydrate content. Through local control, each mammary gland of the tammar wallaby is able to support the demands of these various stages simultaneously, despite drastic differences in milk volume and composition (Hendry et al., 1998).

Whereas it was originally thought that these adaptations were produced by suckling patterns of the young, further research has shown that control takes place at a transcriptional level in the mother herself, with each stage of lactation expressing genes specific to only that stage (early lactation protein in stage 2a, whey acidic protein in 2b, and late lactation protein in 3), along with several genes throughout the entire lactation (α- and β-CN and α- and β-LG). Characteristic molecular processes dictate the phenotypic changes in each of the stages: for example, in stage 2b whey acidic protein has been implicated in the proliferation of mammary epithelial cells (**MEC**), increasing the secretory capacity of the gland to reach the highest rate of milk synthesis in stage 3 (Brennan et al., 2007). The stages of ACL and their corresponding molecular profiles demonstrate