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Serotonin and calcium homeostasis during the transition period

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ABSTRACT

The transition from pregnancy to lactation puts significant, sudden demands on maternal energy and calcium reserves. Although most mammals are able to effectively manage these metabolic adaptations, the lactating dairy cow is acutely susceptible to transition-related disorders because of the high amounts of milk being produced. Hypocalcemia is a common metabolic disorder that occurs at the onset of lactation. Hypocalcemia is also known to result in poor animal welfare conditions. In addition, cows that develop hypocalcemia are more susceptible to a host of other negative health outcomes. Different feeding tactics, including manipulating the dietary cation-anion difference and administering low-calcium diets, are commonly used preventative strategies. Despite these interventions, the incidence of hypocalcemia in the subclinical form is still as high as 25% to 30% in the United States dairy cow population, with a 5% to 10% incidence of clinical hypocalcemia. In addition, although there are various effective treatments in place, they are administered only after the cow has become noticeably ill, at which point there is already significant metabolic damage. This emphasizes the need for developing alternative prevention strategies, with the monoamine serotonin implicated as a potential therapeutic target. Our research in rodents has shown that serotonin is critical for the induction of mammary parathyroid hormone–related protein, which is necessary for the mobilization of bone tissue and subsequent restoration of maternal calcium stores during lactation. We have shown that circulating serotonin concentrations are positively correlated with serum total calcium on the first day of lactation in dairy cattle. Administration of serotonin's immediate precursor through feeding, injection, or infusion to various mammalian species has been shown to increase circulating serotonin concentrations, with positive effects on other components of maternal metabolism. Most recently, preliminary data suggest that manipulation of the serotonergic axis precalving may positively affect postcalving calcium dynamics. Combined, our research suggests a potential mechanism by which serotonin acts on the mammary gland to maintain circulating maternal calcium concentrations. Further research into serotonin's potential as a therapeutic target could contribute significantly as a preventive strategy against hypocalcemia in early lactation dairy cows.

1. Hypocalcemia and current strategies for prevention and treatment

The transition period in dairy cows is defined as 3 wks precalving to 3 wks postcalving, during which time maternal metabolism changes rapidly. On the day of parturition, a dairy cow produces 10 L or more of colostrum containing at least 23 g of calcium [1], and by later lactation as much as

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50 g of calcium are lost into milk each day to support the growing neonate [2]. A more recent study demonstrates that colostral yields range between 1 and 20 kg, depending on parity, and that an increase in milk production occurs in the first 5 d postpartum, on average about 10 kg [3]. These data demonstrate the large demand for calcium by the mammary gland during early lactation that leaves cows highly susceptible to hypocalcemia. The dysregulation of calcium at the onset of lactation is largely a result of the dairy cow's inability to manage maternal calcium homeostasis while secreting calcium into milk. Typically, circulating calcium concentrations are tightly regulated between 2.0 and 2.5 mM in dairy cows. At the onset of lactation, however, increased demand for calcium by the mammary gland for milk synthesis leads to depletion of circulating maternal calcium stores, often provoking periparturient hypocalcemia (milk fever). Clinical hypocalcemia (defined as 1.4 mM or less of circulating total calcium) has an incidence of between 5% and 10% in the United States dairy cow population, whereas the subclinical form (1.4 to 2.0 mM) has an increased incidence of 25% to 50% [1,4]. In addition, several recent studies suggest that the threshold for subclinical hypocalcemia is underestimated based on poor reproductive outcomes, increased displaced abomasums, and higher incidence of ketosis [5,6]. Older cows are at a much higher risk for developing hypocalcemia because of their decreased ability to mobilize calcium from bone, resulting in a 9% increase of susceptibility with each subsequent lactation [7]. In terms of breed, Jersey cattle are the most susceptible, likely because of the increased calcium content in their milk and higher milk production per unit of body weight [8].

Hypocalcemia is a particularly difficult disease to manage because of its manifestation: the early symptoms in stage I of the disease are often short-lived and hard to detect, largely because they are not outwardly exhibited by the cow, and can only be detected by measuring blood calcium concentrations. By the time the cow has moved on to stage II, characterized by decreased body temperature, lack of coordination when walking, and muscle tremors, significant intervention in the form of intravenous calcium administration is often required, resulting in an estimated 14% production loss [9,10]. The economic impact of hypocalcemia is enormous: considering the 9.2 million cows in the U.S. dairy industry with a cost of $125 and $300 per case of subclinical and clinical hypocalcemia, respectively, given treatments and lost milk yield, there is an estimated cost of $900,000,000 annually [11,12]. Although these estimates are purely economic, there are also animal welfare concerns, given that the cow maybe unable to stand or walk until identified by the farmer. Potentially more troubling than the physical and economic ramifications of hypocalcemia is the fact that the subclinical form is nearly impossible to identify in a production setting, as cows do not display obvious clinical symptoms [13] and therefore, may be predisposed to a host of subsequent health challenges.

Hypocalcemia can be considered a "gateway disease" because its incidence is positively correlated with a variety of other health concerns [1,4]. Calcium is required for both smooth muscle contraction and proper immune function, among other essential functions. In the dairy cow, the contraction of smooth muscle is responsible for rumen and gut motility and both uterine and teat sphincter contraction. Dysregulation of these processes contributes to a variety of common transition disorders, including ketosis and fatty liver, displaced abomasum, dystocia, metritis, and mastitis, in addition to increased susceptibility to infectious disease [1,14–16]. Furthermore, subclinical hypocalcemia specifically has been linked to greater risk of fever and metritis as well as decreased pregnancy rates and longer intervals to pregnancy [6]. Given that the calcium insults to maternal physiology resulting in hypocalcemia typically occur very early in lactation before any of these later physiological, immunologic, and metabolic conditions are realized, the ramifications of the disease must be considered beyond the immediate symptoms and into the cow's entire lactation and subsequent lactations.

Although there are prevention strategies currently used in the United States, they are often difficult to implement effectively. To stimulate demineralization of bone, which is the primary source of calcium during lactation, a transient hypocalcemia must occur [17]. To this end, the current primary target for hypocalcemia prevention is through manipulation of the diet at the end of the dry period with the 2 major strategies being administration of low-calcium diets (LCD) and adjustment of the dietary cation-anion difference (DCAD). Transient hypocalcemia is induced on feeding the LCD, thereby stimulating calcium resorption from the bone and increasing calcium absorption from the small intestine to increase available calcium reserves [18]. For the prevention of milk fever, a diet of 8 to 10 g of calcium per day has been shown to have the greatest effect, but LCD with this little calcium is difficult to achieve mainly because the primary forage of alfalfa is quite high in calcium [19]. Conversely, the strategy of DCAD manipulation is to increase availability of absorbable dietary anions and decrease the number of absorbable dietary cations through use of dietary anionic salts [1]. Although there is no doubt that this strategy aids in the prevention of milk fever [20], there are 2 major concerns: the first is that the salts decrease palatability, reducing feed intake and predisposing the cow to other energy–related transition disorders. The second issue is that anionic salts are quite expensive, adding additional cost onto an already costly period in the cow's life [18]. In addition, a low DCAD diet is typically implemented during the 3 wk immediately prepartum, creating the need for 2 separate groups of cows in the dry pen. Further work has been done with respect to calcitriol (1,25 dihydroxyvitamin D3, the active form of Vitamin D) or oral calcium/metabolite administration, but these results have been shown to be largely impractical and dependent on timing of administration [15]. Improvement of these prevention strategies depends on a more thorough understanding of the physiological mechanisms that govern calcium homeostasis in the dairy cow. Our laboratory has shown that manipulation of a key regulator of calcium dynamics, serotonin, may have significant impact as a novel therapeutic target in the prevention of hypocalcemia.

2. Early lactation calcium homeostasis

Proper maintenance of circulating calcium concentrations is essential to a successful lactation. Several pathways