Sustainable Milk Production from a Lactation Biology Perspective

Shinichi Yonekura[1(✉)] and Mst Mamuna Sharmin[2]

[1] Faculty of Agriculture, Shinshu University, 8304 Kami-Ina, Minamiminowa, Nagano, Japan
yonekura@shinshu-u.ac.jp

[2] Department of Dairy and Poultry Science, Faculty of Veterinary and Animal Science, Hajee Mohammad Danesh Science and Technology University, Dinajpur 5200, Bangladesh

Abstract. World per capita consumption of fresh dairy products is projected to increase by 1.0% p.a. and production is projected to grow at 1.6% p.a. over the coming decade (2020–2029). To meet up this additional demand, raising high producing dairy cows with proper nutrition and environment is obvious in the modern dairy industry. However, the high-yielding dairy cows are more susceptible to nutritional and environmental stresses than the lower milk-producing cows. This review discusses how exposure to nutritional and environmental stresses can cause abnormalities in mammary epithelial cells (MEC), the site of milk synthesis. In addition, the intracellular mechanisms related to milk yield are described. Recent accumulated data suggested that the unfolded protein response (UPR)-induced increase in endoplasmic reticulum biogenesis and MEC loss as the mechanism for the increase and decrease in milk yield, respectively. Therefore, an understanding of the role of ER biogenesis in enhancing secretory activities and MEC death to reduce milk yield in the context of UPR at early lactation, will be helpful for the final setup of an average lactation persistency and the producers to overcome the economic loss due to heat stress in the dairy industry.

Keywords: dairy cows · endoplasmic reticulum biogenesis · heat stress · mammary epithelial cells · milk production

1 Introduction

The role of the dairy cow to supply the increasing demand for the milk and milk products of the world's growing population is undeniable. In the last few decades, the demand for milk and dairy products has multiplied in the daily diet of individuals. World per capita consumption of fresh dairy products is projected to increase by 1.0% p.a. and production is projected to grow at 1.6% p.a. over the coming decade (2020–2029) [1]. To meet up this additional demand, raising high producing dairy cows with proper nutrition and environment is obvious in the modern dairy industry. However, the high-yielding dairy cows are more susceptible to nutritional and environmental stresses than the lower milk-producing cows [2]. Continuous elevation of ambient temperature (2.5 °C from 1901 to 2012; IPCC 2013) has a negative impact on dairy cattle productive parameters such

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as milk yield, milk composition, growth, and reproduction. This review discusses how exposure to nutritional and environmental stresses can cause abnormalities in mammary epithelial cells, which were the site of milk synthesis. In addition, the intracellular mechanisms related to milk yield are described.

2 Physiology of Milk Production in the Mammary Gland

The mammary gland contains a cluster of alveoli, each of which are the terminal point after a branching network of numerous ducts. A single layer of epithelial cells surrounds the lumen of each alveolus. These mammary epithelial cells (MECs) synthesis the milk components utilizing the nutrients absorbed from the circulating blood [3].

During the lactation period, secretory activity and the number of MECs have a large influence on milk production. Knight and Peaker [4] demonstrated that during early lactation period, there is an increase in milk yield due to the increase of number of MECs and secretory activity per cell. Here, the number of MECs and secretory activity were evaluated on the basis of DNA mass and RNA/DNA ratio respectively. Capuco et al. [5] conducted a comparative study using the nucleic acid content collected from mammary gland samples at different stages of lactation. The study showed that the MEC population increased at 14 days of lactation because the amount of total DNA content was highest at that time. Milk production per MEC increased from early to peak lactation, indicating that MEC secretory capacity was constantly increasing.

Moreover, Boutinaud et al. [6] identified that, secretory capacity per cell and secretory cell population are the principal factors for increasing the milk yield from parturition to peak lactation. At the end of peak lactation, milk production gradually reduces due to the gradual reduction of MEC number. A earlier study discovered that a 17% reduction in DNA mass (resumed as cell number) in dairy cows is sufficient to reduce the 23% milk yield from peak to end of lactation. [5]. In case of goat, that reduction rate was 19% and 20% for DNA content and milk yield respectively, from peak to end of lactation [4]. Therefore, any change in the secretory activity or number of MEC is the major cause for fluctuating the milk yield, which in turn, leads to lactation persistency elasticity. However, the increased number and secretory activity of cells enhance the production of milk and vice versa. In fact, the regulatory mechanism of MECs number and secretory activity in the mammary gland remains unclear.

3 Nutritional Stress and Milk Yield

The global milk production has become double by the past decade. Concomitantly, high-yielding dairy cows are experiencing various types of physiological stresses as a result of periparturient transitional modification. The decrease in dry matter intake before calving [7] and the increase in milk yield at the onset of lactation [8], demands for the higher amount of nutrients [9]. Above are the important and common significance of physiological stress. As a result, it is a common experience of high yielding dairy cows to suffer from negative energy balance (NEB) condition, which in turn causes different types of metabolic disorders [10, 11]. The NEB is one of the major consequences for the

reduction of milk yield [12]. The reduction of milk production also declines the lactation curve as well as lactation persistency [13].

Therefore, it is inevitable for the dairy physiologists to uncover the cause for fluctuation of milk yield during early lactation, consequently, the dairy industry suffers economically. The invention of new technology, for example average lactation persistency will be benificial to reduce the health problems of dairy cows. Therefore, enough attention should be paid for the manipulation of moderate lactation persistency by uncovering the cause for increase and decrease of milk yield during early lactation.

4 Heat Stress and Milk Yield

Heat stress (HS) is a significant environmental factor in the production of dairy cows in tropical and subtropical countries around the world that affect several variables including feed intake and milk production. The projected milk production loss due to heat stress only in the USA is 6.3% by the end of the 21st century [14], and the financial burden estimated annually ~$900 million for the dairy industry [15]. Even advanced management facilities (i.e. shading, fans) and cooling strategies are unable to prevent these enormous losses. It has long been assumed that HS causes decreased dry matter intake (DMI), which decrease milk yield and protein content in dairy cows. However, studies [16, 17] suggested that the decrease in milk production in HS accounts for 35% only by reduced feed intake, and the rest is for a shifting post-absorptive metabolism and nutrient partitioning. These results suggest that factors other than a reduction in energy intake may be responsible for reduced milk production, but the other factors and their mechanics are unknown. The detrimental effects of HS on animal welfare and production will likely become more of an issue in the future if the earth's climate continues to warm as predicted (Intergovernmental Panel on Climate Change - IPCC, 2007) and some models forecast extreme summer conditions in most USA animal producing areas.

5 Association Between Unfolded Protein Response and Milk Synthesis in the Endoplasmic Reticulum

The endoplasmic reticulum (ER) is the principal site for biosynthesis of protein, steroid, cholesterol and lipids. The enhancement of global protein synthesis, change of calcium homeostasis, deprivation of nutrients and failure of posttranslational modification disrupt the normal synthetic capacity of ER, thereby leading to the accumulation of unfolded proteins [18]. Higher amounts of unfolded proteins imbalance the ER homiostasis. In this condition, unfolded protein response (UPR; an adaptive network of signaling cascades) is activated by three stress sensor transmembrane proteins: PKR-like endoplasmic reticulum kinase (PERK), inositol requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6) [19]. During stressful condition of ER, functional PERK halts the translation of general protein and increases the production of ATF4 (a transcription factor) through the phosphorylation of eukaryotic initiation factor 2α (eIF-2α) [20]. In extreme or persistent ER stresss condition, ATF4 enhances the transcription of C/EBP homologus protein (CHOP), which functions as a transcription factor to induce apoptosis of cell [21].

Previous studies suggested that UPR bears a vital role for the production of milk in MECs. XBP1, a transcription factor of UPR signaling cascade, is responsible for increased amount of milk protein synthesis in MECs [22, 23]. Those studies implies that XBP 1 has a positive impact on the secretory capacity of MECs. We also discovered that IGF-1 enhances XBP1 expression in bovine MECs to stimulate ER biogenesis and thus increase milk production [24].

On the other hand, the UPR has a negative influence on the milk yield. We found that increased expression of UPR-induced CHOP correlates negatively with milk yield in mammary gland tissues during early lactation [25]. The inverse relationship among both CHOP and milk yield indicates that the number of MECs is decreasing. When a cell suffers from HS, it becomes more prone to apoptosis [26]. Accumulating evidence indicates that ER stress-mediated apoptotic cell death plays a critical role in HS-induced cellular damage [27, 28]. We also found that HS induced ER stress-mediated apoptosis in MEC [29]. Thereby, UPR has a major impact on secretory capacity and cellular apoptosis.

6 Conclusions

Finally, UPR-mediated increase of ER biogenesis and reduction of MEC number are identified as the mechanism for increase and decrease of milk yield, respectively. This review partly fulfils the knowledge necessary for establishment of an average type of lactation persistency. Therefore, an understanding regarding the influence of ER biogenesis in increasing the secretory activity and MEC loss in reducing the milk yield in connection with UPR at the onset of lactation, will be effective for finalizing the average lactation persistency. It will also be helpful for the producer to overcome the economic loss due to heat stress in dairy industry.

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