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Limiting factors for milk production in dairy cows: perspectives from physiology and nutrition

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Abstract

Milk production in dairy cows increases worldwide since many decades. With rising milk yields, however, potential limiting factors are increasingly discussed. Particularly, the availability of glucose and amino acids is crucial to maintain milk production as well as animal health. Limitations arise from feed sources, the rumen and digestive tract, tissue mobilization, intermediary metabolism and transport, and the uptake of circulating nutrients by the lactating mammary gland. The limiting character can change depending on the stage of lactation. Although physiological boundaries are prevalent throughout the gestation–lactation cycle, limitations are aggravated during the early lactation period when high milk production is accompanied by low feed intake and high mobilization of body reserves. The knowledge about physiological constraints may help to improve animal health and make milk production more sustainably. The scope of this review is to address contemporary factors related to production limits in dairy cows from a physiological perspective. Besides acknowledged physiological constraints, selected environmental and management-related factors affecting animal performance and physiology will be discussed. Potential solutions and strategies to overcome or to alleviate these constraints can only be presented briefly. Instead, they are thought to address existing shortcomings and to identify possibilities for optimization. Despite a scientific-based view on physiological limits, we should keep in mind that only healthy animals could use their genetic capacity and produce high amounts of milk.

Lay Summary

With increasing milk yields in dairy cows, potential limiting factors are intensively discussed. The present review addresses physiological and nutritional constraints that are considered limiting for milk production. The limiting character can change depending on the stage of lactation. Especially after parturition, the limited availability of glucose and amino acids does not only restrict lactational performance but also immune function. Further limitations imposed by feed, intestinal absorption, intermediary metabolism, and nutrient uptake by the mammary gland are described. Moreover, the impact of environmental (heat stress, photoperiod length) and management-related factors (e.g., rearing intensity, dry-period length) on milk yield are elucidated. However, the physiological constraints addressed in this review give space for improvements. Of course, boundaries are set by the farming system, climate, etc. that cannot be overcome. Efforts in improving welfare, husbandry, feeding, and management are likely to further enhance milk production, but will simultaneously improve other traits like reproductive performance and animal health. The existing variation in metabolic adaptation to different environmental stimuli provides further potential for appropriately selecting cows fitting best to the respective conditions. However, increasing yearly milk yields must not be dismissed as driving forces worsening animal health. Only healthy animals can perform well and produce high amounts of milk.

Introduction

Worldwide, yearly milk production in dairy cows increases almost linearly since many decades (FAOSTAT, 2021). Currently, there seems to be no plateau or end of lactation performance in sight (Pulina et al., 2020). Brito et al. (2021) summarized figures on current genetic trends and milk yield development of, for example, Canadian or U.S. dairy breeds. Continuous selection toward higher milk yield along with improvements in management, housing, feeding, and veterinary care resulted in high-yielding dairy cows with individuals producing more than 35,000 kg of milk per year (Hoard's Dairyman, 2020). Milk production is a function of the number and activity of secretory epithelial cells (Akers, 2000; Capuco et al., 2003; Boutinaud et al., 2004), where potential limiting factors may

exert direct and indirect effects. The essential role of glucose and amino acids (**AA**) with regard to milk production is well recognized (Clark, 1975; Cant et al., 2002). However, how much milk can a dairy cow produce? Where are the physiological limits? These and similar questions did not arise recently, but already much earlier, when the scientific picture of the relationships between endocrine and metabolic processes and lactation outcome became more comprehensive (Bines and Hart, 1982). Already in the 1980s, researchers discussed if the cows' genetic capacity for milk production was reached and if further increases of milk yield would provoke the antagonism to fitness traits (Kennedy, 1984). Now, almost 40 years later, average milk production per cow more than doubled in many countries, and nowadays, performance level

pushes us to investigate the issue when the overall capacity of the lactating dairy cow would be finally reached. Moreover, many dairy cows are suffering from health disorders that are primarily attributed to the high performance level and associated failures of metabolic and immunological adaptation, although the relationship between the occurrence of the so-called production diseases and high milk yield is not definitely clarified (Gröhn et al., 1995; Fleischer et al., 2001). The awareness and a deeper knowledge about physiological constraints may help to further improve animal health and produce milk more efficient and sustainable.

The scope of this review is to give in short an overview on various factors that are presently considered limiting milk production in dairy cows from a physiological perspective. The question how much milk a cow can actually produce cannot be answered here. Depending on the stage of lactation, the focus is set on factors that are currently considered as physiological and nutritional boundaries for milk production in general with respect to further negative impacts on animal health, reproductive performance, and environment. Besides these physiological constraints, selected exogenous environmental and management-related factors affecting animal performance and physiology are discussed. Figure 1 illustrates factors imposing limitations to milk production in dairy cows. However, this short review cannot entirely cover all physiological aspects in detail. Potential solutions and strategies to overcome or to alleviate physiological constraints can only be presented briefly in passing and are thought to address existing shortcomings and to identify possibilities for optimization. The implementation of targeted measures related to physiological limits, however, shall not primarily pursue the aim of further pushing milk production, though positive effects are very likely along with improvements of animal health, reproductive performance, etc. Despite a scientific-based view on physiological limits, we should keep in mind that only healthy animals feeling comfortable could use their genetic capacity and produce high amounts of milk.

Feed Intake and Feed Sources

The digestive system of dairy cows is dominated by the rumen, where plant fibers (i.e., structural non-starch carbohydrates such as acid detergent fiber [**ADF**] and neutral detergent fiber [**NDF**]) are degraded and used energetically by microbes. Furthermore, dietary crude protein (**CP**) sources and minerals (e.g., cobalt) support microbial growth. Shortly before parturition and particularly during the early lactation period, dry matter intake is not sufficient to cover the energetic and nutrient requirements of the cow. Furthermore, the limited capacity of rumen fill enables resumption of feed uptake only after rumen content was emptied. Depending on dietary composition, ruminal fermentation and passage rate may be limiting factors for initiating dry matter intake (**DMI**). On the other hand, dietary fiber degradation by rumen microbes takes time. Therefore, feed intake should be maximized whenever possible by the use of feed ingredients with a high palatability, but not lowering rumen passage rate and overall digestibility (Grummer et al., 2004).

Microbial fermentation of dietary carbohydrates provides the rumen host with volatile fatty acids (**VFAs**) that are mainly directed toward gluconeogenesis and milk fat synthesis (Aschenbach et al., 2010). High milk yields, particularly during early lactation, require high amounts of energy and nutrients. Relative to the energetic requirements for maintenance, the additional needs for milk production assumed at 50 to 60 kg/d of a 650-kg cow may amount to a four- to fivefold greater level (for calculations, see the recommendations for energy and nutrient supply in dairy cows, e.g., NRC, 2001). Classical types of roughage used as feedstuffs in dairy cow nutrition include grazed (e.g., pasture and rangeland) and preserved forms (e.g., silage, hay) besides crop residues and byproducts (e.g., straw, hulls from soy and sunflowers). Roughages are characterized by a relatively high fiber and rather low energy and nutrient content. Consequently, exclusive feeding of cows with even high-quality herbage and on well-managed pastures can energetically support only milk production levels up to around 30 kg/d (Bargo et al., 2003; Kolver, 2003), while greater yields are accompanied by considerable mobilization of body fat stores (see chapter below), or can be only achieved by supplementary concentrates (Zbinden et al., 2017). However, maintenance of rumen activity requires a minimum dietary fiber content in the diet, that is, physically effective ADF and NDF (Varga et al., 1998; Zebeli et al., 2012, and recommendations of NRC, 2001, and other feed evaluation systems, e.g., NorFor, 2011 or INRA, 2018). In contrast, too high amounts of starch-based concentrates
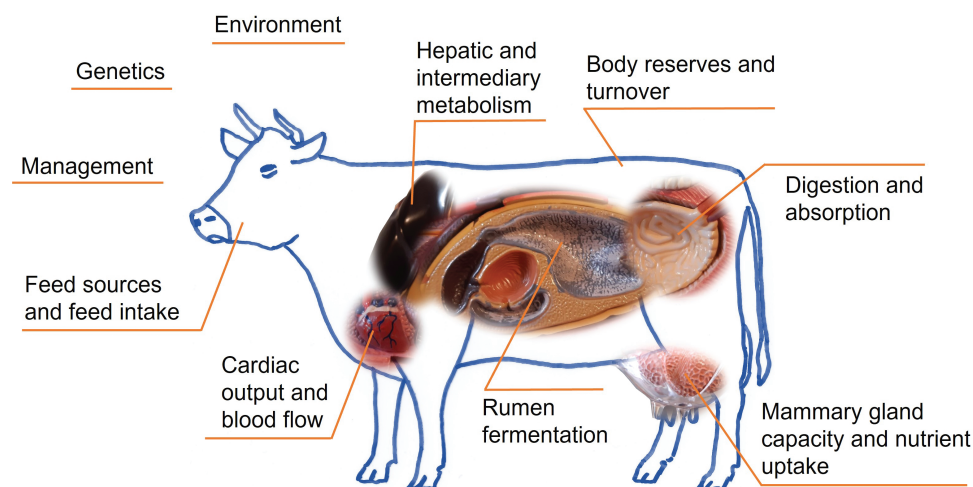

Figure 1. Factors related to limitations of milk production in dairy cows.

relative to the forage content (concentrate amount in the diet > 60%) offered in only few portions may result in (subclinical) rumen acidosis (**SARA**) as consequence of retarded rumination activity and lacking buffering substances from saliva (Humer et al., 2018; Neubauer et al., 2020). Rumen acidosis in turns reduces DMI and rumen passage rate. Especially in early lactating cows, a considerable risk for developing SARA emanates from the necessity of feeding high amounts of concentrates in relation to the low roughage intake to support the energy requirements of milk production. Supplementary concentrates (mainly cereals or byproducts from soybeans, rapeseed, cotton, etc.) contain high amounts of starch, protein, and fat, and are indispensable sources of additional energy and nutrients. Only the combination of different types of concentrates allows the formulation of balanced diets where nutrients can be utilized most efficiently and that can energetically support higher milk production levels compared to classical sole roughage diets. When feeding high amounts of cereal-based concentrates containing significant amounts of carbohydrates in non-rumen-protected form, the additional use of buffer substances may help (NRC, 2001) to reduce the risk of developing SARA. In general, high grain diets should include feed components that naturally show a low rumen degradability of starch (e.g., maize kernels vs. wheat). Similarly, protein-rich feedstuffs with a high degree of rumen-protection (e.g., beer draff, corn gluten) should be given preference over dietary CP sources that are rapidly degraded to ammonia in the rumen (e.g., grass). Overall and independent from feed ingredients, significant energy losses and a low efficiency are characteristic for rumen degradation processes of dietary components with the need of a subsequent resynthesis of, for example, glucose and proteins. However, diet formulation must ensure that sufficient energy and nitrogen are (synchronously) available for the rumen microbes not restricting their development and growth. Estimates on figures characterizing microbial protein synthesis in relation to energy supply can be found in NRC (2001). Otherwise, excessive CP is excreted via urine and feces, with concomitantly higher metabolic stress imposed by elevated plasma urea concentrations negatively affecting, for example, the immune system (Spek et al., 2013; Raboisson et al., 2014a). To sum up, microbial fermentation products from the rumen are alone not sufficient to cover the needs of high-yielding dairy cows, especially during early lactation. Therefore, nutrients by-passing the rumen play a significant role in current dairy cow feeding. For many years, the supply with microbial and undegraded feed protein was assumed to be sufficient in terms of quantity and AA pattern (Bines and Hart, 1982). Meanwhile, methionine, lysine, and histidine may be first limiting for milk production (Huhtanen et al. 2002) and are supplemented in rumen-protected form (Schwab and Broderick, 2017). Similarly, the limited capacity of microbial synthesis of B-vitamins and the need of an additional supplementation in high-yielding dairy cows are increasingly discussed (Seck et al., 2017).

Digestive Tract and Nutrient Absorption

Earlier reports attested the rumen by-pass nutrients only a minor role in the supply of animal requirements (e.g., Bines and Hart, 1982). Of course, milk yields were much lower at that time compared with the current production levels. As stated in the previous chapter, due to restrictions of rumen digestive capacity and the need of higher dietary nutrient

and energy density as consequence of increased performance, high-quality and intact by-pass nutrients such as proteins, starch, and fat that are absorbed at the duodenum are becoming increasingly important to support the rising lactational needs during the first weeks of lactation. However, postruminal digestive and absorptive capacity can be assumed limited throughout the lactation period. For instance, excessive dietary starch might not be fully digested and absorbed at the duodenum, and therefore passes to the large intestine where it is subject to microbial fermentation (Owens et al., 1986). Although VFA production in the hindgut is similar to the rumen, the absorption rate of nutrients and amount of VFA produced in the hindgut are rather low, and the overall energetic efficiency of starch-based carbohydrate utilization after microbial breakdown is low (Harmon et al., 2004). However, detailed figures on the duodenal absorptive capacity of glucose, AA, and FAs are scarce. Figures on starch arrival at the duodenum and limiting factors for intestinal starch digestion in ruminants were reported by Owens et al. (1986) and Harmon et al. (2004). We can assume that current dairy cow diets containing a high proportion of concentrates (>60% in the total ration) fed along with maize silage provide even greater amounts of rumen-protected starch appearing at the duodenum as compared to older reports. Huntington et al. (2006) investigated the starch digestion in growing cattle, and estimated that up to 1.5-kg starch reached the duodenum based on earlier data published by Harmon et al. (2004). Further research is warranted to evaluate the current capacity of duodenal starch digestion and glucose absorption. Another way to alleviate energy shortages is the dietary supply with fat sources. Again, their application is commonly restricted to approximately 5 to 6% of the total diet to avoid a depression of fiber degradation and rumen passage (Rabiee et al., 2012; Weld and Armentano, 2017). Therefore, higher amounts of dietary fat should be provided in rumen-protected form. More details on the regulation and capacity of FA absorption were recently published by Bionaz et al. (2020). Besides a minimal and local use of some nutrients (e.g., glucose or short-chain fatty acid in enterocytes), the majority of absorbed nutrients is drained from the intestinal tissues by the portal vein and lymph system, transported to the liver, and distributed across the body. Physiological limitations in terms of transport capacities are currently not known for dairy cows.

Body Reserves, Body Tissue Turnover, and Intermediary Metabolism

Besides dietary contributions to the overall energy and nutrient pool, body tissues (e.g., adipose tissue [**AT**], skeletal muscles, bones) represent a dynamic reservoir of various nutrients (e.g., minerals like calcium and phosphorus from bones, AA from skeletal muscle degradation). The amount of stored nutrients seems not be a limiting factor per se. However, their turnover temporarily imposes physiological boundaries to the organism (Bauman and Currie, 1980; Drackley, 1999). For instance, several kilograms of calcium are stored in the skeleton. However, the abrupt increase of calcium requirements for milk production at onset of lactation exceeds the circulating calcium pool in plasma consisting of only a few grams (Goff, 2014). Consequently, the delayed endocrine adaptation (including calcitonin, parathyroid hormone, vitamin D, serotonin, etc.) to sufficiently provide calcium may result in hypocalcemia that is associated with reduced peak milk yield,

DMI, and an elevated risk for the development of further production diseases such as displaced abomasum, ketosis, and mastitis (Reinhardt et al., 2011; Venjakob et al., 2017). Approximately 2 to 3 d postpartum, a coordinated regulation of calcium homeostasis with mobilization, absorption, and excretion is widely achieved (Hernández-Castellano et al., 2017a,b; Kessler et al., 2018).

According to literature reports, the amount of mobilizable body fat (mainly stored in visceral and subcutaneous AT) accounts up to 120 kg (Chilliard, 1992; Raschka et al., 2016). For compensation of the negative energy balance (**NEB**) after parturition, AT lipids and skeletal muscle proteins are mobilized (Grummer, 1993; Drackley, 1999; Gross et al., 2011). For a more details on the physiology of AT, readers might refer to other excellent research articles and reviews providing more details (e.g., Mann et al., 2016; McNamara et al., 2016). However, overconditioning of cows during the preceding dry period must not be equated with a larger reservoir of body reserves. Instead, overconditioning adversely affects animal health after parturition as cows with a high body condition score substantially mobilize more fat tissues compared to leaner cows (Locher et al., 2015; Schuh et al., 2019). This aggravates metabolic load as lipolysis occurs at an excessive level likely resulting in the development of steatosis and ketosis (Bobe et al., 2004). Concomitantly and most relevant for physiological limits of milk production during early lactation, cows suffering from ketosis show a depression of DMI and a reduced milk production (Rukkwamsuk et al., 1999; Raboisson et al., 2014b). Furthermore, the characteristically elevated concentrations of nonesterified fatty acid (**NEFA**) and ketone bodies in first weeks of lactation (Gross et al., 2011) impair the animal's immune system (Suriyasathaporn et al., 1999; Sordillo et al., 2009). Therefore, it is not surprising that the highest incidence rates for metabolic and infectious diseases such as ketosis, fatty liver disease, mastitis, and lameness can be observed during this early lactation period (Ingvartsen, 2006; Ingvartsen and Moyes, 2013; Vergara et al., 2014; Brunner et al., 2019).

Low insulin and elevated bST concentrations trigger the lipolysis of triglycerides stored in adipocytes (Bines and Hart, 1982; Campbell and Scanes, 1988). Concomitantly, the high metabolic priority of the lactating mammary gland after parturition and the prevailing low insulin sensitivity of peripheral tissues widely inhibit a re-uptake of glucose and FA into AT (De Koster and Opsomer, 2013; Gross and Bruckmaier, 2019). Among other enzymes involved in lipolysis, hormone-sensitive lipase is activated (Greenberg et al., 2001; Locher et al., 2011; van der Kolk et al., 2017), and glycerol (used for gluconeogenesis) and FA are released. Hence, we assume that there are no rate-limiting steps in lipolysis and skeletal muscle breakdown that would restrict milk production. Instead, we are facing the problem that NEFA are excessively released after parturition (e.g., in overconditioned dairy cows, or cows with a severe NEB; Locher et al., 2015; Schuh et al., 2019). Released FA are primarily transported to the liver, but FA oxidation also occurs to a lower extent in skeletal muscles (Schäff et al., 2013). Increasing NEFA concentrations activate the key regulators of FA oxidation such as transcription factors of the peroxisome proliferator-activated receptor (PPAR) family that trigger further processes related to FA transport, uptake, and finally oxidation (Desvergne et al., 2006; van der Kolk et al., 2017). Here, carnitine is an essential substrate for the transport of long-chain FAs across the inner mitochondrial membrane, where FA are subject of β-oxidation after their activation with coenzyme A (Longo et al., 2016). For more information on the role of PPARs, carnitine, and β-oxidation, please, refer to reviews going more into detail (e.g., Desvergne et al., 2006; Ringseis and Eder, 2011; van der Kolk et al., 2017; Ringseis et al., 2018). However, the capacity of the liver to completely oxidize NEFA during the early lactation period is limited (Armentano et al., 1991). We can identify two major limiting factors: 1) limited availability of carnitine during and capacity of the carnitine shuttle system for importing FA, 2) limited capacity for β-oxidation and subsequent degradation of formed acetyl-CoA in the tricarboxylic acid (**TCA**) cycle. Carnitine is synthesized from lysine and methionine, i.e., two AAs that are currently considered first limiting for milk production as well. Research showed that the supplementation of l-carnitine could enhance β-oxidation and reduce hepatic triglyceride accumulation in the liver (Carlson et al., 2007; Ringseis et al., 2018). Limiting substrate for the TCA cycle capacity is oxaloacetate that is simultaneously required for gluconeogenesis (White, 2015). Glucogenic precursors such as propionate, and AAs such as alanine, cysteine, glycine, serine, and threonine can enter the TCA cycle and do further support gluconeogenesis (Aschenbach et al., 2010).

In recent years, there is increasing evidence that FA from lipolysis may impair insulin sensitivity in dairy cows (McFadden and Rico, 2019). Particularly, the role of ceramide in the regulation of energy expenditure and nutrient partitioning (via modulating insulin signaling and interaction with fibroblast growth factor 21 and adiponectin; McFadden and Rico, 2019; McFadden, 2020) requires further research. Davis et al. (2021) observed a positive correlation between plasma ceramide concentrations and milk yield.

Nevertheless, the excessively released FAs temporally exceed the hepatic capacity for oxidation during early lactation. Alternatively, abundant NEFA are re-esterified to triglycerides and remain in the liver. However, extreme lipid accumulation in the liver results in steatosis that is associated with low feed intake, milk yield, and reproductive performance (Bobe et al., 2004; Gross et al., 2013). Fatty liver develops particularly during early lactation when the hepatic export of triglycerides via very low-density lipoprotein (**VLDL**), whose transport capacity is low in dairy cows anyway, is additionally reduced (Gross et al., 2013; Kessler et al., 2014). Furthermore, plasma concentrations of cholesterol and lipoproteins such as low-density lipoprotein, high-density lipoprotein, and VLDL are low during early lactation, and despite the upregulation of rate-limiting and further enzymes involved in cholesterol homeostasis (Schlegel et al., 2012; Kessler et al., 2014; Gross et al., 2015a), the crucial role of cholesterol and apolipoproteins in hepatic triglyceride export could be speculated to be another limiting factor for milk production in dairy cow physiology.

A second alternative pathway eliminating abundant FA from circulation is the formation of ketone bodies such as acetone and beta-hydroxybutyrate (BHB). Hyperketonemia may result in subclinical and clinical ketosis with an associated depression of milk production, reduced reproductive success, and DMI (McArt et al., 2012). A reduction of DMI further aggravates the energy deficiency and enhances lipolysis of AT with the consequence of even more NEFA arriving at the liver and overwhelming the local oxidation capacities. Just as serious are the inhibiting effects of NEFA and BHB on immune cells (Suriyasathaporn et al., 1999).

Recently, elevated concentrations of ketone bodies in plasma were shown to reduce glucose concentrations independently from the stage of lactation (Zarrin et al., 2013, 2017). Thus, the low glucose concentrations in early lactation are likely to further decline and impose a physiological boundary for milk production that is depending on this essential substrate.

Glycogenolysis and gluconeogenesis are directly related to circulating glucose levels. Whereas glycogen stores in liver and skeletal muscle are very limited, gluconeogenesis in dairy cows is of major importance besides duodenal absorption of glucose derived from the intestinal starch digestion (Aschenbach et al., 2010). Figures on glucose production and needs of high-yielding dairy cows can be found in the review paper of Aschenbach et al. (2010). Whereas lactate and glycerol appear significant substrates for gluconeogenesis during the NEB in early lactation, particularly propionate from the rumen fermentation and AAs (both from intestinal absorption and muscle breakdown) are of importance. Despite an upregulation of gluconeogenesis between late pregnancy and early lactation, glucose concentrations are at a low level during the very first weeks of lactation, where milk production is concomitantly increasing (Hötger et al., 2013). Given its essential role for lactose production and milk fat synthesis, glucose is undoubtedly a limiting factor for daily milk production. More than 85% of the glucose produced are directed to the mammary gland to support lactation (Bickerstaffe et al., 1974; Chaiyabutr et al., 1980). However, providing more glucose does not necessary increase daily milk yield (Al-Trad et al., 2009). Instead, other organs, tissues, and functional compartments that are concomitantly competing for glucose (e.g., the immune system, reproductive tissues) are benefitting from an improved glucose metabolism (Trevisi et al., 2012; Thompson-Crispi et al., 2014; Bradford et al., 2015). At the same time, lipolysis of AT is reduced and ketone body concentrations are lower when glucose concentrations are elevated (Grossen-Rösti et al., 2018; Malacco et al., 2020). Dietary supply with glucogenic precursors during the NEB as well as glucose sparing agents such as conjugated linoleic acids that depress milk fat synthesis and thus glucose output could ameliorate glucose shortages after parturition (Bauman et al., 2008; Larsen and Kristensen, 2013; Ma et al., 2015).

Skeletal muscle serves as an important source of AA for milk synthesis, particularly during its mobilization in early lactation. The balance between mobilization and regeneration of muscle tissue is controlled among other factors via the mammalian target of rapamycin and the ubiquitin–proteasome system (Sadri et al., 2016; Yang et al., 2020). Their interaction with the endocrine regulation of tissue turnover (e.g., by insulin) must be considered in the dynamic regulation of nutrient partitioning between the mammary gland and other peripheral tissues.

Blood Flow and Nutrient Uptake by the Mammary Gland

Absorbed and de novo synthesized nutrients are transported and distributed via the blood stream to the target tissues including the mammary gland. Besides concentrations of substrates in blood, the mammary blood flow determines the supply of the mammary gland (Davis and Collier, 1985). It is noteworthy that cardiac output and blood flow are not constant throughout the lactation–gestation cycle. Substantial increases in both mammary blood flow and cardiac output

were observed about the time of parturition (Linzell, 1974; Götze et al., 2010) affecting the exchange of nutrients across the capillaries into the mammary gland for the subsequent synthesis of milk components (Prosser et al., 1996). In addition, vascularization of the mammary gland increases during pregnancy (Yasugi et al., 1989; Matsumoto et al., 1992; Djonov et al., 2001). Although the endocrine mechanisms involved in vascularization and blood flow are out of the scope of the present review, the use of bovine somatotropin is of practical relevance as it increases both cardiac output and mammary blood flow accompanied by an increase of milk production (Peel and Bauman, 1987). However, an elevated mammary blood flow does not causally increase daily milk yield (Lacasse and Prosser, 2003; Brown and Allen, 2013). Many other limiting factors as partly outlined here must be taken into account. As pointed out by Davis and Collier (1985) and Komatsu et al. (2005), the rate of nutrient transport into the mammary epithelial cells rather than delivery to the cells may be another rate-limiting step for milk production. Experimental data showed that elevated glucose concentrations in plasma did not linearly increase glucose entry rate into the mammary gland (Cant et al., 2002; Xiao and Cant, 2005). There are a number of specific transport systems enabling the uptake of AAs, glucose, or FAs into the mammary gland (Miller et al., 1991). For further details, readers are advised to refer to recent experimental and review papers (e.g., Zhao and Keating, 2007a, b; Gutgesell et al., 2009; Cant et al., 2018). Besides substrate availability, also kinetics and endocrine regulation of transporters depending on the physiological stage of the cow must be assumed to be limiting for milk synthesis. For instance, glucose transporters express a differential sensitivity toward endocrine mediators such as insulin manifesting in, for example, insulin-dependent and insulin-independent representatives (Zhao and Keating, 2007a, b). Furthermore, their expression within a certain tissue such as the mammary gland or AT changes with the lactational stage of the cow (Mattmiller et al., 2011; Jaakson et al., 2018; Karis et al., 2020). Consequently, overall tissue responsiveness and glucose utilization can be regulated and adjusted to the current needs and substrate availability (Gross et al., 2015b; Karis et al., 2020).

Environmental Factors Limiting Milk Production

Independent from a balanced diet formulation, animal health, and genetic capacity, there are a number of environmental factors restricting milk production. In this article, two examples, the impact of heat stress and photoperiod shall be addressed only shortly as many excellent reviews on these topics are available (e.g., Kadzere et al., 2002; Dahl, 2008, Dahl et al., 2012; Roth, 2020). Climate change is an emerging challenge that aggravates heat stress conditions for dairy cows in many regions worldwide (Gauly and Ammer, 2020). Therefore, heat stress must be considered a major threat imposing limits to milk production as it decreases not only daily milk yield, but also DMI, animal health, and reproductive key figures (Roth, 2020). It should be noted that independent from the ambient temperature higher daily milk yields go along with more endogenous heat production originating from the digestive tract and metabolism. Certainly, the reduction of DMI and rumen fermentation due to heat stress can be considered the major drivers for reducing milk production as less nutrients can be

supplied for milk synthesis. Concomitantly with the decrease in DMI, a transient NEB arises that is accompanied by a mobilization of body reserves as described above. Cattle breeds with a greater heat tolerance (e.g., cross-bred cows) could be an alternative to keep dairying in regions with increasing heat stress days (Gaughan et al., 2010; Freitas et al., 2021). Furthermore, cooling devices or increasing dietary energy content via supplementary fat may be considered supporting means to alleviate thermal stress (Sammad et al., 2020; Levit et al., 2021). However, special attention must be paid to the use of dietary components accounting for the maintenance of rumen function, that is, avoidance of SARA, use of rumen-protected nutrients, etc.

During recent years, the impact of photoperiod length on milk production was extensively studied (Dahl et al., 2000, 2012; Lacasse and Petitclerc, 2021). Whereas long-day photoperiods had a persistent effect on daily milk production during established lactation, short-day photoperiods during the dry-period resulted in a greater milk production in the subsequent lactation (Dahl et al., 2000; Dahl, 2008). The underlying endocrine mechanisms have been elucidated during the last years (e.g., Dahl et al., 2012; Lacasse et al., 2014; Ponchon et al., 2017). Besides positive effects of daylight exposure on milk yield, calcium homeostasis around parturition is positively affected (Özçelik et al., 2017).

Genetic Capacity and Variation of Metabolic Adaptation

Given the enormous differences in dairy cow feeding, housing, and management conditions, it is hardly possible to determine the maximum genetic capacity for yearly milk production of dairy cows. Cows of breeds intensively selected toward milk production such as Holsteins are likely to produce more milk than dual-purpose or beef cows, although long-term selection of strains within a breed kept under different environmental conditions may result in a divergent lactational performance (e.g., North American vs. New Zealand Holstein strains; Lucy et al., 2009; Grala et al., 2011).

Moreover, a considerable variation of metabolic adaptation to identical feeding and management conditions exists among animals within a herd although selection targets were identical (Kessel et al., 2008; Gross and Bruckmaier, 2015). Therefore, it is not surprising that metabolic stress is not necessarily related to the overall lifetime performance (Gross et al., 2016). Obviously, there is no negative relationship between increased yearly milk production, disease occurrence, and culling, although culling risk increases in high-yielding dairy cows with a greater likelihood to develop health disorders (Beaudeau et al., 2000; Rilanto et al., 2020). Higher milk yields are undoubtedly more demanding in terms of dairy cow nutrition and management. Furthermore, a greater milk production is associated with a greater metabolic load particularly in early lactation, which increases the risk and susceptibility toward different production diseases (Ingvartsen et al., 2003; McArt and Neves, 2020; Macmillan et al., 2021).

Management Aspects and Epigenetic Regulation of Mammary Gland Capacity

In addition to all listed factors above, management of dairy cows exerts significant constraints on milk production. Epigenetic regulation of milk production in dairy cows was comprehensively described by Singh et al. (2010). Early metabolic and fetal programming, respectively, may affect the production outcome of the offspring. Recently, studies showed that e.g., heat stress in pregnant dairy cows impairs lifetime milk production of daughters and granddaughters (Dado-Senn et al., 2020; Laporta et al., 2020). Also at an early stage of life in calves, feeding level with milk until weaning determines their future milk production (Soberon and van Amburgh, 2013; Korst et al., 2017). In comparison with calves receiving a restricted amount of milk, calves fed milk or milk replacer ad libitum produced more milk during their first lactation (Soberon et al., 2012; Korst et al., 2017). Furthermore, the rearing intensity of heifers during the prepubertal period impacts the future lifetime performance (Sejrsen and Purup, 1997). Being more specific, overfeeding during this phase promotes the development of greater fat pad instead of parenchymal tissue due to lower circulating bST concentrations (Sejrsen et al., 1982; Purup et al., 2000; Akers, 2017a). For further details on mammary gland development and function, the reader may consult the reviews of Akers (2017a, b).

Increasing milking frequency (e.g., three or more times vs. two times daily) was shown to increase daily milk production (Wall and McFadden, 2012; Ferneborg et al., 2017), whereas once-daily milking reduced daily milk yield in dairy cows (Stelwagen et al., 2013). Similarly, cows in automatic milking systems are milked on average more than two times daily and have a higher milk yield than cows milked only two times a day (Tse et al., 2018).

The impact of dry period length on dairy cow heath and milk yield in the subsequent lactation was shown in a number of research and review papers (van Knegsel et al., 2013; Chen et al., 2016; Kok et al., 2017). This aspect gained more attention in dairy cow management as with the overall increasing milk yields during the last decades cows needed to be dried-off while still producing considerable amounts of milk. Not only economic interests are decisive for adjusting dry period length. Furthermore, the start into lactation is a challenging period for dairy cows, particularly for overconditioned dairy cows. Hence, a shortening or omission of the dry period goes along with a reduced milk production but concomitantly lowers the metabolic load after parturition in the subsequent lactation (Chen et al., 2016).

Conclusions and Outlook

Currently, selection targets in dairy cows consider primarily traits related to longevity and fitness and are less oriented toward higher performance. However, milk production will further continue to increase as the physiological constraints addressed in this review give space for improvements. Of course, boundaries are set by the farming system, climate, etc. that cannot be overcome. Overall, dietary nutrient and energy availability seems the major limiting factor for milk production. Hence, glucose and AAs are the most limiting nutrients determining the amounts of milk volume and milk components, but also essential for the immune system. Efforts in improving welfare, husbandry, feeding, and management are likely to further enhance milk production, but will simultaneously improve other traits like reproductive performance and animal health. The existing variation in metabolic adaptation to different environmental stimuli provides further potential for appropriately selecting cows fitting best to the

respective conditions. However, increasing milk yields must not be dismissed as driving forces worsening animal health. Only healthy animals can perform well and produce high amounts of milk.

Conflict of interest statement

The author declares no conflicts of interest.

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