

Lactational challenges in transition dairy cows

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Abstract. Lactation evolved to be the core functional system of providing maternal care in mammalian species. The mammary gland provides an ideally composed nutrient source for the newborn. In addition, colostrum provides passive immunisation after birth, and each suckling process supports the establishment and maintenance of a close mother–offspring bonding. The importance of lactation for the survival of the offspring is represented by a high metabolic priority of the mammary gland within the organism of the lactating animal. Therefore, animal breeding for high milk production has been quite successful, and modern breeding methods have allowed an enormous increase in the performance within only few generations of cows. Mainly in early lactation, most of the available nutrients are directed to the mammary gland, both those from feed, and those mobilised from body tissue. Therefore, milk production can be maintained at a high level despite a negative energy balance. However, the high metabolic load and mobilisation of body tissue requires adequate endocrine and metabolic regulation, which can be successful or less successful in individual animals, i.e. the dairy cow population consists of both metabolically robust and metabolically vulnerable dairy cows. While robust animals adapt adequately, vulnerable cows show often high plasma concentrations of non-esterified fatty acids and β -hydroxybutyrate, and are prone to various production-related diseases. In pasture- or forage-based feeding systems, an additional challenge is a limited availability of nutrients for milk production. Forage feeding without complementary concentrate leads to enormous metabolic disorders in high-yielding cows, but is tolerated in dairy cows with a moderate genetic-performance level.

Additional keywords: adaptation, evolution, lactation, metabolism.

Received 30 September 2016, accepted 29 March 2017, published online 3 May 2017

Introduction

The present review describes the importance of lactation, which has developed through evolution, and which has adapted to the needs of milk production in dairy business. Due to the success of animal breeding, various challenges for both the adaptation of the metabolism of the dairy cows and of the farm management have arisen during the past decades. Cows on pasture and total mixed ration (TMR)-managed cows have many similar lactational challenges during the transition period and beyond. Most of the scientific information available is on cows managed under intensively managed (TMR) systems. In the present review, we will also provide specific facts on cows managed under pasture conditions, as far as available.

The importance of lactation in ruminant species and consequences for dairy cow breeding

The role of lactation has, through evolution, manifested as a method of providing intensive maternal care for the newborn to ensure its survival (Ofstedal 2012; Fig. 1). Milk secretion provides a species-specific tailored source of nutrients, energy, bioactive components and minerals. In addition, lactation enables passive immunisation of the newborn through colostrum, and supports a mother–offspring bonding, all of which are important pre-requisites for the survival of the newborn (Tyler *et al.* 1999).

Each suckling event contributes to the establishment and maintenance of a close bonding between the mother and the offspring via the release of oxytocin, prolactin, and other endocrine factors, not only into the blood circulation but also within the central nervous system (Bridges 2015). The effect of the establishment of mother–offspring bonding during each suckling is also an effect seen in dairy cows. If lactation starts with calf suckling before the cows are moved onto machine milking, the release of oxytocin and milk ejection are often disturbed during the first milkings after the changeover to machine milking (Marnet and Negrão 2000). Similarly, if a cow gets used to a certain machine-milking routine, disturbed milk ejection occurs in response to changes in the milking environment or milking routine (Bruckmaier 2005) and, most surprisingly, disturbed milk ejection also occurs in response to calf suckling if the cow has been machine-milked for a period of time beforehand (Tancin *et al.* 1995, 2001). This indicates that there is also an effect such as cow bonding to the milking machine. In precocious species such as bovines, with their rather mature newborn, a rapid start of milk secretion at a high production level is required immediately postpartum. High amounts of nutrients and energy are needed already at the start of lactation to cover the requirements for growth and development, and for the physical activity of the calf that stays continuously with the mother in the wild, and also in suckler

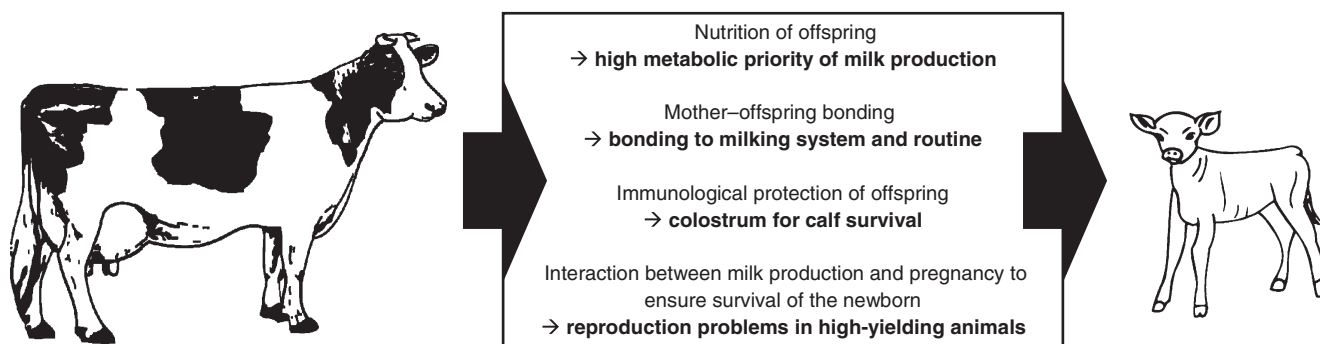


Fig. 1. Major tasks of lactation in maternal care, and resulting challenges for modern dairy cows.

cow husbandry. Therefore, the nutrition of the calf has the highest priority within the cow's metabolism, predominantly at the start of lactation when the calf with its pseudo-monogastric digestive system is fully dependent on milk (Stobo *et al.* 1966; Huber 1969). Even during periods of insufficient nutrient and energy supply to the cow herself, milk production of the mammary gland is maintained at a high level, and the cow is mobilising body tissues if necessary. This metabolic priority of the mammary gland diminishes in later stages of lactation, concomitantly with a decline in milk yield and when the calf increases its own feed intake to establish the organ and functional development of the rumen fermentation system (Stobo *et al.* 1966; Huber 1969; Guilloteau *et al.* 2009). Despite the deficiency of dietary energy, the milk production shortly after parturition is maintained and even further increases the risk of metabolic disorders, whereas feeding-induced deficiency in later lactational stages causes an immediate reduction in milk production (Sejrsen *et al.* 1982; Gross *et al.* 2011a). However, the calf can survive with a low amount of milk or even without milk at this stage. The importance of milk for calf nutrition decreases, and the continued lactation and suckling becomes increasingly important for mother–offspring bonding as an important component for survival of the offspring. However, the metabolic priority of the early lactating mammary gland that has developed during evolution, combined with dairy cow breeding for high milk production, has steadily increased the demands by the mammary gland throughout decades (Oltenucu and Algers 2005), a process that is still ongoing.

On the basis of the evolutionary origin of lactation and its high metabolic priority in early lactation, dairy cow breeding for high milk production in the modern dairy cow has been most successful, with enormous increases in production levels within the past 50 years (Capper *et al.* 2009). Modern breeding methods such as artificial insemination and embryo transfer have increased the efficiency and shortened the generational interval. The success of breeding is most prominent for the milk production in the early stages of lactation when most of the available nutrients are directed towards the mammary gland (Bauman and Currie 1980). This is possible because nutrient uptake by the gland occurs mostly independent of insulin and, thus, independent of the homeostatic regulation in the cow's body (Gross *et al.* 2011b). Because feed intake in early lactation cannot cover the requirements for energy and nutrients during this period, the high-yielding dairy cow mobilises considerable amounts of fat

and protein stores, and hepatic gluconeogenesis providing glucose mainly for the synthesis of lactose in the mammary gland runs at a maximum capacity. Furthermore, the onset of lactation is characterised by an increased demand for minerals such as calcium (Horst *et al.* 1997; Hernández-Castellano *et al.* 2017). The required metabolic adaptation to serve the nutrient demands of various tissues and organs is not always fully successful and considerably increases the risk of metabolic disturbances and production-related diseases during early lactation.

Nutrient partitioning and metabolic challenges in dairy cows

Homeostatic regulation keeps a metabolic equilibrium in the cow's body for maintenance, deposition and mobilisation of energy and nutrient reserves. Due to its pivotal role in the survival of the offspring, milk synthesis has developed a high priority for energy and nutrient supply within the mammalian body during evolution. This directed way of energy and nutrient partitioning has been coined as homeorhesis, meaning the orchestrated or coordinated control of metabolism of body tissues necessary to support a dominant physiological process or state (Bauman and Currie 1980). Any nutrient deficiency is aimed to be fully compensated for by the mobilisation of body reserves, at least for a limited period of time. Homeorhesis does not guarantee overall metabolic equilibrium if the energy and nutrient resources are limited. Therefore, if there is a gap between uptake and requirement for maintenance, performance and reproduction, homeorhetic regulation can lead to metabolic disorders, even to the point of severe metabolic diseases (Sordillo and Raphael 2013; Raboisson *et al.* 2014).

The metabolic priority of either the conceptus or the mammary gland changes throughout all functional stages of these tissues. Interactions also occur between lactation and the ovarian cyclical activity postpartum. The survival of the newborn has priority over a potential new pregnancy, which is mediated by several endocrine systems. Hormones such as insulin, insulin-like growth factor-1 (IGF-1), leptin, adiponectin and thyroid hormones are all dramatically changed during the early part of lactation, mainly in high producing animals, to mediate the required metabolic adaptations (Hammon *et al.* 2009; Gross *et al.* 2011b; Singh *et al.* 2014). However, these hormones are also involved in the follicular development and,

thus, re-establishment of a cyclic activity postpartum, and their characteristic changes during metabolic adaptation also have a negative influence on the ovarian activity (Kawashima *et al.* 2012). Even the energy supply during the dry period can play a crucial role for the early development of the ovarian cycle postpartum because the follicular development does already start towards the end of pregnancy (Castro *et al.* 2012). In addition, an increased clearance of ovarian steroids through the liver occurs during lactation, caused by increased hepatic blood flow (Sangsrivong *et al.* 2002). The resulting low plasma concentrations of progesterone and estrogens can be the cause of lacking oestrus symptoms and early embryonal death.

If cows at a very high production level are pregnant, the enormous metabolic load results in impaired growth of the fetus. Thus, high-yielding dairy cows have been demonstrated to express a low embryo quality and reduced placental and fetal development, as compared with non-lactating animals (Leroy *et al.* 2005; Kamal *et al.* 2014; Van Eetvelde *et al.* 2016). The metabolic dominance of the conceptus increases towards the last weeks of pregnancy (Wallace *et al.* 1996, 1997, 2005; Symonds *et al.* 2004) whereas milk secretion becomes increasingly a part of the homeostatic regulation during ongoing lactation (Gross *et al.* 2011a; Mattmiller *et al.* 2011). However, the importance of competition for energy and nutrients between the conceptus and the mammary gland, even at the end of pregnancy, is small because energy and nutrient requirements for maintenance and pregnancy increase only by 20–25% (Moe and Tyrrell 1972). This does not interfere with the needs for milk secretion because cows do not yield very much milk during this period or are dried off. In addition, animal breeding for high milk production does not considerably change the needs of the developing fetus.

Colostrum formation and passive immunisation of the newborn calf

During the periparturient phase, the first secreted milk plays a crucial role in ungulates, namely through passive immunisation of the newborn via immunoglobulins (IgG) from colostrum to bridge the early weeks of life until the offspring are able to produce their own antibodies (Erhard *et al.* 1999). Furthermore, colostrum provides numerous bioactive components and growth factors such as insulin, IGF-1, IGF-binding proteins and lactoferrin (Blum and Baumrucker 2002; Sacerdote *et al.* 2013; Park and Nam 2015). The formation of colostrum follows a defined sequence of events, which is regulated by endocrine systems during the period shortly before parturition. The transfer of IgG starts at an early stage of lactogenesis, and it ceases at parturition, when synthesis and secretion of lactose, protein and milk fat commence. The volume of colostrum is assumed to be higher in dairy than in beef cows (Guy *et al.* 1994b). The variation in colostrum yield and IgG content is enormous, but reports on potential dilution effects are inconsistent. In contrast to the findings of Guy *et al.* (1994a), recent studies have observed no potential dilution effects with respect to time of first milking, nor a relationship of colostrum yield to the overall production level of the cow (Baumrucker *et al.* 2010; Gross *et al.* 2014; Kessler *et al.* 2014; Samarütel *et al.* 2016). However, a newborn calf cannot take up voluntarily more than 2 kg of colostrum, and the

additional amount of colostrum including its IgG, which is often present in dairy cows, is abundant and remains unused. Timing of parturition as well as lactogenesis and colostrogenesis are regulated via endocrine signals. Changes of plasma progesterone (P4) and prolactin concentrations are reported to be key events that mediate the initiation of both parturition and onset of lactation while colostrum formation is inhibited. It is generally accepted that P4 represses periparturient lactogenesis during pregnancy and that the decrease in plasma P4 at parturition permits the activation of mammary epithelial cells to respond to lactogenic hormones (Schams and Karg 1969; Hoffmann *et al.* 1973; Convey 1974; Guy *et al.* 1994b).

Although P4 has been shown to suppress periparturient lactogenesis (Smith *et al.* 1973; Vermouth and Deis 1975; López-Fontana *et al.* 2012), Gross *et al.* (2014) actually obtained a substantial amount of colostrum before the concentration of P4 dropped in cows experimentally milked before parturition, indicating that colostrum IgG influx is already occurring during high P4 plasma concentration and continues until parturition. Thereafter, the active transport of IgG into the mammary gland is abruptly stopped and components highly concentrated in colostrum are steadily diminishing while milk yield increases (Wall *et al.* 2015). Selection for higher milk yields during past decades makes it difficult to dry-off modern dairy cows by abrupt cessation of milking, when they are still producing 40–50 kg/day (Leitner *et al.* 2007). Therefore, it is likely that the mammary gland in cows undergoing a regular dry period today is able to secrete considerably more colostrum before the drop of P4 when compared with cows almost 40 years ago. Like most aspects of mammary function, it is likely that the mechanisms of colostrogenesis are additionally affected by local autocrine or paracrine factors within the mammary gland, e.g. variation in IgG content and colostrum composition between individual quarters (Baumrucker *et al.* 2014). These mechanisms may act in concert with or independently of endocrine signals during colostrogenesis and lactogenesis, contributing to the high variation in colostrum yield and quality, as observed recently (Gross *et al.* 2014).

Feed intake and endocrine and metabolic adaptations during the periparturient period

Feed intake is low around parturition and increases much slower than milk production. Therefore, the periparturient period, i.e. the time of metabolic changes from pregnancy to lactation and the first weeks of lactation requires an enormous capacity of the cow metabolism to adapt. Although the metabolic load is known to be highest along with the negative energy balance (NEB) after parturition, the homeorhetic adaptation with respect to lactation already starts before calving. In most cases, even the declining feed intake ante partum is sufficient to cover nutrient requirements in late-gestation cows and to maintain a positive energy balance. Despite no obvious additional need for energy shortly before parturition, insulin and IGF-1 concentrations already start to decline, and the release of growth hormone (GH) and mobilisation of adipose tissue commence (Rhoads *et al.* 2004). The drop in the concentration of circulating thyroid hormones, leptin, adiponectin, insulin and IGF-1 enables the

initiation of lipolysis, while concomitantly inhibiting lipogenesis (Bell 1995; Block *et al.* 2001; Kuhla *et al.* 2016). In the adipose tissue of cows, the rise in phosphorylation of hormone-sensitive lipase is assumed to be responsible for hydrolysis of stored triglycerides under the stimulation of catecholamines (Sumner and McNamara 2007; Elkins and Spurlock 2009; Locher *et al.* 2011). Serotonin (5-HT) also plays an important role in lactogenesis as an autocrine regulator of the mammary gland (Hernandez *et al.* 2011, 2012). Concomitantly to the metabolic adaptations taking place shortly before parturition, circulating 5-HT, likely originating from mammary tissue, increases steadily until calving (Laporta *et al.* 2014), and affects, besides calcium homeostasis, glucose metabolism of dairy cows (Laporta *et al.* 2013; Weaver *et al.* 2016).

Specific metabolic adaptations during early lactation

The period of transition from late gestation to early lactation involves considerable metabolic adaptation in dairy cows. After parturition, the amount of energy and protein required for the maintenance of body functions and milk production cannot be met, because feed intake is insufficient. This period is characterised by mobilisation of body fat, protein and mineral stores, so as to cover the requirements for milk production and maintenance, and also growth in the case of first-lactation heifers. The necessary adaptation is reflected by changes in several blood parameters (Fig. 2). For example, the concentration of glucose decreases, whereas the concentrations of β -hydroxybutyrate (BHBA) and non-esterified fatty acids (NEFA) increase, concomitantly with related changes in the endocrine system. The physiological changes collectively represent

the metabolic load, which is defined as the burden imposed by the synthesis and secretion of milk (Knight *et al.* 1999). With increasing production levels, the sudden high nutrient demand for milk production after parturition and the associated metabolic load increasingly exceed the adaptive capacity of many cows, and this leads to an increased incidence of health problems (Fleischer *et al.* 2001). Calcium imbalances may manifest immediately after calving as milk fever (Horst *et al.* 1997; Hernández-Castellano *et al.* 2017). Health problems that may develop include metabolic and related diseases such as ketosis, retained placenta, mastitis, displaced abomasum, laminitis or reproduction problems (Goff and Horst 1997). An affected cow may enter a vicious circle and may become a typical 'problem cow', as postpartum disorders have been observed to be interrelated and one metabolic disorder may predispose the cow to other disorders. Correa *et al.* (1993) observed that ketosis is a risk factor for displaced abomasum and metritis. Erb and Grohn (1988) observed that milk fever plays a central role in predisposing the cow to disorders such as ketosis, retained placenta, displaced abomasum and metritis. Ingvarsen *et al.* (2003) concluded that periparturient changes in hormones and metabolites may potentially compromise the immune competence and lead to an increased susceptibility of bacterial infections during this period, including endometritis and mastitis. Goff and Horst (1997) described in their review that most of the metabolic diseases in dairy cows occur within the first 2 weeks of lactation, when the metabolic load is observed to be the highest (Gross *et al.* 2011a), and the aetiology of many health problems can be traced back to the metabolic load dealt with during the first 2 weeks of lactation.

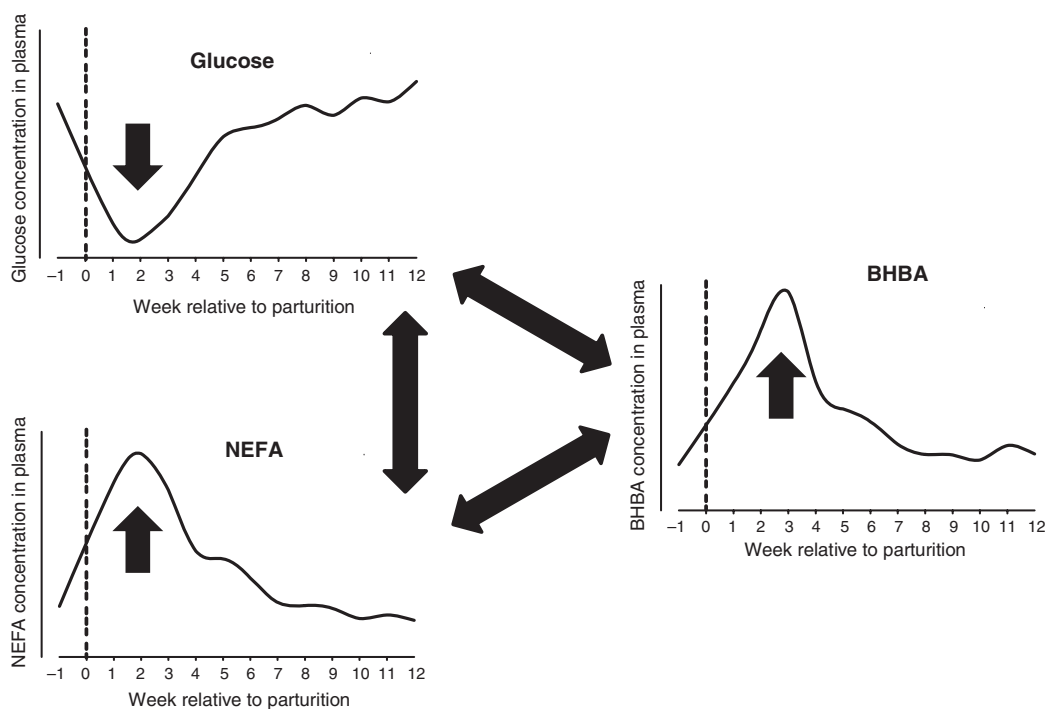


Fig. 2. Characteristic metabolic adaptations and their interactions in transition dairy cows. Data are adjusted from Gross *et al.* (2011a). BHBA, β -hydroxybutyrate; NEFA, non-esterified fatty acids.

Metabolic disorders are forced by the NEB through an inadequate feed intake around parturition, which increases only slowly, in contrast to milk production which starts mostly at a rather high level and increases further despite energy deficiency (Grummer 1993; Ingvarsten and Andersen 2000; Kessel *et al.* 2008).

A key nutrient for milk synthesis is glucose. More than 80% of the glucose turnover is used by the mammary gland for the synthesis of lactose during peak lactation (Bauman and Currie 1980). Therefore, hepatic gluconeogenesis and glycogenolysis increase to a maximum at the start of lactation. Only a small amount of glucose not needed for lactose synthesis is available for oxidation as an energy source for the mammary gland and other tissues (Lemosquet *et al.* 2009). Lipids, therefore, become the main energy source. To cover the increased needs of fatty acids as an energy source and for milk fat synthesis, body lipid stores are mobilised and circulate in blood as NEFA, while lipogenesis is simultaneously reduced. Further adaptations are the mobilisation of amino acids and peptides from protein reserves in skeletal muscle tissues (von Soosten *et al.* 2012) and other body tissues (such as the uterus), for use in protein synthesis and energy metabolism, mobilisation of calcium from bones, and the increased gastrointestinal absorption (Bauman and Currie 1980).

Hormones are essential for the regulation and coordination of the metabolic adaptations. A key mechanism of adaptation is the decrease of plasma insulin concentrations, combined with insulin resistance, and simultaneously rather high plasma concentrations of glucagon. Along with enhanced sensitivity to catecholamines, this is one of the main triggers to activate hormone-sensitive lipases in adipose tissue and, hence, fat mobilisation (Locher *et al.* 2011). Low circulating insulin is involved in the uncoupling of the somatotrophic axis in the liver via downregulation of the hepatic GH receptor (Kobayashi *et al.* 1999; Rhoads *et al.* 2004). Consequently, plasma GH concentrations increase, while plasma IGF-1 concentrations remain low (Gross *et al.* 2011b; Kessler *et al.* 2013). A direct effect of GH is the stimulation of lipolysis from adipose tissue and this effect is supported by enhanced sensitivity to β -adrenergic effects of catecholamines. While plasma insulin concentrations are low, the high concentrations of GH and NEFA induce an additional insulin resistance in the peripheral tissues. NEFA can be used as a priority source of oxidation for energy delivery in the liver and other tissues. In addition, the liver releases the NEFA, after transformation to very low-density lipoproteins, to other tissues via the blood, a surplus of NEFA is esterified in the liver, accumulates there, and may cause fatty liver syndrome (Kessler *et al.* 2014; Gross *et al.* 2015a).

Due to ruminal fermentation, glucose is scarcely absorbed directly from feed, except from some slowly rumen-degradable feeds, such as maize. However, most glucose even then does not reach the peripheral circulation because it is metabolised in the gastrointestinal tract. Thus, glucose is predominantly derived from hepatic gluconeogenesis in ruminants. Hepatic gluconeogenesis depends on the overall tricarboxylic acid (TCA) cycle activity, especially the oxaloacetate availability and, particularly, on the availability of substrates, such as propionate, lactate, amino acids and glycerol. A high level

gluconeogenesis draws on oxaloacetate reserves, therefore reducing the availability of oxaloacetate in hepatocyte mitochondria. Consequently, the oxidation of fatty acids via the TCA cycle is limited, and an alternative metabolic pathway is activated through enhanced synthesis of ketone bodies from acetyl-CoA in the liver.

While most tissues are under control of insulin, glucagon and other hormones, the glucose uptake of the mammary gland during early lactation is independent of insulin and, instead, occurs via active transport mediated by hormone-independent glucose transporters (GLUT1, GLUT3). Thus, the uptake of glucose by the mammary gland from the blood circulation is not inhibited while the other body tissues release metabolic reserves, hence causing a catabolic status of the cow. Later in lactation, the glucose transport into the mammary gland becomes increasingly a part of the homeostatic regulation, as indicated by a higher expression of the insulin-sensitive glucose transporter GLUT4 (Mattmiller *et al.* 2011; Gross *et al.* 2015b).

Ketosis occurring in early lactation dairy cows is caused by excessive BHBA formation due to exceeding the capacity of the liver to oxidise all the mobilised NEFA. Zarrin *et al.* (2013, 2014a, 2014b) investigated the effects of elevated ketone body concentrations via BHBA infusion on metabolism and on the mammary immune response during mastitis. Induced hyperketonemia resulted immediately in decreased glucagon and glucose concentrations (Zarrin *et al.* 2013). In addition, the elevated concentrations of BHBA caused a reduced increase of milk somatic cell count, and changes of cytokine expression in mammary tissue, as well as a reduced increase of glucagon in response to the inflammatory challenge (Zarrin *et al.* 2014a). The metabolic adaptations to infused BHBA were independent of the stage of lactation, as has recently been confirmed in both dry and early lactating dairy cows (Zarrin *et al.* 2017).

Individual differences in success or failure of metabolic adaptation and risk of production-related diseases

The required metabolic adaptations can be successful, but can also lead to metabolic disorders (Hachenberg *et al.* 2007; Kessel *et al.* 2008). Individual cows differ with respect to the capability to adapt to the needs for milk production, even if housing, feeding and performance are identical. Many individuals mobilise beyond the needs, causing increased concentrations of NEFA and BHBA (Kessel *et al.* 2008; van Dorland *et al.* 2009), whereas others do not show considerable changes in plasma metabolites.

Thus, many cows are able to overcome the period of NEB without developing metabolic disorders, whereas other cows under identical housing and feeding conditions and with similar production levels are not (Kessel *et al.* 2008). The complex system of adaptation differs among cows (Jorritsma *et al.* 2003). This has been confirmed by several scientific investigations that have shown that the endocrine and metabolic adaptations to support milk production in early lactation vary among individual cows (Jorritsma *et al.* 2000; Hachenberg *et al.* 2007; Kessel *et al.* 2008; van Dorland *et al.* 2009). It is not possible to avoid the metabolic challenge as

such, because milk production at the start of lactation is too high (3–4 fold of the actual feed intake) to have the requirements of energy and nutrients met by adequate feed intake during this period.

The variation among individual cows in adapting successfully to the metabolic load related to lactation may have a genetic basis. A genetic cause behind the occurrence of production-related diseases is well acknowledged, although not yet fully understood (Ingvarlsen *et al.* 2003; Drackley *et al.* 2005). During lactation, we observed dairy cows that had already had a higher amplitude of metabolic changes in early lactation, repeatedly responding more intensely to an induced energy deficiency in later lactation (Gross and Bruckmaier 2015). Thus, the adaptive performance seems to be not just a short-term interaction between the cow and the environment. Cows with an optimal adaptive performance that do not develop health disorders would be most suitable to select for breeding programs aimed at breeding for metabolic robustness in dairy cows. Robustness in dairy cows may be described as the ability of a cow to function well in the environment, and be resilient to the changes in the climate, production systems or herds (Strandberg 2009). Ten Napel *et al.* (2009) defined robustness as the ability of a cow to maintain homeostasis, and Ellen *et al.* (2009) introduced health as the main concept when exploring robustness in dairy cattle. Maintenance of homeostasis in the dairy cow is principally facilitated by the liver, which is the primary site for coordinating the body metabolism, including glucose homeostasis, detoxification and steroid hormone synthesis and degradation (Swanson 2008).

Several research groups have tried to identify parameters that act as indicators for the robustness or metabolic imbalance of a cow, regarding disorders postpartum (e.g. Reist *et al.* 2003; Hachenberg *et al.* 2007; Graber *et al.* 2012). Several studies have focussed on identification of indicators for an increased risk of metabolic and related disorders (Simianer *et al.* 1991; Uribe *et al.* 1995; Jeong *et al.* 2016; Jamrozik *et al.* 2016; Vukasinovic *et al.* 2017). Cameron *et al.* (1998) identified a NEB prepartum and a high body condition score as important risk factors for displaced abomasum. In another study, high concentrations of NEFA and BHBA, as a response to the periparturient NEB, were associated with an increased risk of abomasal displacement (LeBlanc *et al.* 2005). In addition, high plasma concentrations of NEFA and urea, and concomitantly low blood glucose concentrations between 6 and 17 days postpartum were identified to be major risk factors for hepatic lipidosis (Jorritsma *et al.* 2001). Hammon *et al.* (2009) found a relationship between high liver fat content and impaired hepatic glucose metabolism. Low plasma glucose concentrations during the first week after parturition were indicative of an increased risk of ketosis in the weeks thereafter (Reist *et al.* 2003). However, we recently reported that even extreme changes in metabolites (BHBA, NEFA) in early lactation, investigated in one single lactation in each animal, were not related to reduced longevity (Gross *et al.* 2016). Thus, it is still unclear how important a genetic component is for the metabolic adaptation relative to short-term environmental effects that influence the metabolic phenotype of an individual cow.

Special challenges of pasture- and forage-based feeding systems

In several countries, including Switzerland, a favourable climate allows for pasture-based dairy production and is conducive to low-input agricultural systems. In such systems, the diet of the cow consists largely of ‘home-grown’ forages, often supplemented with small amounts of concentrates.

A high level of forage in the ration allows only a limited production level in dairy cows (Jamieson 1975; Edwards and Parker 1994; Kolver and Muller 1998). Along with the limited physical capacity of the reticulo-rumen, a sole forage and pasture diet may not be energy- and nutrient-dense enough to meet the lactational requirements and may further aggravate the energy and nutrient deficiency, particularly in early lactation, if the genetic production potential dairy cows is very high (Balch and Campling 1962).

If genetically high-yielding dairy cows cannot meet their nutrient and energy requirements, the production level remains below the genetic potential. Despite enormous metabolic adaptation to maintain, to the extent possible, the limited supply for the mammary gland, these animals usually restrain their production and are, thus, more prone to health disorders. This, in turn, may adversely affect welfare of the animals. The increasing milk yield per cow may increase the cow’s metabolic load, which makes her more vulnerable to the development of metabolic and related disorders. Reducing milk yield per cow as a solution to this problem may not be preferred, as this would be accompanied by a decreasing efficiency of the cow demonstrated by higher costs per kilogram milk and a higher environmental burden as a result of the increased methane emission and higher dietary nitrogen losses per kilogram milk. However, several studies have shown that a high milk production does not necessarily lead to metabolic diseases (Gröhn *et al.* 1995; Ingvarlsen *et al.* 2003), i.e. a successful metabolic adaptation is possible, despite the unavoidable NEB in early lactation.

Feeding modern dairy cows according to their nutrient requirements and to maintain normal rumen function is the key factor for sustainable milk production. Although well managed pasture has a high nutritional value, a pasture-dominant diet has limitations with respect to the energy density (Kolver and Muller 1998) and nutrient balance (Bruinenberg *et al.* 2002). Mobilisation of body fat reserves indicates that forage-fed, high-producing cows require supplemental energy to express their genetic potential for milk production (Kolver and Muller 1998). These requirements may be even more pronounced in grazing cows than in cows fed herbage in the barn, as additional energy expenditure for walking activity and thermoregulation needs to be taken into account (Kaufmann *et al.* 2011; Dohme-Meier *et al.* 2014). In addition, the changing quality of the pasture across seasons can affect the metabolism of the dairy cow (Kaufmann *et al.* 2012). In spring and autumn, the concentration of soluble carbohydrates (WSC) in fresh and preserved pasture can increase to the extent that the recommended intake of WSC for dairy cows is significantly exceeded. High intake of WSC can cause rumen acidosis (Münger *et al.* 2014) and is suspected to lead to associated health problems such as laminitis.

Another issue with a predominant pasture-based diet is that, in spring and autumn, pasture can be very high in protein (i.e. 30% crude protein, or higher, is not uncommon). If all this protein cannot be utilised by the rumen microbes, the excess dietary nitrogen will be absorbed from the rumen as ammonia, which will be detoxified in the liver and converted into urea via the energy-consuming (ATP) urea cycle. Some of the urea will be excreted via milk, but, by far, most of it is excreted in the urine and, in grazing cows, this will contribute to the environmental problem of nitrogen leaching (Pacheco *et al.* 2010).

Forage-based dairy farming with a low concentrate input, as is commonly practiced in Switzerland and New Zealand, is highly suitable for organic farming conditions. Thanner *et al.* (2014a) suggested that cows in mid-lactation with a lower genetic potential for milk production seem better able to compensate for the reduced energy and nutrient availability in a grazing system without concentrate supplementation than do cows with a higher genetic potential. However, differences exist no longer when cows of either genetic potential are compared in advanced lactation (Thanner *et al.* 2014b). Kolver and Muller (1998) concluded from their study with high-yielding dairy cows that high nutrient intake from pasture can be achieved, but a marked loss of body condition was observed to maintain milk production, and supplemental energy is needed for milk production greater than 25–30 kg/day. However, it must be emphasised that, in that study (Kolver and Muller 1998), the cows were already beyond peak-lactation and, therefore, beyond the homeorhetic control of metabolism prioritising nutrients for milk synthesis in the mammary gland. Higher-yielding dairy cows, i.e. cows with a lactational performance >7500 kg, receiving only forage in early lactation were most prone to dramatically elevated plasma concentrations of NEFA and BHBA until Week 8 of lactation, as compared with animals of similar performance, but with supplementary concentrate (Zbinden *et al.* 2016). However, lower-yielding animals could perform well without additional energy supplementation in early lactation (Zbinden *et al.* 2016). A transient NEB is inevitable in high-yielding dairy cows directly after parturition. It seems that the risk of metabolic and related disorders increases if the NEB is maintained for a longer period.

Concluding remarks and outlook

Precision livestock farming provides instruments to ensure welfare of the individual animal. A continuous surveillance, including metabolic aspects, is required to ensure well-being of the animal. However, animal-health disorders are usually diagnosed when clinical signs are already apparent, and confirmed by invasive blood sampling. Moyes *et al.* (2013) showed that the need exists to develop automated real-time surveillance systems based on biomarkers for early on-farm detection of animals at risk. Physiological imbalance (PI) has been defined as the deviation of physiological parameters from the normal, including an increased risk of developing production diseases (clinical or subclinical) and reduced production or reproduction (Ingvarsen 2006). If PI can be prevented through feeding and management, its early detection may reduce the risk of certain diseases, particularly in early lactation.

Frequent and routine blood sampling may not be the optimal method to predict risk of clinical disease in lactating dairy cows. Therefore, it is of major interest to identify alternative and additional biomarkers (and their combination) for PI and for early identification of specific subclinical diseases adversely affecting the welfare of dairy cows. Sampling of substrates for diagnosis must be performed non-invasively and at an individual cow level during recurring events (e.g. daily milking). In this respect, automatised recording (non-invasive) of rumination and locomotion behaviour, as well as rumen pH, together with data obtained from potential biomarkers in milk, may provide tools for early detection of a PI. The implementation of technical devices in dairy farms to measure directly and non-invasively changes in milk composition (e.g. somatic cell count to detect mastitis, progesterone for cyclic activity, MIR spectra) becomes more and more common and has the potential to detect the development of metabolic disorders at an early stage.

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