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Understanding diversity of hepatic metabolism and related adaptations in the early lactating dairy cow

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Summary

The onset of lactation in dairy cows represents a major metabolic challenge that involves large adaptations in glucose, fatty acid, and mineral metabolism to support lactation and to avoid metabolic dysfunction. The complex system of adaptation can differ considerably between cows, and may have a genetic base. In the present review, the variation in adaptive reactions in dairy cows is discussed. In these studies, the liver being a key metabolic regulator for understanding the variation in adaptive performance of the dairy cow was the main focus of research. Liver function was evaluated through gene expression measurements; to explain the associated phenotypic variability and to identify descriptors for metabolic robustness in dairy cows. Hence, the identified genes involved act as a connecting link between the genotype encoded on the DNA and the phenotypic expression of the target factors at a protein level. The integration of phenotypic data, including gene expression profiles, and genomic data will facilitate a better characterization of the complex interplay between these levels, and will improve the genetic understanding necessary to unravel a certain trait or multi-trait such as metabolic robustness in dairy cows.

Keywords: dairy cow, early lactation, hepatic metabolism, adaptive reactions, robustness

Zum Verständnis der Besonderheiten des Lebermetabolismus und entsprechende Anpassungen bei der Milchkuh in Frühlaktation

Der Laktationsbeginn stellt für die Milchkuh eine grosse metabolische Herausforderung dar, die bedeutende Anpassungen im Stoffwechsel von Glucose, Fettsäuren, und Mineralstoffen verlangt, um Stoffwechselstörungen zu vermeiden. Die komplexen Anpassungen können erheblich – vermutlich durch genetische Unterschiede – zwischen Individuen variieren. In dieser Übersichtsarbeit werden die metabolischen Anpassungsreaktionen von Milchkühen dargestellt und diskutiert, die Inhalt einer Reihe von Studien der Abteilung Veterinär-Physiologie während der vergangenen sechs Jahre waren. Im Mittelpunkt der Studien stand die Leber, deren Anpassungen als entscheidend erachtet werden für erfolgreiche oder weniger erfolgreiche Stoffwechselanpassungen. Die Leberfunktion wurde während der Studien in wiederholt durchgeführten Biopsien in Form der mRNA Expression vieler Kandidatengene erfasst, die als Schlüssel der jeweiligen Stoffwechselwege klassifiziert wurden. Es wurde versucht, die phänotypische Variation der Tiere durch Genexpressionen zu erklären, und Faktoren für metabolische Robustheit zu identifizieren. Darüber hinaus wurde die mRNA Expression der Kandidatengene als zusätzliche analytische Ebene zwischen Phänotyp und Genotyp zur Erklärung der metabolischen Biodiversität als wertvoll erachtet. Die integrative Betrachtung der drei Ebenen Genotyp, Transkript und Phänotyp bringen neues Licht in deren Zusammenspiel und werden nach Auswertung der genomischen Typisierungen der Versuchstiere neue Erkenntnisse für die Beschreibung multifaktorieller Merkmale wie der metabolischen Robustheit bei der Milchkuh zulassen.

Schlüsselwörter: Milchkuh, Frühlaktation, Lebermetabolismus, Anpassungsreaktionen, Robustheit

Start of lactation remains major adaptive challenge

The dairy cow of today is continuously adapting to the changeable environment in which she produces. Apart from unavoidable variation in feed supply and feed quality, she has to cope with husbandry practices challenging her adaptive response such as an alpine summer grazing (van Dorland et al., 2006) commonly practiced in Switzerland. In addition, changing environmental climatic conditions and consumer's demand for efficiently produced and healthy dairy products need to be realized by the present dairy cows. Nonetheless, the major challenge of the dairy cow may remain a natural occurring physiological event, which is the onset of lactation following parturition. The physiological changes associated to this event take largely place during a time-frame from 3 weeks before to 3 weeks after parturition, defined as the "transition period" (Drackley, 1999). The physiological changes include responses towards homeorhetic control during which energy and nutrient partitioning is prioritized to the mammary gland for synthesis of milk (Bauman & Currie, 1980). In the face of the low availability of energy and nutrients at the start of the lactation due to low feed intake after parturition, homeorhetic control dominates, and triggers mobilization of body fat, protein and mineral stores in order to satisfy the additional requirements for the rapidly increasing milk production. Milk synthesis has highest priority at the start of lactation. Initially, milk (and colostrum) was synthesized to ensure survival of the offspring. As calves slowly develop a functional rumen, dependence on milk diminishes and with it the priority of the mammary gland for nutrients and the underlying homeorhetic control. This may be well demonstrated by Gross et al. (2011) in which it was observed that despite a negative energy balance (NEB), milk production shortly after parturition was maintained and increased even further, whereas induced deeper NEB (through feed restriction or feed energy dilution) in later lactational stages caused an immediate reduction of milk production.

The metabolic priority of the mammary gland after parturition that developed during evolution, combined with dairy cow breeding for high milk production has increased the demands of the mammary gland steadily throughout decades (Oltenacu and Algers, 2005). Also in Switzerland, milk yield per cow and total milk production has increased, whereas the number of cows and dairy farms decreased (Bundesamt für Landwirtschaft BLW, Fachbereich Tierische Produkte und Tierzucht, Auswertung MD 2009/2010) during the last decade (Fig. 1). The genetic progress for increased milk was not adequately followed by an increase in feed intake. The transition period requires therefore an enormous adaptive performance of the cow's metabolism. For this reason, most disease incidences are observed in early lactation. In addition, the etiology of many metabolic diseases can be traced back to the first 2 weeks after parturition (Goff and Horst, 1997).

In Switzerland, this period may particularly be challenging for the dairy cow as the Swiss agricultural policy aims to promote low input and efficient agricultural systems in which the cultivation of "home-grown" forages with little input of concentrates is emphasized to cover most of the energy and protein requirements of the dairy cow.

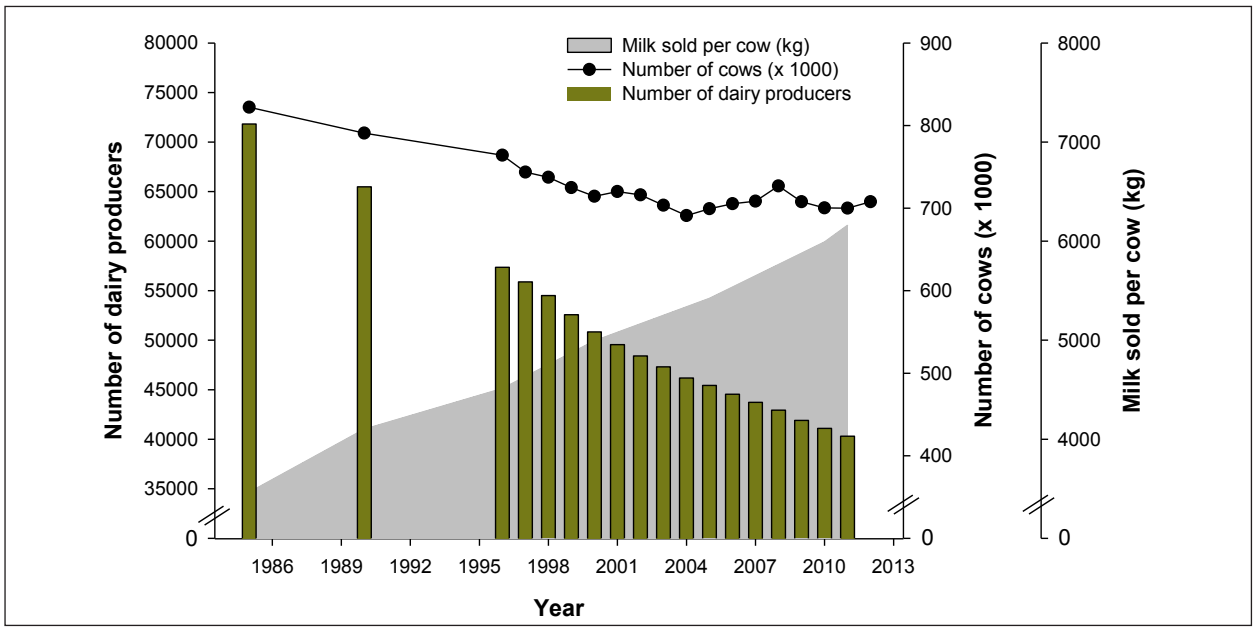

Figure 1: Development of the number of farms, the average quantity of milk sold (A), and the average quantity of milk sold per hectare (agricultural land) and cow in Switzerland (B) (Bundesamt für Landwirtschaft BLW, Fachbereich Tierische Produkte und Tierzucht, Auswertung MD 2009/2010).

Impaired course of adaptation

Adaptation cannot be described as being successful or not. It is obvious that most cows will reach the adapted stage eventually, unless they die from the metabolic challenge of early lactation. One would therefore rather assess the course of adaptation as being successful or not. An unsuccessful course of adaptation is recognized by the occurrence of diseases such as hypocalcaemia, retained placenta, fatty liver, ketosis, metritis, and even mastitis. Reduced reproductive performance based on different pathophysiological dysfunctions during the postpartum period is another consequence of poor adaptive performance. In addition, a dairy cow may enter a vicious cycle of health disorders, as most of the listed diseases are interrelated. Hence, Correa et al. (1993) observed that milk fever and dystocia were risk factors for several other disorders. Erb and Grohn (1988) also concluded that postpartum disorders are interrelated, and they observed that milk fever plays a central role in linking up to other disorders such as ketosis, displaced abomasum, and metritis. Ingvartsen et al. (2003) concluded that periparturient changes in hormones and metabolites may potentially compromise the immune competence and lead to an increased susceptibility to bacterial infections during this period, including endometritis and mastitis. Vernay et al. (2012) indeed observed differential effects from changed glucose and insulin concentrations on mammary mRNA expression of several immune parameters in dairy cows after lipopolysaccharide (LPS) challenge.

Despite the interrelation between the mentioned diseases, the failure of a successful course of adaptation may be assumed to be described by multiple scenarios. Hence, during the transition period, the successful course of metabolic adaptation (without disease occurrence) to the changed demands for energy and nutrients in early lactation depends on the intensity and dimension of the challenge (environment) and on the physiological adaptive capacity of the cow.

Descriptives in plasma for metabolic challenge during early lactation

The dimension of metabolic challenge the dairy cow faces in early lactation may be characterized by commonly observed, and probably most frequently documented adaptive responses in plasma, including low levels of glucose, increasing concentrations of non-esterified fatty acids (NEFA or rather free fatty acids), followed by increasing levels of ketone bodies (acetone, acetoacetate and β-hydroxybutyric acid (BHBA)) (van Dorland et al., 2009a; Graber et al., 2010; Gross et al., 2011). The three plasma metabolites describe to a great extent the metabolic situation during early lactation, and their levels reflect the adaptive capacity of the cow in face of the challenge. In short, low glucose concentrations in early lactating dairy cows result from low feed intake, insufficient gluconeogenesis and increased uptake of glucose by the mammary gland. Low plasma glucose levels in the dairy cow trigger several catabolic processes, but may also have a direct effect on gluconeogenesis by upregulating gluconeogenic enzymes to emphasize metabolism of precursors other than propionate (Kreipe et al., 2011). The elevated energy demand in very early lactation is covered by oxidation of fatty acids derived from intensive lipolysis of adipose tissue. The shortage of glycogenic precursors relative to the large amount of lipogenic precursors, and the priority for gluconeogenesis, may lead to drainage of oxaloacetate from the tricarboxylic acid cycle (TCA) cycle (van Knegsel et al., 2005). Insufficient oxaloacetate to react with acetyl-CoA for citrate formation and further metabolism in the TCA cycle, leads to incomplete oxidation of fatty acids and enhances ketone body synthesis instead. The BHBA is commonly used as indicator for impairment of metabolism, whereby a level of 1.4 mmol/L is set as minimum level for the definition of subclinical ketosis (Geishauser et al., 2000). Van Dorland et al. (2012) demonstrated that intravenous infusion of BHBA decreased plasma glucose concentration in mid lactating dairy cows, which suggests that BHBA can aggravate the metabolic situation during early lactation. Apart from ketogenesis, liver steastosis may occur when the high uptake of free fatty acids by the liver, which is a concentration depended process (Zammit, 1983), exceeds the fatty acid oxidation capacity of the liver.

Other plasma parameters than glucose, NEFA, and BHBA that undergo changes during the periparturient period and that are well documented include glucagon, insulin, IGF-I, T_3, T_4, leptin, urea, albumin, protein, triacylglycerides, and cholesterol (Hammon et al., 2009; Graber et al., 2010; Gross et al., 2011).

Adaptive capacity of the early lactation dairy cow

With regard to the adaptive capacity of the dairy cow, it has been suggested that the variation between cows to adapt successfully to lactation has a genetic base (Ingvartsen et al., 2003; Drackley et al., 2005; Graber et al., 2010), possibly associated with breeding dairy cows for increased milk production during the last decades. Simianer et al. (1991) and Fleischer et al. (2001) confirm that there is an increased risk of impaired metabolic adaptation with increasing milk production levels. In Switzerland, this development is illustrated by the positive relationship between veterinary costs and milk yield of the cows (Grundlagenbericht 2010, ART, Zentrale Auswertung). However, some studies show that high milk production does not necessarily lead to metabolic diseases (Gröhn et al. 1995; Ingvartsen et al. 2003), i. e. a successful course of metabolic adaptation is possible despite a negative energy balance which cannot be avoided in early lac-

tation. Hence, Kessel et al. (2008) and van Dorland et al. (2009a) observed differential responses in plasma from early lactation dairy cows that experienced a similar NEB. Ingvartsen et al. (2003) proposed from their position paper, abnormal body mobilization and immune competence, rather than milk production per se, to be causal for metabolic and immune status. Interestingly, the highest susceptibility for production-related diseases like ketosis, lameness, mastitis or displaced abomasum occurs already before the peak of milk yield (Goff & Horst., 2006), and concurrently with the greatest rate of increase of milk production (Ingvartsen et al., 2003), which is also the period of the nadir of energy balance and the greatest rate of body tissue mobilization.

Liver as site to understand an impaired or successful course of adaptation

Closely linked to the changes in plasma is the liver. The liver is the principle site for whole-body homeostatic and homeorhetic control of metabolism and thus for maintenance of (adaptive) performance, and may itself be causal and contributing to metabolic and related disorders (e.g. fatty liver, ketosis, metritis, lameness) during impaired or suboptimal function. The liver plays a key role in the metabolic adaptation as it coordinates and interconvert nutrients to support pregnancy and lactation.

Over the last decade, hepatic gene expression data have increasingly been used to investigate mechanisms underlying physiological functions and to explain the associated phenotypic variability during early lactation under controlled specific experimental conditions, including induced severe NEB, hepatic steatosis, ketosis (Loor et al., 2007; McCarthy et al., 2010), or under field conditions (Graber et al., 2010). Gene expression measurements, or rather RT-qPCR allow the quantitative determination of a huge number of factors in a very small sample (20 mg). A liver biopsy can easily be performed on cows, even under field conditions (Graber et al., 2010), and allows repeated sampling at different metabolic stages. Hence, it has been shown that the hepatic mRNA abundance of a number of factors is very similar within a cow liver, but different between cow livers (van Dorland and Bruckmaier, 2010a). This is an important precondition for repeated biopsy sampling of the same organ to compare the mRNA abundance at different time points. However, the tissue size obtained during conventional biopsy methods can be limiting for methods at a protein level such as Western blotting. Alternatively, the quantitative determination of functional factors at a transcript (mRNA) level has advantages. Although mRNA does not necessarily reflect the activity of an enzyme or receptor, correlations between mRNA expression and activity or concentration of the protein are close for several enzymes (e.g. for hepatic pyruvate carboxylase (PC) enzyme activity and PC mRNA abundance (Greenfield et al., 2000). However, compared to protein concentrations or enzyme or receptor activity, the changes of the mRNA abundance of the various factors are rather small (up to 3-fold) in most of the performed studies (Loor et al., 2006; Loor et al., 2007; Hammon et al., 2009; van Dorland et al., 2009a). Obviously, these small changes are of significant importance for the activity or concentration of the respective hepatic protein. Hence, because protein synthesis and enzyme activity are short-term regulated at post-transcriptional levels the transcript is expectedly less under short-term environmental influence, therefore more stable and thus provides a more constant information about a certain factor.

Variation in adaptive responses between transition dairy cows under field conditions

Variation between cows for liver transcripts was intensively studied by Graber et al. (2010), who were the first to include a large number of cows (n = 232 from 64 farms) for evaluation of liver metabolism by means of mRNA abundance of genes encoding key parameters involved in metabolic processes around parturition under field conditions. The high number of cows included in this study enabled to increase understanding about the variation between early lactation dairy cows for liver transcripts, which may have a genetic basis. In this field study, blood and liver samples were collected in week 3 prepartum (20 ± 7 d prepartum; −3 wk), in week 4 postpartum (24 ± 2 d postpartum; +4 wk), and in week 13 postpartum (89 ± 4 d postpartum; +13 wk). Blood plasma was assayed for concentrations of glucose, NEFA, BHBA, cholesterol, triglycerides, urea, albumin, protein, insulin, IGF-1, leptin, 3,5,3'-triiodthyronine (T_3), and thyroxine (T_4). Liver samples were measured for mRNA abundance of 26 candidate genes encoding enzymes and nuclear receptors that are involved in gluconeogenesis, fatty acid β-oxidation, fatty acid and triglyceride synthesis, ketogenesis, citric acid cycle, cholesterol synthesis, and the urea cycle (Fig. 2). The selection of investigated candidate genes was based on their key-roles in controlling the respective metabolic pathways that are assumed to play major roles for the cows' adaption to lactation.

From the significant changes in concentrations of the measured plasma parameters across the observed timepoints, it was concluded that the cows in the study experienced a marked and individually very different metabolic load in early lactation, demonstrated by changes of plasma NEFA concentrations (Fig. 3a). Similarly, significant changes in mRNA abundance were observed across the transition period for most of hepatic candidate genes (PEPCKm and c, PC, G6PC, ACSL1, CPT1A, CPT2, ACADM, ACADVL, ACLY, GPAM, GPD2, CS, ASS1, OCT, PPARα, SREBF1, and LXRα). As described in the previous paragraph, timely changes in mRNA abundance

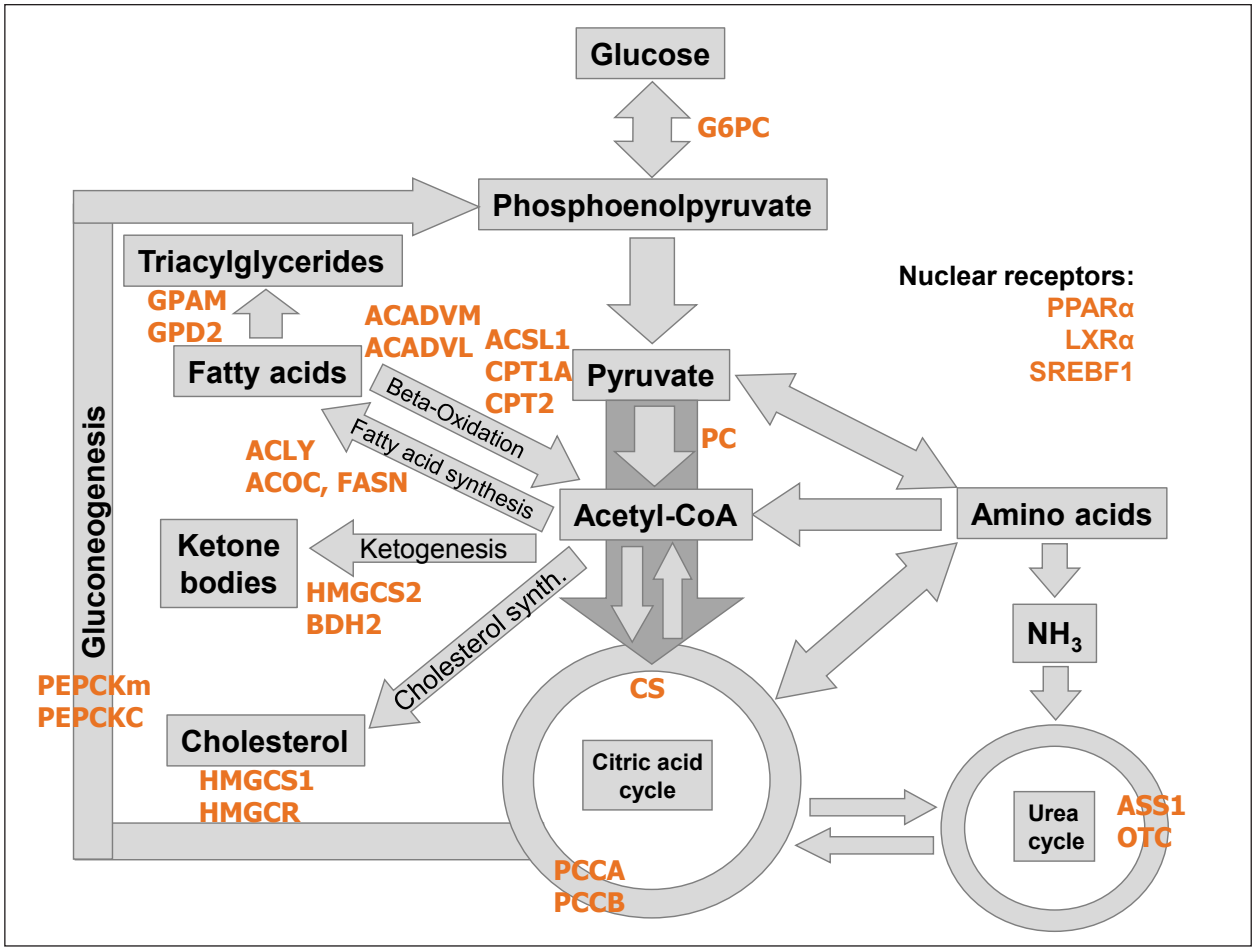

Figure 2: Schematic representation of key metabolic processes in the liver including the measured target genes (ACADM, acyl-CoA dehydrogenase, medium chain; ACADVL, acyl-coenzyme A dehydrogenase, very long chain; ACoC, Acetyl-CoA-Carboxylase; ACSL1, acyl-CoA synthetase long-chain 1; ASS1, argininosuccinate synthetase 1; BDH2, 3-hydroxybutyrate dehydrogenase 2; CPT1A, carnitine palmitoyltransferase 1A; CPT2, carnitine palmitoyltransferase 2; CS, citrate synthase; FASN, fatty acid synthase; GPAM, Glycerol-3-phophate acyltransferase; GPD2, glycerol-3-phosphate dehydrogenase 2; G6PC, Glucose-6-phosphatase; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HMGCS1, 3-hydroxy-3-methylglutaryl-coenzyme A synthase 1; HMGCS2, 3-hydroxy-3-methylglutaryl-coenzyme A synthase 2; LXRα, liver X receptor α; OCT, ornithine transcarbamylase; PCCA, propionyl-CoA carboxylase alpha; PCCB, propionyl-CoA carboxylase beta; PPARα, peroxisome proliferators-activated receptor α; PC, pyruvate carboxylase; PEPCKc, cytosolic phosphoenolpyruvate carboxykinase; PEPCKm, mitochondrial phosphoenolpyruvate carboxykinase; SREBF1, sterol regulatory element binding factor 1).

were small (up to 1.5 cycles, i. e. up to 2.8-fold change of expression), confirming data from other studies evaluating liver transcripts, but significant for most of the hepatic parameters measured (PEPCKm and c, CPT1A, CPT2, CS, ACLY, HMGCS1 and 2, and PPARα). This implies that the physiological state relative to parturition can be well characterized by the selected and measured target liver transcripts.

The variation between cows for the candidate liver transcripts at each time-point was observed to be small too, illustrated by mRNA abundance of ACADVL (Fig. 3b) showing the individual mRNA abundance of ACADVL in cows across sampling time-points). The small variation between cows for liver transcripts obviously underlies the marked responses for blood plasma parameters between cows. These findings raise the question if the observed variation between cows under field conditions would be large enough to characterize the metabolically robust dairy cow through liver transcripts under field conditions. In addition, it was observed, from the total calculated correlation coefficients between concentrations of plasma parameters and liver transcripts that only 19.5 %, 21 %, and 9.5 % evaluated in –3 wk, +4 wk and +13 wk, respectively, were observed to be significant (van Dorland et al., 2010b). This means that plasma parameters can only be used to a certain extent as descriptive for liver functioning (at the level of mRNA), and therefore, it may be concluded that the augmentation of metabolic characterization at the level of metabolites, hormones and growth factors, by a vast number of parameters at

a transcript level provides a more complete image of the physiological events underlying adaptation to milk production (Bruckmaier and van Dorland, 2010).

Characteristics of the metabolically robust dairy cow

As discussed previously, the failure of a successful course of adaptation may be assumed to be described by multiple scenarios, and so may the metabolically robust dairy cow. Robustness in dairy cows may be explained by the cow's ability to function well in the environment, and being resilient to the changes in the climates, production systems or herds (Strandberg, 2009). Ten Napel et al. (2009) defined robustness as the cow's ability to maintain homeostasis in which the liver plays a crucial role. Ellen et al. (2009) introduced health as a main concept in exploring robustness in dairy cattle. The latter concept was used in Graber et al. (2012), who performed a retrospective study in which dairy cows from the field study (Graber et al., 2010) were either classified as metabolically robust or vulnerable based on the occurrence of various metabolic and (re)productive disorders in their previous lactations. With use of discriminant analysis, variables were identified that best explained the differences between metabolically robust and vulnerable cows, which were parity, plasma triglycerides, glucose and mRNA abundance of carnitine palmitoyltransferase 2 (CPT2) in week 3 prepartum. In week 4 postpartum, identified significant parameters were parity, plasma glucose and urea. Based on the identified plasma and liver variables, this evaluation was successful in differentiating metabolic robust from vulnerable cows, as characterized by past health performance data. However, the evaluation resulted in a correct classification of only < 70 %.

At a farm level, robustness is commonly known as the so-called "unauffällige Kuh" (unnoticeable cow) versus a "problem" cow that needs the farmers' attention for its repetitively poor health status. In van Dorland et al. (2009b), this concept was used to increase understanding of the physiology underlying metabolic load and to test the hypothesis that adaptive responses in liver from dairy cows under field conditions with high metabolic load (based on high plasma NEFA, BHBA, and low glucose levels) differ from cows with no metabolic load ("unauffällige Kuh") in week 4 postpartum. Their findings revealed that the "unauffällige Kuh" showed generally higher mRNA abundance for genes related to lipid biosynthesis and lower mRNA abundance for genes related to fatty acid oxidation (Tab. 1). In addition, pyruvate carboxylase mRNA level was not upregulated in the "unauffällige Kuh" (Tab. 1), which indicates no specific adaptation in these cows to the source and availability of gluconeogenic precursors such as lactate and amino acids.

These observations demonstrate that liver transcripts are additive to the understanding of metabolic biodiversity in early lactation dairy cows. Furthermore, the results obtained under field conditions largely confirmed documented hepatic adaptations experimentally in case of McCarthy et al. (2011) with induced deeper NEB, in case of Hammon et al. (2009) with steatosis, and in case of Loor et al. (2007) with induced ketosis. Obviously, the adaptive capability of the liver is little affected by environmental influences dur-

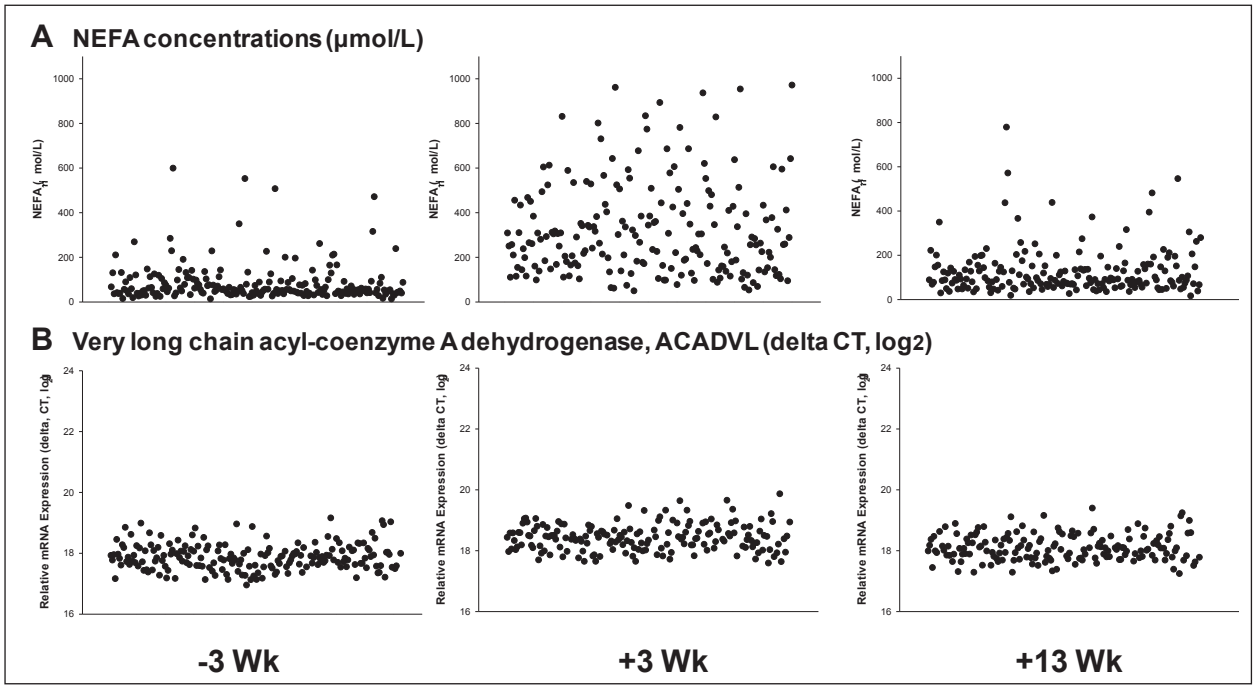

Figure 3: Individual adaptation reactions in cows for NEFA concentration (A) and mRNA abundance of ACADVL (B) across time-points.

Table 1: Abundance of mRNA of genes related to key metabolic pathways in the liver of dairy cows with different metabolic loads in week 4 pp (van Dorland et al., *2009b*).

Parameter	Metabolic load[a]		*P-Value*		
	GRP + *(n = 30)*	GRP – *(n = 30)*	Load	Parity	Breed
Gluconeogenesis related parameters[b]					
PEPCKc	21.6 ± 0.11	21.7 ± 0.10	0.70	0.35	0.67
PEPCKm	11.6 ± 0.13	11.0 ± 0.18	0.11	0.28	0.03
PC	18.6 ± 0.13	17.9 ± 0.12	< 0.001	0.74	< 0.001
G6PC	20.2 ± 0.09	20.2 ± 0.09	0.89	0.08	0.11
Fatty acid oxidation related parameters[b]					
ACSL1	17.3 ± 0.10	16.8 ± 0.11	0.01	0.13	0.12
CPT1A	15.0 ± 0.11	14.7 ± 0.12	0.21	0.15	0.75
CPT2	16.5 ± 0.07	16.2 ± 0.08	< 0.01	0.64	0.10
ACADM	19.0 ± 0.10	19.3 ± 0.11	0.02	0.49	0.73
ACADVL	18.7 ± 0.07	18.2 ± 0.08	< 0.001	0.27	0.87
Fatty acid & triacylglyceride synthesis related parameters[b]					
FASN	12.8 ± 0.15	13.7 ± 0.20	< 0.001	0.22	0.06
ACC	7.63 ± 0.10	8.43 ± 0.16	< 0.001	0.15	0.96
GPAM	16.6 ± 0.08	17.3 ± 0.10	< 0.001	0.05	0.31
GPD2	8.27 ± 0.12	8.60 ± 0.13	0.02	0.29	0.09
Nuclear receptors[b]					
PPARα	17.9 ± 0.08	18.2 ± 0.08	0.03	0.36	0.03
SREBF1	14.3 ± 0.12	14.7 ± 0.10	0.02	0.30	0.80
LXRα	16.4 ± 0.12	17.1 ± 0.10	< 0.001	0.04	0.16

[a] GRP+, cows with glucose concentrations of < 3.0 mmol/L, NEFA concentrations of > 300 µmol/L, and BHBA concentrations of > 1.0 mmol/L in week 4 pp; GRP-, cows with glucose concentrations of > 3.0 mmol/L, NEFA concentrations of < 300 µmol/L, and BHBA concentrations of < 1.0 mmol/L in week 4 pp.

[b] ACADM, acyl-CoA dehydrogenase medium chain; ACADVL, acyl-coenzyme A dehydrogenase very long chain; ACC, Acetyl-CoA-Carboxylase; ACSL1, acyl-CoA synthetase long-chain 1; CPT1A, carnitine palmitoyltransferase 1A; CPT2, carnitine palmitoyltransferase 2; FASN, fatty acid synthase; GPAM, Glycerol-3-phosphate acyltransferase; GPD2, glycerol-3-phosphate dehydrogenase 2; G6PC, Glucose-6-phosphatase; LXRα, liver X receptor α; PPARα, peroxisome proliferators-activated receptor α; PC, pyruvate carboxylase; PEPCKc, cytosolic phosphoenolpyruvate carboxykinase; PEPCKm, mitochondrial phosphoenolpyruvate carboxykinase; SREBF1, sterol regulatory element binding factor 1.

ing high metabolic load. Therefore, the observed differences may aid in revealing the genetic component underlying optimal adaptive performance in dairy cows.

Involving the genome: direction of future research

A genetic component responsible for the occurrence of production- related diseases, and therefore adaptive performance is well acknowledged, although not yet understood (Ingvartsen et al., 2003; Drackley et al., 2005). The difference between cows adapting to lactation at protein and mRNA level illustrate the metabolic flexibility of the present dairy cow with multiple causes leading to impairment of adaptation and development of disease. This information forms an ideal base to continue research at the level of the genome. At present, it is unknown where exactly the genome regions or genes are located that encode several phenotypic parameters defined to be related with metabolic robustness, and which variants of a gene (good or bad) the animal possesses. The integration of phenotypic data, including gene expression profiles, and genomic data will facilitate a better characterization of the complex interplay between these levels, and will improve the genetic understanding necessary to unravel a certain trait or multi-trait such as metabolic robustness in dairy cows. The generated knowledge may be used for the development of SNP-based selection tools, which may drastically improve the selection for metabolically robust dairy cows in the future, and thereby allow a considerable reduction of time and costs in relation to currently traditionally applied methods to evaluate the breeding value of dairy cattle. A selection for metabolically stable dairy cows would ensure efficient milk production without compromising health and wellbeing.

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