Metabolic programming: background and potential impact for dairy cattle

"Metabolic programming": achtergrond en mogelijke impact bij melkvee

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ABSTRACT

Metabolic programming is defined as a nutritional intrauterine and/or early postnatal stimulus or insult at a critical period of development with lasting or lifelong significance. Thus growth, milk yield and fertility as decisive parameters for the productivity of ruminants are influenced not only by genetic and environmental factors, but also by epigenetics. In the past decade, knowledge of the impact of metabolic programming in humans and rodents in their later lives has increased considerably. Despite striking differences between the metabolic systems of ruminants and those of monogastric species, metabolic programming has a marked impact on the ruminant species as well. Especially during the first weeks of life, an adequate supply of nutrients is pivotal. Recent studies have demonstrated the advantages of intensified feeding of the preweaning calf for achieving better performance in the resulting dairy cow. Further research will be needed to elucidate the potential of specific tools to manipulate metabolic programming for the purpose of improving the productivity and fertility of cattle.

SAMENVATTING

Metabolic programming wordt gedefinieerd als het fenomeen waarbij een nutritionele stimulus of *insult* die tijdens een belangrijk moment in de ontwikkeling van het dier – met name tijdens de intra-uteriene en vroeg postnatale fase – optreedt, gedurende het verdere leven van het individu een bepaalde invloed blijft uitoefenen. Op basis hiervan blijkt dat belangrijke parameters in de rundveehouderij, zoals groei, melkproductie en vruchtbaarheid, niet alleen door genetica en milieu worden beïnvloed maar ook door zogenaamde epigenetische factoren. Sinds de laatste jaren is de kennis omtrent de impact van *metabolic programming* op de gezondheid van mensen en knaagdieren sterk toegenomen. Alhoewel er zeer grote verschillen zijn tussen het metabolisme van monogastrische dieren en dat van herkauwers, blijkt *metabolic programming* ook bij deze laatste van belang te zijn. Vooral tijdens de eerste levensweken is de voorziening van een voldoende hoeveelheid voedingsstoffen van doorslaggevend belang. Zo werd in een recent onderzoek aangetoond dat een doorgedreven voedering van het kalf alvorens het wordt gespeend, een positief effect heeft op zijn latere melkproductie. Bijkomend onderzoek is echter nodig om na te gaan hoe en in welke mate specifieke maatregelen kunnen aangewend worden om via *metabolic programming* de productiviteit en de vruchtbaarheid van runderen te verbeteren.

INTRODUCTION

Metabolic disturbances such as ketosis and fatty liver are a major constraint in the dairy industry (Duffield *et al.,* 2000). Their pathogenesis is closely linked to the first weeks of lactation when increases in feed intake lag behind increases in milk production (Bobe *et al.*, 2004). The concomitant negative energy balance (NEB) tends to be more pronounced in high yielding dairy cows than in substandard animals. The NEB represents a distinct risk factor for metabolic disturbances. In cows suffering from fatty liver, increased insulin resistance has been demonstrated compared to the insulin resistance of clinically healthy cows (Hayirli *et al.*, 2002; Kaske *et al.*, 2004). In general, however, cows are able to cope with NEB because homeorrhesis of lactation favors the supply of sufficient energy and substrates for milk production. Thus, there is no inevitable relation between milk yield and the incidence of metabolic disturbances per se. Instead, there is general consensus that metabolic disturbances develop as a result of the insufficient adaptation capaci-

ties of the affected cows, a fact which underscores the impact of individual disposition (Herdt, 2000; Ingvartsen and Andersen, 2000). At present, the main strategies for reducing the prevalence of metabolic disturbances in dairy herds focus on optimizing transition cow management. The ultimate goal is to maximize feed intake during the first weeks of lactation, which is generally considered to be the most effective tool for preventing production diseases (Grummer *et al.*, 2004). Another different and challenging approach could be to use specific tools to modify the individual dispositions of dairy cattle to cope with metabolic disturbances. It has been suggested that feed intake capacity, glucose homeostasis, insulin resistance and obesity are the key issues determining this disposition (Herdt, 2000). Strikingly, it is exactly these four factors that are the focus of the investigations of researchers in human medicine who are looking for the underlying causes of the increasing prevalence of obesity and diabetes in recent decades. It is within this context that the concept of metabolic programming has been developed. It is the aim of this paper to summarize the present knowledge derived from epidemiological and experimental studies and to draw at least preliminary conclusions concerning the future of the dairy industry.

THE CONCEPT OF PROGRAMMING: A HISTORICAL VIEW

The idea of an epigenetic perinatal programming of regulatory systems in the organism was first suggested 35 years ago (Dörner, 1975), and was then substantiated in terms of a "fuel-mediated teratogenesis" by Freinkel and Metzger, (1978),who demonstrated that the pups of diabetic rats developed hyperinsulinemia. Thereafter, it took 15 years until a generally accepted definition of metabolic programming as "a stimulus or insult at a critical period of development with lasting or lifelong significance" was recognized (Lucas, 1991). Within the past fifteen years, an enormously increasing number of studies using animal models (predominantly rodents) have been conducted that have given more detailed insight into the qualitative and quantitative aspects of the impact of metabolic programming. The "thrifty phenotype hypothesis" (Hales and Barker, 2001) suggested that an unfavorable intrauterine nutritional supply influences the metabolic and endocrine constellation of the fetus leading to reduced birth weight, which favors survival under detrimental nutritional conditions after birth. More recently, the "predictive adaptive response hypothesis" proposed that the degree of mismatch between the pre- and postnatal environments determines the forthcoming disposition for subsequent diseases such as diabetes, coronary heart disease and hypertension (Gluckman and Hanson, 2004). Environmental factors are also able to program the regulatory systems of an organism during periods of developmental plasticity in postnatal life. Hence the terms "developmental programming" and the "developmental origins of adult health and disease" may be more appropriate (Armitage *et al.*, 2005).

METABOLIC PROGRAMMING OF HUMANS AND RODENTS

Impact of intrauterine nutrient supply

Epidemiological studies revealed evidence that the risk of developing obesity, diabetes type 2 and coronary heart disease is markedly increased if the birth weight of human subjects was either low (Hales and Barker, 1993; Ravelli *et al.*, 1999) or, on the other hand, above average (Plagemann *et al.*, 1997; Dabelea *et al.*, 1999; Holemans *et al.*, 2003).

Such epidemiological results encouraged various groups to investigate the mechanisms of metabolic programming in experimental studies predominantly utilizing rodents. The feeding of pregnant rats a protein-restricted diet became a frequently used model for studying intrauterine environmental effects (Desai and Hales, 1997; Plagemann *et al.*, 2000; Fernandez-Twinn *et al.*, 2005). The offspring of such rats exhibit morphological and functional peculiarities: the size of pancreatic Langerhans islets and the number of ß-cells are reduced, the insulin content of the ß-cells is 50 % lower and the insulin secretory response to glucose is impaired compared to control animals (Holness *et al.*, 2000; Bertram and Hanson, 2001; Ozanne, 2001). After weaning, glucokinase activity in the liver is reduced by 43 % compared to control rats, whereas the activity of phosphoenolpyruvate-carboxykinase, a key enzyme in gluconeogenesis, is increased by 50%. In the adult offspring of rats fed a protein restricted diet during pregnancy, the activity of insulin signal transducing molecules in fat and muscle tissue is reduced, resulting in the diminished glucose uptake of these cells via GLUT-4 (Ozanne *et al.*, 1998; Fernandez-Twinn *et al.*, 2005; Ozanne *et al.,* 2005).

The biological mechanisms of metabolic programming are still poorly understood. According to the present conception, metabolic programming is caused by epigenetic modifications of non-imprinted genes induced by the developmental environment (Wu *et al.*, 2006; Godfrey *et al.*, 2007). As a result, gene expression continues to be modified throughout life without alteration of the DNA sequence. Such a mitotically heritable alteration of gene expression induces a non-genomic tuning of phenotype through developmental plasticity ("Genetic proposes, epigenetic disposes"; Crews and McLachlan, 2006). These effects can even be passed on to more than one succeeding generation.

In conclusion, undernutrition and/or stress during intrauterine development trigger adaptive responses which support postnatal survival in an environment with scarce nutrient supply. However, if high-quality nutrients are available in abundance after weaning, this adaptation leads to an increased risk of cardiovascular and metabolic diseases in adult life. Insulin resi-

stance may develop in later life, while reproductive performance and the lifespan of these animals are often reduced when compared to control animals (Breier *et al.*, 2001; Simmons *et al.*, 2001; Vehaskari *et al.*, 2001; Guzmán *et al.*, 2006).

Impact of postnatal nutrition

In rats, a life-long programming of the metabolism can also be induced by the postnatal nutrition regime. If pups are fed milk formula containing increased lactose concentration ("pup in a cup model") via an intragastric cannula between days 4 and 24 of life, within 24 h they develop a hyperinsulinemia comparable with that developed by pups fed an isoenergetic, fat-based milk formula. Despite a normal diet being started on day 25, reduced glucose tolerance was still found on day 270. In addition, pups initially fed a lactose-based milk formula became obese and insulin resistant compared with their controls (Patel and Srinivasan, 2002). Hyperinsulinemia, hyperleptinemia, early-onset obesity and glucose intolerance were also found in adult rats that were overfed from postnatal days 3 to 21 by adjusting the litter size of the mothers to three rather than the normal litter size of ten (Boullu-Ciocca *et al.*, 2005).

More than 30 years ago, researchers found that the amount of feed consumed by rats during the suckling period determined appetite and feed intake capacity in later life (Oscai and McGarr, 1978). The overfeeding of rat pups by adjusting the litter size to four resulted in a persistent increase of intake capacity after the animals were full grown. Further in-depth studies using immunocytochemistry revealed evidence that the percentage of NPY-immunopositive neurons per total number of neurons in the arcuate nucleus of the mediobasal hypothalamus was higher in postnatally overfed rats compared to controls (Heidel *et al.*, 1999; Plagemann *et al.*, 1999). These results may provide one explanation for the life-lasting hyperphagia found in those rats, since NPY is known to be a potent orexigenic neurohormone. Postnatal undernutrition, on the other hand, has been found to result in hypophagia.

Gender differences

Several studies suggest the existence of sexually dimorphic responses to metabolic programming. The reported effects of gender are inconsistent. In guinea pigs, fetal growth restriction appears to impair insulin sensitivity in females but not in males (Thavanesaran *et al.*, 2002). In children, girls are known to be intrinsically more insulin-resistant than boys. Whether this phenomenon is due to differences in metabolic programming is a matter of controversy. In female rats, insulin resistance as a result of intrauterine protein restriction develops later in life, a response which is not found in male rats (Sudgen and Holness, 2002; Fernandez-Twinn *et al.*, 2005).

Table 1. Effects of intensified feeding of preweaned calves on their subsequent lactational yield; d = day, wk = week, MR = milk replacer, CP = crude protein, xF = crude fat, BW = body weight, DIM = days in milk.

Breed	Groups/ Total number	Age	Feeding Restrictive	Intensive	Milk yield Int. vs. Restr.	Reference
Danish Holstein	2 / 20	d 1-4 d 5-42	Colostrum 4.6 L/d milk	Colostrum suckling the dam twice daily, each time 30 min	+ 775 kg (p = 0.15)	Foldager and Krohn, 1994
Danish Holstein	7 / 140	d 1-4 d 5-42	Colostrum 4.6 L/d milk	Colostrum milk ad libitum	+ 572 kg (p < 0.10)	Foldager *et al.*, 1997
Israelian Holstein	2 / 40	wk 1-6	Totally 28 kg MR (23% CP, 15% xF)	Suckling the dam thrice daily	+ 453 kg (p = 0.08)	Bar-Peled *et al.*, 1998
Holstein Friesian	3 / 60	 wk 1 wk 2-5 wk 6-8	MR (27% CP, 15 % xF) 1.25% of BW 2.25% of BW 1.25% of BW	MAT (27% CP, 20 % xF) 1.25% of BW 2.25% of BW 1.25% of BW	+ 649 kg (200 DIM) (p = 0.04)	Ballard *et al.*, 2005
Israelian Holstein	2 / 36	d 1-2 d 3-60	Colostrum MR (23 % CP, 12 % xF)	Colostrum milk	+ 1,250 kg (p < 0.01)	Moallem *et al.,* 2006
Holstein Friesian	2 / 80	d 1 d 2–42	Colostrum MR (21.5% CP, 21.5% xF) 1.2% of BW	Colostrum MAT (30.6% CP, 16.1% xF) 2.1% of BW	n. s. (60 DIM)	Rincker *et al.*, 2006
Holstein Friesian	4 / 52	d 1-7 d 8-35/42	Colostrum MR (22% CP, 20% xF) 1.25% of BW	Colostrum MR (28% CP, 20% xF) 1.25% of BW	+ 921 kg (p < 0.01)	Drackley *et al.*, 2007

METABOLIC PROGRAMMING IN RUMINANTS

Impact of intrauterine nutrient supply

The principle of fetal programming represents a common feature among mammals, including ruminants (Taylor and Poston, 2007). It must be emphasized, however, that most research on metabolic programming is focused on reducing the incidence of chronic diseases affecting humans in late adult life (Guilloteau *et al.*, 2009). In contrast, most research on metabolic programming in animals is focused on increasing weight gain in growing animals and on improving fertility performance and metabolic resilience in adult food animals (Breier *et al.*, 2006).

Dairy cows are often inseminated as early as 60 days post partum in order to achieve a short calving interval. However, at this point in time many cows are still coping with a more or less pronounced NEB. This metabolic constellation may affect the embryo, as has been demonstrated in heifers (Swali and Wathes, 2006). The restricted feeding of ewes (70% of control feed allowance) from 60 days before until 7 days after mating, followed by adequate feeding of the ewes during the remaining gestation period resulted in increased fetal ACTH concentrations between days 110 and 145 of gestation in twin fetuses, but not in singleton fetuses, as compared to fetuses from ewes that were fed 100% throughout the periconceptional period (Edwards and McMillen, 2002).

Two studies with sheep revealed that an energy restriction during early pregnancy caused only minor effects on birth weight, metabolic constellation and muscle fiber composition of the offspring (Gardner *et al.*, 2005; Daniel *et al.*, 2007). Another study demonstrated, however, that maternal undernutrition (50% of requirements between days 28 and 78 of gestation) induced increased body weight in the lambs during later life and dysregulated glucose uptake (Ford *et al.*, 2007).

Maternal energy restriction in late gestation seems to have an even stronger influence on the offspring. On day 120 of gestation, fetuses of ewes fed a severely restricted diet from days 100 to 120 of gestation had higher GH- and lower IGF-1, glucose and insulin concentrations than fetuses of control-fed ewes (Bauer *et al.*, 1995). Accordingly, the fetal somatotropic axis is nutritionally regulated in late gestation. Additionally, the level of maternal nutrition during late pregnancy affects the insulin resistance of the lambs. A maternal feed restriction (50% of requirements) from day 110 until term did not influence either the birth weight or the growth rate until 1 year of age. However, intravenous glucose tolerance tests at days 63 and 250 revealed a profound dysregulation of insulin secretion in those lambs experiencing undernutrition during late intrauterine development (Gardner *et al.*, 2005). The results indicate that intrauterine programming of the metabolism endures readjustment of the metabolic constellation during post-weaning adaptation of ruminants to roughage diets.

In beef cows, a protein supplementation during late gestation did not affect the birth weight of calves compared to other calves from non-supplemented dams. However, the weight at prebreeding was higher for heifers from protein-supplemented dams. Thus, fetal programming affected the postweaning body weight and fertility of heifers, since the pregnancy rates were higher for heifers from cows supplemented with protein during late gestation than for heifers from non-supplemented dams (Martin *et al.*, 2007).

Finally, birth weight was found to affect postnatal weight gains in lambs fed ad libitum; lambs with a high birth weight gained more weight than substandard lambs ($p = 0.08$; Greenwood *et al.*, 1998).

Impact of postnatal feeding intensity

By definition, metabolic programming takes place in a narrow timeframe that is characterized by the plasticity of the regulatory systems and during which the key regulatory hypothalamic neuropeptides and receptors can be permanently programmed by nutritional factors (Taylor and Poston, 2007). Although the appropriate timeframes have not yet been defined for ruminants, there are clear hints that the early postnatal feeding level produces long-lasting consequences.

In modern rearing systems, the restricted feeding of milk replacer (MR) and the early weaning of calves are practiced to lower rearing costs. There is increasing evidence, however, that intensified early nutrition may not only improve the constitution of the calf in the short term, but may also have a long-term positive impact on its performance (Jasper and Weary, 2002). Although the experimental approaches to investigating this issue have differed markedly, the positive effect of intensified feeding of calves on milk yield in the first lactation has been confirmed in several studies (Table 1). Thus, an appropriate amount of MR has to be fed in the first weeks of life. If the aim is to achieve a daily weight gain of 400 g in a calf with a body weight of 50 kg, then the calf needs to be fed roughly 16 MJ ME/day, which corresponds to about 1 kg MR per day – an amount which, unfortunately, is not achieved in most rearing systems (Kaske *et al.*, 2009). One possible explanation could be the influence of early feeding levels on the development of the mammary gland. In fact, a high feeding level during the first eight weeks of life was accompanied by an intensified development of the mammary parenchymal mass, DNA and RNA of Holstein heifer calves compared to moderately fed controls. Interestingly, the first weeks of life were found to be decisive because a higher feeding intensity between weeks 8 and 14 of life did not affect the development of the mammary gland (Brown *et al.*, 2005).

In addition, the early development of rearing calves has an impact on subsequent fertility since increased body weight and girth at 30, 180 and 450 days of life

were found to be associated with a reduced age at first calving (Brickell *et al.*, 2009).

The consequences of postnatal feeding on the insulin status were investigated in further experiments. Female Holstein Friesian calves were fed from days 2 - 50 either standard MR or isonitrogenic lactose-reduced MR, in both cases at a low and a high feeding level (lactose supply 8.3, 16.6, 4.8, 2.4 g/kg BW/d). Thereafter, standard MR was fed at a low feeding level to all calves until day 75, followed by a silage-based diet for growing heifers ad libitum (Kaske, unpublished). At the age of 1 year, the growth rates of calves fed low-lactose MR during the first seven weeks of life were still significantly lower compared to calves fed standard MR. The peripheral insulin response (as quantified by hyperinsulinemic euglycemic clamps) at the age of 8 months was not affected by the early postnatal feeding regime, whereas a statistical trend towards lower pancreatic insulin responses (quantified by hyperglycemic clamps) in later life was evident for calves fed low-lactose MR compared to calves fed standard MR.

In conclusion, the intensified feeding of calves, utilizing their impressive growing capacity, seems to be meaningful for the purpose of improving their future performance as heifers. The consequences of the postnatal feeding regime for the metabolic resilience and health status during first lactation are the object of current investigations.

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Bij de dood van een hond

Dit zijn de vier laatste strofen uit *Bello, de trekhond*. De dichter Charivarius (Gerard Nolst Trenité, 1870 - 1946) had het beest na wat afdingen gekocht van een dierenbeul.

Ja, je poten staan wat krom nou,
Door dat tuig, dat zat je zo slecht …
Bello! Niet zo'n zucht! Waarom nou?
Wees gerust – dat komt terecht!

't Is hier nog wel wat uit te houen,
Wel gezellig, hé, en warm!
Koest nou! Koest nou! Niet zo douwen,
Met je kop zo onder m' arm!

Zo. Laat ik je hier nou leggen;
O, wat dankbaar kijk je m' aan!
Laat ons voortaan – wil je zeggen –
Poot-in-hand door 't leven gaan …

En zo praat'ik boud en blijde …
Even strekt' hij nog zijn poot …
Zachtkens zonk zijn kop op zijde …
Een zucht. En toen was Bello dood.