Symposium review: Macronutrient metabolism in the growing calf

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INTERPRETIVE SUMMARY

Macronutrient Metabolism in the Growing Calf. *Gerrits, W.J.J.* Recent interest in increasing rates of body weight gain in heifer calves before weaning are based on the promise of an increase in milk production during first lactation. Macronutrient metabolism in growing calves is reviewed, with the objective to provide insights useful for developing novel feeding strategies. Reasons for the low efficiency of utilization of dietary protein for growth are discussed. Carbohydrates from the milk replacer are preferentially oxidized and are not deposited as body fat. Insulin sensitivity decreases rapidly after birth, and at prolonged feeding of lactose, calves need alternative routes of glucose disposal.

GROWTH AND DEVELOPMENT SYMPOSIUM: POST-WEANING AND BEYOND

Macronutrient Metabolism in the Growing Calf

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Abstract

Recent interest in increasing rates of body weight gain in heifer calves before weaning are based on the promise of an increase in milk production during first lactation. This increase is usually realized by increasing milk or milk replacer intake, delaying the onset of rumen development. Simultaneously feeding of liquids and solid feeds (SF) brings about new challenges. Macronutrient metabolism in growing calves is reviewed, combining literature from heifer and veal calves with the objective to provide insights useful for developing novel feeding strategies. Growing calves are not efficiently retaining digested N when compared with other growing species. Energy and protein appear to be simultaneously limiting growth. With the possible exception of very young calves, low responses to incremental intakes of amino acids indicate that the limiting amino acid rarely explains the low efficiency of N utilization. Nonetheless, there are indications that disproportionate oxidation of amino acids as a result of amino acid imbalance may occur, notably in splanchnic tissues.

Long-chain fatty acids, absorbed from the milk or calf milk replacer (CMR) are preferentially deposited as body fat, but this strongly depends on the need for ATP, fueled by the oxidation of carbohydrates. Hence, fatty acid oxidation typically decreases with an increased feeding level. Insulin sensitivity in calves is quite high at birth, but decreases independently of feeding strategy in early age to very low levels when compared with other species. Even though changes in insulin sensitivity may be provoked by early life nutrition, these effects are small and rather transient. In heavy calves, insulin sensitivity is invariably low. Large effects of dietary treatments on postprandial glucose and insulin responses, as often observed, are unlikely to be caused by differences in insulin sensitivity. Unlike in pigs, *de novo* fatty acid synthesis is not a significant route of disposal of glucose absorbed from the intestinal tract. Instead, high lactate fluxes in milk-fed calves suggest this may be an important route of disposal.

When combining the feeding of milk or CMR with solid feeds, estimation of the contribution of the individual ration components is difficult, and interactions inside the gastro-intestinal tract complicate the estimation of their feeding value. There are indications in veal calves that use of nutrients absorbed from a CMR is not dependent on the level of intake of solid feeds.

Key words: calves, nutrient utilization, glucose metabolism, amino acid utilization, milk replacer

INTRODUCTION

Recent interest in increasing rates of body weight gain in heifer calves before weaning are based on the promise of an increase in milk production during first lactation. Even though a recent meta-analysis revealed that variation in pre-weaning ADG explained less than 3% of the variation, an increase of 100 g/day in liquid DM intake in calves with an ADG exceeding 500 g/day could increase first lactation milk production by 66 kg, which could be doubled when combined with increased starter intake (Gelsinger et al., 2016). In veal production, high rates of body weight gain are typically achieved. From both a welfare and economic perspective, there is a strong incentive to replace a considerable portion of the calf milk replacer (CMR) by solid feeds (SF) in the diet (see e.g. Webb et al. (2015)), and feeding schedules in which 50% of the energy intake originates from SF are no exception anymore. In heifers, developing feeding strategies to achieve high rates of ADG deserves attention, as increasing DMI without considering its composition ignores the altered contribution of maintenance requirements of protein, energy but also of minerals to total requirements. Simultaneous feeding of milk or CMR and SF brings about new challenges. First, an increase in CMR intake generally reduces the intake of starter grains (Yunta et al., 2015, Gelsinger et al., 2016). In addition, several possible interactions between CMR and SF influence the nutritional value of these ration components. Most of these interactions occur in the gastro-intestinal tract, starting at the onset of rumen development and include recycling of urea originating from AA from the CMR (Berends et al., 2014b), milk leakage into the rumen (Labussière et al., 2015), influences of SF on passage rate kinetics of the liquid or vice versa (Berends et al., 2015b). Despite all of these possible interactions, the vast majority of macronutrients not retained in the body are lost during post-absorptive metabolism. The priorities of the calf for retaining or oxidizing macronutrients are believed to depend on intake, within bounds of priorities or capacities determined by evolution. This manuscript reviews macronutrient metabolism in growing calves, combining literature from heifer and veal calves with the objective to provide insights useful for developing novel feeding strategies.

PROTEIN

In milk-fed calves, utilization of digested N for N retention is typically around 70% and decreases with increasing body weight below 50% when body weight increases above 150 kg (Figure 1). It should be noted that the between study variation is substantial. These values correspond with the meta-analysis by Zanton and Heinrichs (2008), stating that for milk-fed heifer calves, between 40 and 50% of ingested N was retained, corresponding with a utilization of digested N for N retention between 50 and 60% in the young calves included in their analysis. Incremental efficiencies of N retention, however, are lower and drop from 50 – 65% at BW below 70 kg (Donnelly and Hutton, 1976, Blome et al., 2003, Labussiere et al., 2008) to values between 20 and 40% at BW above 150 kg BW (Gerrits et al., 1996, Labussiere et al., 2008). Occurrence of urea recycling and difficulties predicting postruminal

N digestion complicates the analogy with weaned calves, but it is expected that the incremental efficiencies measured in calves fed milk or CMR represent an upper limit to the range to be achieved in weaned calves. The incremental efficiency for using nitrogen for deposition is much lower than for that of other growing farm-animal species. The reasons for the apparent low priority of calves to deposit amino acids that are absorbed from the intestinal tract can be manifold, and some have been extensively discussed by Van den Borne et al. (2006a).

Protein and Energy Dependent Phases Extra energy absorbed from the gastro-intestinal tract has been demonstrated to increase N efficiency, regardless the level of N intake (Gerrits et al., 1996, Zanton and Heinrichs, 2008, Berends et al., 2012).This indicates that the concept of protein and energy dependent phases, commonly used in pigs (Whittemore and Fawcett, 1976, Halas et al., 2018) and broilers (Eits et al., 2002) does not hold for calves, and hence, energy and protein are always simultaneously limiting. This was nicely demonstrated in steers, where abomasal infusion of methionine or energy from various sources independently increased N efficiency regardless the source of energy infused (Schroeder et al., 2006). This likely connects to the low incremental N efficiency, as also in pigs, it has been demonstrated that incremental N efficiency drops with age, and distinct protein and energy dependent phases have been shown more difficult to detect in older pigs. It is likely that the extent to which protein and energy limit the rate of body weight gain depends on body weight, consistent with the drop in N efficiency with age.

Limiting Amino Acids In any of the studies reported in Figure 1, the low efficiency of N utilization could have been caused by one or more amino acids, limiting the rate of protein deposition. In milk-fed calves above 100 kg BW, the incremental efficiency of all amino acids for deposition in the body was analyzed in two experiments in which protein intake varied over a wide range. It was based on the idea that the incremental efficiency of at least one indispensable amino acid would be higher than the reported incremental efficiency of 30% for total protein (Gerrits et al., 1996). The incremental efficiencies reported varied within a rather narrow range of 11 to 29% for all indispensable amino acids (Gerrits et al., 1998), but were higher for the conditionally essentials arginine and cystine. It was concluded that single limiting amino acids are not the cause for the low incremental efficiency of N utilization. This corresponds to the observations by (Batista et al., 2016) in steers, who found the incremental response of N retention to abomasal infused lysine to be close to 40% in the presence of an excess of all other essential amino acids, co-infused into the abomasum. For young calves, this may be different, as significant improvement of ADG has been reported after addition of single amino acids in young calves, e.g. addition of lysine in the first experiment reported by Hill et al. (2008) and methionine by Chagas et al. (2018). It is notoriously difficult to prepare a CMR severely deficient in a single amino acid for the study of incremental responses. Even in calves below 6 weeks of age, responses of ADG have been demonstrated low or absent (experiment 2 and 3 for methionine, and 4 for threonine (Hill et al., 2008); methionine (Castro et al., 2016); isoleucine+threonine (Morrison et al., 2017). When crudely estimating the incremental efficiency of utilization of the added amino acids in these studies from responses in ADG, assuming a fixed concentration of each amino acid in ADG (Gerrits et al., 1998), these appear to be below 30% for methionine (experiment 2, 3 from Hill et al. (2008), Castro et al. (2016), Chagas et al. (2018), threonine in experiment 4 from Hill et al. (2008) and around 40% for isoleucine when including 10 % of plasma protein (Morrison et al., 2017). The incremental response to lysine in the first experiment by Hill et al. (2008) was exceptionally high, i.e. 80% for the lowest two CP diets.

Asynchronous absorption of amino acids and glucose has been demonstrated to increase body fat deposition in heavy milk-fed calves, leaving N efficiency virtually unaffected (Van den Borne et al., 2006c). However, asynchronous supplementation of lysine and threonine in a

CMR in which about 75% of the protein originated from soluble wheat protein was found to reduce N efficiency from 46 to 35%. Interestingly, when the asynchronous absorption was corrected for by intravenous infusion of lysine and threonine, the increase in N retention was markedly lower compared with enteral supplementation (Van den Borne et al., 2012). They concluded that an amino acid imbalance in the splanchnic tissues may result in disproportionate AA oxidation.

Urea Recycling Recycling of urea has been demonstrated and measured in ruminants (Sarraseca et al., 1998). It is commonly assumed to be triggered by low N concentrations in the rumen, but it cannot be excluded that the availability of urea in the circulation affects urea recycling. The influence of dietary crude protein content on urea recycling has been recently reviewed in cattle (Batista et al., 2017). In milk-fed calves, urea production is high and largely originating from milk amino acids. In a study combining MR with low-protein SF, Berends et al. (2014b) demonstrated, using a [$^{15}N_2$]urea approach, that for every incremental g of DM from SF intake, nitrogen intake increased by 0.70 g, and nitrogen retention increased by 0.55 g ($P < 0.01$). Of this increase in nitrogen retention, 19% could be directly explained by urea recycling, with the remaining part being explained by increased intake of N via the SF, and an increased N efficiency related to increased ME intake. In a follow-up study, it was demonstrated that the contribution of urea recycling to the nitrogen economy of veal calves was substantially lower when a high-protein concentrate was fed (Berends et al., 2015a). It was concluded that low N availability in the rumen limits microbial growth and rumen fermentation in calves fed low-N SF (93 g of CP/kg of DM), and this effect cannot be compensated for by recycling of urea originating from AA absorbed from a CMR.

In summary, growing calves are not efficiently retaining digested N. Energy and protein appear to be simultaneously limiting growth. With the possible exception of very young calves, low responses to incremental intakes of amino acids indicate that the limiting amino acid rarely explains the low efficiency of N utilization. Nonetheless, there are indications that disproportionate oxidation of amino acids as a result of amino acid imbalance may occur, notably in splanchnic tissues.

FATS AND CARBOHYDRATES

The capacity of young calves to digest lactose has been demonstrated to be high (Huber et al., 1964) and remains high when continued to be exposed to lactose (Gilbert et al., 2015a). Starch seems a rather poor source of glucose for calves. In milk-fed calves, Gilbert et al. (2015a) demonstrated maltase activity to hamper the conversion of starch to glucose, estimating starch fermentation to account for 90% of the starch ingested, and rather independent of the level of starch intake (Gilbert et al., 2015b). The capacity of calves to digest long-chain fatty acids is high and strongly dependent on emulsifying properties, as reviewed by Kertz et al. (2017). Both long-chain fatty acids and glucose are important energy sources as long as calves are fed milk or CMR. Typically, oxidation of long-chain fatty acids depends on the level of feed intake. Van den Borne (2006b) demonstrated in veal calves that the proportion of dietary fatty acids oxidized dropped from nearly 80% to about 30% when feed intake increased from 1.5 to 2.5 the ME requirements for maintenance. Carbohydrate oxidation remained above 90% of intake. Following the observation that 80% of the ^{13}C from orally supplied [U-^{13}C]glucose was recovered as $^{13}CO_2$, and similar recoveries were obtained after feeding [2-^{13}C]glucose, Van den Borne et al. (2007) concluded that *de novo* synthesis of fatty acids is not a major route of disposal of absorbed glucose in calves. It follows that calves will deposit more fat when increasing glucose absorption, but that this almost exclusively originates from sparing fatty acids from oxidation.

GLUCOSE METABOLISM AND INSULIN SENSITIVITY

With rapidly increasing milk or CMR intake after birth, lactose becomes the dominant source for ATP production in calves. With prolonged high intake, however, as common in veal production, problems arise maintaining glucose homeostasis. These problems were already demonstrated in the previous century (Doppenberg and Palmquist, 1991, Hugi et al., 1997, Hugi et al., 1998), influenced by for example age, the level of feeding of the CMR and feeding frequency (Hugi et al., 1997, Vicari et al., 2008a), nutrient synchrony (Vicari et al., 2008b) and protein intake (Gerrits et al., 2008). These problems are characterized by hyperglycaemia, hyperinsulinemia and glucosuria and are connected to a low insulin sensitivity (Hugi et al., 1998). Insulin sensitivity in calves rapidly drops with age. Stanley et al. (2002), found 10 to 20-fold higher insulin sensitivities in Holstein and Jersey calves at 4-5 weeks of age (15 and 25 $x10^{-4}$ $[mU/L]^{-1}$ x min^{-1}, respectively), than Pantophlet et al. (2016c) in Holstein calves of about 190 kg of BW, both using the frequently sampled intravenous glucose tolerance test (FSIGT). Recent developments in feeding strategies of heifer calves have renewed interest in manipulating insulin sensitivity in early life, based on the promise of improved performance and milk production in later life. Although clearly, postprandial glucose and insulin kinetics are influenced by intake of milk or CMR, there is accumulating evidence that these changes are rather unrelated to changes in insulin sensitivity. In young calves, MacPherson et al. (2016) found no effect of doubling CMR intake from 4 to 8 L/day on glucose an insulin responses to a FSIGT, hence concluding that its effect on insulin sensitivity was minimal. Yunta et al. (2015) observed a tendency for a decrease in insulin sensitivity with increasing CMR intake, particularly at 42 d of age. It should be noted that the FSIGT test was performed only after a 5 h fasting period, at which point both glucose and insulin concentrations may still have been elevated. Recently, it was demonstrated that in calves, insulin sensitivity decreases rapidly, by almost 70%, between week 3 and 6 of age, unaffected by weaning (Pantophlet et al., 2016b). It seems therefore that insulin sensitivity in calves is quite high at birth, decreases independently of feeding strategy in early age to very low levels when compared with other species. In agreement, Kesser et al. (2017) recently concluded that even though slight changes in insulin sensitivity may be provoked by early life nutrition, these effects are rather transient and they found no evidence for sustained effects. In heavy calves, insulin sensitivity is invariably low, being rather insensitive to the carbohydrate source in the CMR (Pantophlet et al., 2016c) or to an exchange of lactose for fat (euglycemic–hyperinsulinemic clamp, (Pantophlet et al., 2016a). Large effects of dietary treatments on postprandial glucose and insulin responses, as often observed (see e.g. (Vicari et al., 2008b, a) are therefore unlikely to be caused by differences in insulin sensitivity. Pantophlet et al. (2016b) speculated that the role of insulin-independent glucose transporters such as GLUT-1 may become relatively more important with age. Indeed, despite the low insulin sensitivity in heavy calves, glucose is virtually completely oxidized, regardless of the level of feeding (Van den Borne et al., 2007). In addition, insulin peaks in calves typically follow, rather than precede glucose peaks postprandially (Vicari et al., 2008b), even in young calves (MacPherson et al., 2016, Pantophlet et al., 2016b), which differs from responses in other species and illustrates the absence of cephalic responses to a meal. Hence, insulin sensitivity appears not to be a promising target for early life metabolic programming in calves.

Following the observation that calves oxidize the vast majority of the lactose ingested, it appears that indeed the glucose is transported into the cells. Glucose concentrations often exceed the renal theshold and urinary glucose excretion is commonly observed in heavy veal calves (Hugi et al., 1997, Van den Borne et al., 2006b, Gerrits et al., 2008). Nonetheless, the quantity of glucose excreted via urine rarely exceeds 5% of the daily lactose intake and cannot be regarded a major route of glucose disposal. Unlike other farm-animal species like pigs and broiler chickens, *de novo* fatty acid synthesis from glucose is not a significant route of disposal for glucose in calves, as discussed above. Recent unpublished data in our lab indicate that in milk-fed calves of about 190 kg BW, postprandial fluxes of lactate (i.e. between 2 and 4h after a CMR meal), measured by dilution of a primed, continuous intravenous infusion of [1-^{13}C]lactate and [U-^{13}C]lactate were on average 150 g/hour, which was higher than the glucose flux (70 g/hour), measured during the same time period by dilution of a primed, continuous intravenous infusion of [2-^{13}C]glucose and [U-^{13}C]glucose. Isotopic enrichment of lactate and glucose were measured as lactate M+1, lactate M+3, glucose M+1 and glucose M+6 in plasma. These data indicate that the major portion of glucose and galactose is rapidly converted into lactate during peak absorption. In summary, in heavy milk-fed calves, due to the low insulin sensitivity, substantial quantities of glucose remain in the circulation for 2 to 6 hours after a CMR meal. Only a negligible portion is used for fatty acid synthesis, and quite likely, a major part is converted to lactate for later oxidation. To what extent these mechanisms operate in young calves remains to be elucidated, but the rapid drop in insulin sensitivity after birth suggests the lactate route may play a significant role in young calves as well. It should be noted that ad libitum availability of milk directly after birth may influence the role of lactate, as suggested by the absence of an increase (Schäff et al., 2016) or even a decrease (Frieten et al., 2017) in plasma lactate concentration in intensively milk-fed when compared with restrictedly milk-fed calves.

NUTRIENTS FROM RUMEN FERMENTATION

Rumen development is initiated upon the consumption of solid feeds, triggering the production of VFA. The importance of the composition of the solid feed, in particular the presence of coarse particles via the roughage portion of the SF fraction has been recently reviewed by Khan et al. (2016). In addition, the influence of physical form of starters has been undervalued (Kertz, 2017). The increase in SF intake with age, and thus the increasing importance of VFA in the metabolism of calves is obvious, although weaning strategies differ and there is debate to what extent the roughage portion of the SF component depresses SF intake (Khan et al., 2016).

Evaluation of the contribution of SF to the nutrient requirement of calves is complicated by the simultaneous provision of milk or CMR and SF. At the level of digestion, it is difficult to separate the contribution of the CMR to ileal or fecal excretion. When feeding incremental quantities of SF at a fixed level of feeding of CMR, Berends et al. (2012) demonstrated the apparent total tract digestibility of a SF mixture of concentrates, straw and corn silage (50:25:25 on a DM basis) to be 64 and 60% for DM and energy in calves in a BW range of 108 to 164 kg. Notably, the total tract digestibility of NDF increased significantly with BW from 46 at 108 kg BW to 56% at 164 kg BW. This increase in digestion efficiency with age or body weight was later also demonstrated by Berends et al. (2014a).

When exchanging substantial quantities of CMR for SF components during the weaning transition or during prolonged feeding of CMR as common in veal calves, the experimental design used to estimate the feeding value for these ration components becomes critical. When the studies are conducted over a large age or weight range of the calves, differences in BW between treatments may become problematic. Attempts to exchange SF for CMR, maintaining energy (or protein) intake are problematic when the digestibility, metabolizability or net energy values are not known. Quite often these are the subject of study. To this end, we used a paired-gain approach to study the feeding value of two mixtures of SF with a roughage:concentrate ratio of 50:50 or 20:80 on a DM basis (Berends et al., 2014a). Dry matter intake from SF was targeted to reach 20, 100, 180, and 260 kg of DM for four SF levels, respectively, during the 16-week experimental period, and increased with pre-planned, equal weekly increments. The quantity of CMR provided was adjusted every 2 weeks based on BW to achieve similar targeted rates of carcass gain across treatments. The reduction in CMR provided (in kg of DM) to realize equal rates of gain with inclusion of SF (in kg of DM) was considered to represent the feeding value of the SF mixture relative to the CMR. The feeding value of the 20:80 SF mixture was found to be 10% higher compared with that of the 50:50 SF mixture. The feeding value of SF relative to that of MR also increased substantially with age. This approach is suitable for estimating the nutritional value of the SF component relative to that of a CMR, typically studied over a large age or weight range. For this reason, less suited to study feeding strategies around the weaning transition.

The end-products of fermentation, absorbed from the (developing) rumen young calves can be easily metabolized in a way comparable to that of functional ruminant. As long as milk or CMR and SF are fed simultaneously, i.e. before the weaning transition or prolonged as commonly done in veal production, it is unknown to what extent interactions between nutrients absorbed from the rumen or from intestinal digestion of milk or CMR occur. Unpublished data from our lab in calves of 125 – 250 kg BW indicate identical responses of energy and nitrogen retention to incremental intakes of protein, fat and lactose from a CMR between calves fed 15 or 40% of the gross energy intake from SF in a paired-gain setting. No interactions were found between the nutrient added via the CMR and the level of SF feeding. Incremental efficiencies of fat and lactose for energy gain were both 70%, and for protein it was 40%, independent of the level of SF feeding. This indicates that nutrients absorbed from rumen fermentation and from intestinal CMR digestion may be used in an additive manner. Whether this is the also the case in young calves remains to be determined.

OUTLOOK

Combining data from heifer and veal calf studies provides a unique opportunity to characterize the potential of calves in terms of macronutrient utilization, providing interesting leads for adapting feeding strategies to altered objectives, for example increasing pre-weaning body weight gain or reducing environmental nutrient losses. The efficiency of utilizing dietary proteins for body weight gain rapidly decreases with age, rather independent of dietary amino acid composition, emphasizing the importance of adapting dietary protein concentrations with progressing age. Acknowledging the importance of energy, absorbed from the intestinal tract can contribute to further improving protein efficiency. Whereas dietary carbohydrates, absorbed from a CMR will be almost exclusively used as a fuel, dietary fat can also be deposited as body fat. A strong reduction of insulin sensitivity occurs in early life, independent of diet composition. Although this leads to a shift in the type of substrate available, it does not prevent oxidative carbohydrate metabolism. The concept of additivity of nutrients absorbed from rumen fermentation and from CMR needs further exploration when simultaneously feeding of solid feeds and CMR.

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Figure 1. Efficiency of utilization of digested N for N retention in calves with increasing body weight. All data selected are of calves fed exclusively on milk replacer containing dairy proteins as the only protein source. Data from Roy et al. (1970) ○, Gerrits et al. (1996) Δ, Labussiere et al. (2008) ●, Diaz et al. (2001) ×, Van der Togt and Gerrits (1998) ◊, unpublished ♦, Van den Borne et al. (2006b) +.