The Benefits of Feeding Methioine During the Transition Phase

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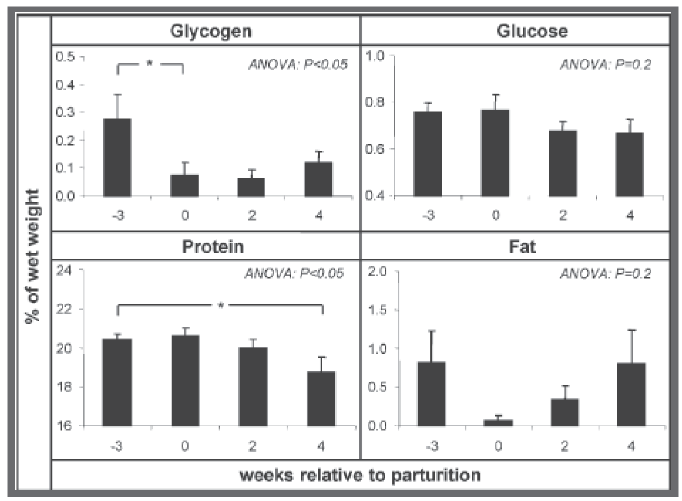
Immediately after calving, the cows are at the highest risk of suffering a disease; a high incidence of diseases during this period impacts their performance on the rest of the lactation and often, impacts their ability to reproduce normally. Since they cannot consume enough feed to keep-up with their milk production, they lose a great deal of body weight. Cows will lose over 100 pounds immediately after calving to meet the high demand for nutrients. Body weight loss after calving is normal, in fact, it is accepted that cows will lose between 0.5 and 1 point of body condition score within the first quarter of the lactation cycle.

Nutrition management during the periparturient period may have implications for the immune function and metabolic health (Waldron, 2014). During this period of negative nutrient balance, the cows mobilize body reserves, including fat, protein and glycogen for milk production, direct oxidation and hepatic gluconeogenesis. Despite much attention have been devoted to the mobilization of fatty acids and its impact on liver health, it is important to highlight that cows loose up to 44 lbs of protein during early lactation (Khula et al, 2011).

Van der Drift et al., 2012, hypothesized that much of this protein breakdown may be used as amino acid donors for liver gluconeogenesis, therefore, muscle breakdown would serve as glucose precursor during periods of negative energy balance. The authors evaluated the mobilization of muscle protein by analysis of plasma 3-methylhistidine, an indicator of muscle protein breakdown and concluded that higher mobilization of protein around calving might restrict ketone body production due to higher availability of glucogenic precursors. Khula et al. concluded that muscle and amino acid losses continually progress within the first weeks of lactation, muscle glycogen and fat storages are already exhausted immediately after parturition. The authors stated that there is a fast (within hours) allocation of glucose (from glycogen) and fatty acids and a later allocation of amino acids. Therefore, the body mass losses experienced by the cow during the transition period are due to the quick use of glycogen, and the longer and chronic use of fat and protein. While protein and amino acids losses are continuous during the first few weeks of lactation, muscle glycogen and fat storages are readily exhausted immediately after parturition (Figure 1).

Figure 1: Muscle glycogen, fat and protein content of cows (% of wet weight) during the periparturient period.



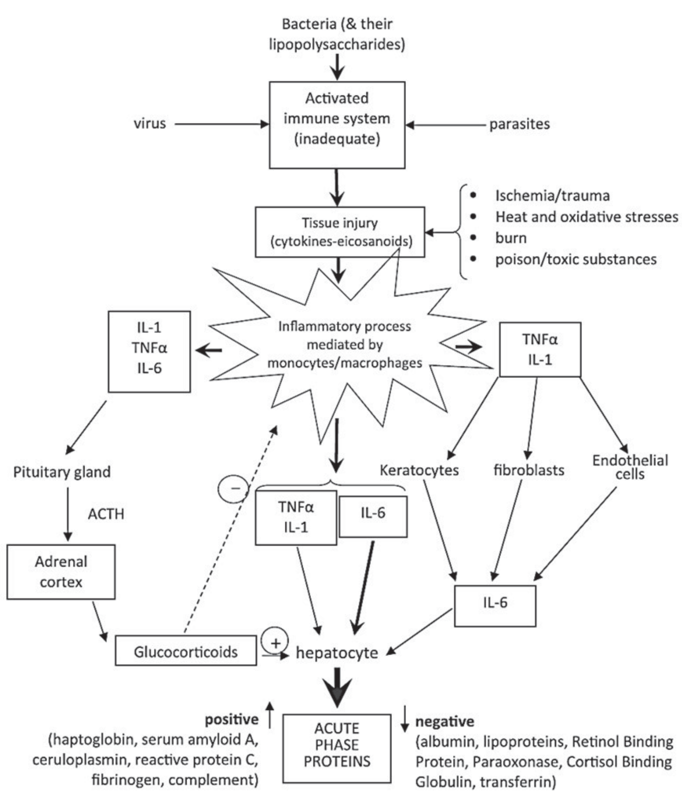
McCarthy et al. (1968) hypothesized that Methionine (Met) deficiency in ruminants may limit hepatic very-low density lipoprotein (VLDL) synthesis and be a causative factor of ketosis. Rate of hepatic VLDL synthesis was subsequently demonstrated to be lower in ruminants than monogastrics (Pullen et al., 1990). This inherent feature of ruminants is particularly important at parturition when the homeorhetic adaptations in the animal lead to marked increases in blood non-esterified acids (NEFA) which are taken up by liver, hence, increasing the susceptibility for hepatic lipidosis (Grummer, 1993).

Grummer (1993) proposed that utilization of triacylglycerol (TAG) for VLDL synthesis after parturition is impaired when the level of hepatic Met is insufficient. Feeding a diet enriched with methionine is important in the synthesis of Apoprotein B and in the synthesis of Phosphatidyl Choline, both necessary for the formation of Very Low Density Lipoproteins; that are required for ensuring transport of the fat away from the liver (Durand, 1992). More recent work has established an association between low levels of serum Met during the first 14 days postpartum and severe hepatic lipidosis (Shibano and Kawamura, 2006). The work of Dalbach et al. (2011) demonstrated that it is feasible to increase the serum concentration of Met during the first 2-weeks postpartum by feeding rumen-protected Met. This is particularly important for the animal not only because of the key role of Met in milk protein synthesis but also for intra-hepatic VLDL synthesis, production of glutathione and taurine [intracellular antioxidants; (Atmaca, 2004)], and provision of methyl groups (Finkelstein, 1990). At least in non-ruminants, the latter has been demonstrated to be an important aspect of overall Met utilization in liver namely because methylation serves as a way to regulate gene expression, protein function, and RNA processing.

Cows during the transition period are immuno suppressed (Goff, 2006) this predisposes the cow to be susceptible to infections. If the cow suffers a disease like mastitis or metritis the immune system responds with inflammation, increased body temperature, heart and respiration rate. Under such stressful conditions, reactive oxygen metabolites (ROM) are an end product of the metabolism. When present in excessive concentration, (ROM) can be toxic to the cells. Lipid peroxides are linked to systemic inflammation. They are generated when intracellular lipids react with ROM and when they are present; they are the cause of inflammation (Bradford, 2012). One of the most common ways that nutrients are involved in animal health is due to their role as antioxidants (Waldron, 2014). Severe inflammation or marginal anioxidant protection can lead to extensive tissue damage (Zhao and Lacasse, 2008).

The onset of lactation is a time when the ROM increase drastically, at least in part because of the doubling of metabolic rate in the liver. ROM are oxygen containing molecules that are chemically reactive. They are the result of normal metabolism of oxygen and the cells defend against ROM damage with enzymes referred to as “antioxidants”. Increased ROM are significant contributors (or consequence of) to systemic imflammation. Reducing the oxidative stress can only be beneficial to the cow, particulartly during the transition phase. If ROM are produced in excess and the cell’s antioxidant enzymes are unable to counteract this effect in the short-term, ROM can cause significant cellular damage. Antioxidants help the cow to control the ROM, Vitamin E and A and Se are know antioxidants and their impact on cow’s health during transition is well reported (Sordillo et al., 2009). Preventing ROM accumulation and also providing substrates for antioxidant enzymes during the transition phase may help the cow to have a healthier lactation and better overall performance. A current model of the interrelationships between

Figure 2: Current model depicting the likely causes of tissue damage (e.g. liver, rumen epithelium, mammary gland, reproductive tract) and the inflammatory response during the transition period with and without the incidence of infectious disease (Bertoni and Trevisi, 2013).

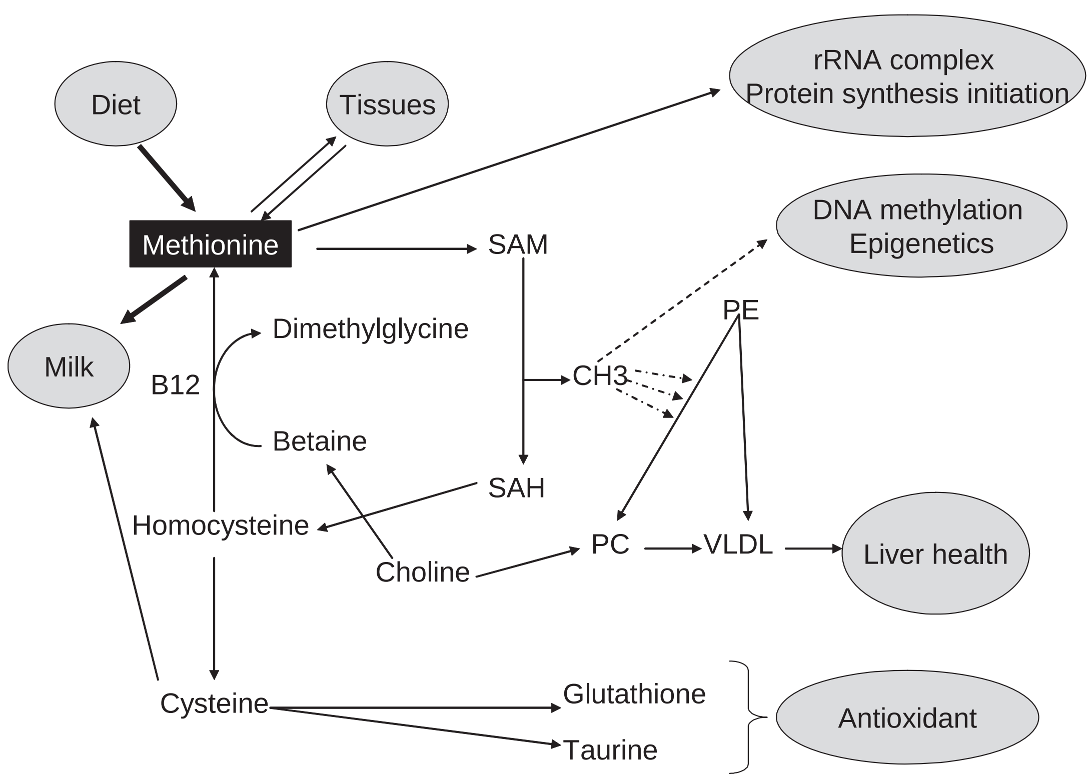


inflammation and oxidative stress was reported recently (Figure 2).

The inflammatory events induced by an infectious agent, oxidative stress, and/or their combination act directly on the liver through the pro-inflammatory cytokines including IL-6, TNFα, and IL-1. The liver (hepatocytes) has intracellular proteins (receptors) that can sense the cytokines, which upon binding to these receptors (e.g. nuclear factor kappa-beta (NFKB) responds by altering the gene expression (mRNA), and subsequently protein synthesis, of a selected group of proteins classified as the "acute-phase proteins (APP)". The so-called "positive AAP" are increased by inflammation, while the "negative APP" are decreased (Figure 2). Therefore, by following the temporal change in their concentrations we can evaluate the relative state of inflammation of cows during the transition phase.

Methionine is another well-established source of the antioxidants glutathione and taurine (Atmaca, 2004) and its antioxidant properties in other species have been demonstrated (Geumsoo et al., 2014). One of the key antioxidant enzymes in tissues, including the liver, is glutathione peroxidase. This enzyme can be derived in part via methionine (Figure 3). Preventing ROS accumulation and also providing substrates for antioxidant enzymes during the transition phase may help the cow to have a healthier lactation and better overall performance.

Figure 3: The role of methionine in the cow's metabolism



Results from a research trial that validated the impact of feeding a MET enriched diet on the oxidative stress and immune status of cows during transition were recently published (Osorio et al, 2013, 2014). Three groups of cows were fed the same basal diet from 21 days before expected calving day until 28 days after calving. One group of cows received the basal diet deficient in MET, the other two groups were fed the same basal diet enriched with one of two commercially MET sources to achieve a LYS:MET ratio of 2.8:1. The cows fed the MET enriched diets consumed an average of 4.7 extra pounds of feed per day and increased their Energy Corrected Milk (ECM) by 8.6 pounds per day during the first 28 days in milk (Table 1).

Table 1: Dry matter intake, milk, protein, fat yield and ECM from cows fed a Control and methionine enriched diets (MetaSmart and Smartamine) (Osorio et al., 2013)

	Diet			P-value*	
Parameter	Control	MetaSmart	Smartamine	Diet	Met
DMI	29.3	33.5	34.4	.18	.06
Milk yield (lb/d)	78.6	83.9	88.1	.15	.08
Milk protein (%)	3.04	3.26	3.19	.13	.05
Milk fat (%)	4.27	4.68	4.09	.59	.36
Milk protein yield (lb/d)	2.44	2.71	2.73	.08	.03
Milk fat yield (lb/d)	3.61	4.05	3.98	.11	.04
ECM (lb/d)	90.3	98.6	99.1	.09	.03

* Met: Contrast statement of Control vs. MetaSmart + Smartamine

Also, the cows fed the MET enriched diets had higher concentrations of carnitine, essential for the transport of NEFA from the cytosol into the mitochondria for subsequent fatty acid oxidation (Drackley, 1999); a tendency to lower concentration of phosphatidyl choline, important in the assembly/export of fat out of the liver via the formation of VLDL, suggesting a greater potential for liver fatty acid oxidation and a better transport of fat out of the liver via the formation of VLDL (Osorio et al, 2014). Further, the cows fed the methionine enriched diets had lower blood concentrations of Ceruloplasmin and Serum Amyloid A (both "positive APP") indicating a reduced inflammatory response, those cows also had a better antioxidant status indicated by a higher oxygen radical absorbance capacity and glutathione concentration (Table 2).

Table 2: Carnitine, Phosphatidyl Choline, Ceruloplasmin, Serum Amiloyd A, Oxygen Radical Absorbance Capacity and Glutathione from cows fed a Control or methionine enriched diet (MetaSmart or Smartamine) (Osorio et al., 2014)

	Diet			P-value*	
Parameter	Control	MetaSmart	Smartamine	Diet	Met
Carnitine, mg/L	37.5	98.2	66.0	.01	<.01
Phosphatidyl Choline, uM/g of tissue	10.6	7.7	9.1	.15	.07
Ceruloplasmin, umol/l	3.02	2.68	2.71	.03	.009
Serum amiloyd A, ug/ml	61	40.7	43.5	.17	.06
Oxigen Radical Absobance Capacity, mol/L	11.9	12.9	12.4	.05	.04
Glutathione, mM	1.27	1.55	1.73	.09	.04

* Met: Contrast statement of Control vs. MetaSmart + Smartamine

The authors concluded that the cows fed the MET enriched diets during the transition period had higher dry matter intake post-partum, produced more ECM, had a lower systemic inflammatory state, an enhanced liver function and a greater antioxidant capability.

Methionine is a key nutrient in transition cow nutrition, not only as a building block for protein synthesis but as a key intermediate to enhance the metabolic processes. This can lead to better liver function, oxidative and inflammatory status, allowing the cow to withstand the challenges of the transition phase of lactation. The results shown by Osorio et al. support the hypothesis that feeding a MET enriched diet during the transition period is beneficial to cows.

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