Feeding for a Healthy Liver: The Role of Methionine and Choline in Transition Cows

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Take Home Messages

- Choline is a quasi-vitamin that is degraded in the rumen, becoming unavailable to the cow unless supplemented in a rumen-protected form.
- Choline plays a key role in liver lipid metabolism and consistently results in increased milk yield and fat-corrected milk yield when supplemented during the transition to lactation period.
- Methionine is an essential amino acid that is available to the animal within microbial crude protein; however, that supply may not be sufficient for high producing animals.
- Methionine supplementation consistently results in an increase in milk protein yield and plays a role in mediating inflammatory response.
- Limited work has examined choline and methionine simultaneously. Data in cows and cell culture lacks evidence of a significant interaction on production outcomes or indicators of metabolic function or health, which suggests that there are unique biological roles of each nutrient.

The Transition to Lactation Period

The transition for the dairy cow from being dry to lactating is a period of metabolic challenge (Grummer, 1993; Drackley, 1999); however, this period also holds great opportunity for improvements in animal efficiency and health. Many of the challenges associated with the transition to lactation are rooted within energy balance. The voluntary feed intake reduction around the time of calving, coupled with increases in energy requirements to meet the needs of lactation, result in cows entering a state of negative energy balance (NEB) around calving. During periods of NEB, triglycerides (TG) are mobilized from fat stores and the resulting fatty acids and glycerol backbone are transported to the liver to help alleviate NEB. Glycerol can serve as a glucose precursor in the liver, and fatty acids provide milk fat precursors in the mammary gland or are oxidized for energy in the liver. Oxidation of nutrients, including fatty acids, is essential for liver cell functions, including fuelling the energetically expensive pathway of gluconeogenesis (glucose synthesis), by which most of the glucose supply in ruminant animals is generated. The onset of NEB also creates a deficiency in glucose, amino acids, and other nutrients because of low dry matter intake (DMI) during a time of elevated nutrient requirements.

Choline

Choline is a quasi-vitamin that is essential in many species and serves as a precursor for phospholipid synthesis for cell membranes and lipid (fat) transport, as a component in acetylcholine (a predominant neurotransmitter), and as a methyl donor. In nonruminant animals, choline deficiency results in fatty liver, exemplifying its importance in liver function and how it could be applicable to ruminant liver health. Understanding the benefit of choline for ruminants has largely focused on reductions of liver lipid concentration (discussed below). If not fed in a rumen-protected (RP) form, most dietary choline is degraded during rumen fermentation.

Supplementation of rumen-protected choline (RPC) to peripartum dairy cows has been of interest because of the consistent increase in yield of milk or fat-corrected milk. Meta-analyses are a useful tool that allow us to determine if a treatment has an effect across a range of environments and animals by re-analyzing data from multiple studies with similar objectives. A meta-analysis by Arshad et al. (2019), which focused on RPC supplementation and included 23 experiments (74 treatment means; 1,938 cows), demonstrated a significant increase in pre- and postpartum DMI (0.28 and 0.47 kg/d, respectively), increased energy-corrected milk (ECM; 1.61 kg/day weighted mean average), and increased fat and protein yield (0.08 and 0.06 kg/day, respectively). Benefits of RPC supplementation do not appear to be dependent on prepartum dietary energy (Zenobi et al., 2018c) or body condition score (Bollatti et al., 2019).

It is challenging to determine effects of nutritional interventions on health incidences within a single study because of limited animal numbers; therefore, another benefit of meta-analyses is to examine health events over a large pool of animals. Within the meta-analysis, incidence of retained placenta and mastitis, but not displaced abomasum, ketosis, or metritis, were reduced by RPC supplementation. Interestingly, supplementation of RPC may have benefits on production that persist beyond the supplementation period, as demonstrated by tendencies for improved milk yield at 15 and 40 weeks postpartum and improved milk components at 15 weeks postpartum after supplementation during the 3 weeks before and 3 weeks after parturition (Zenobi et al., 2018c). When supplementing prepartum, we also have the potential to influence the calf developing in utero, and improved average daily gain from calving or weaning to 50 weeks of age, and improved immune status and response to a bacterial challenge have been observed (Zenobi et al., 2018a; Zenobi et al., 2018b).

Choline can be used by many tissues within the body but metabolism is primarily within the liver (Pelech and Vance, 1984). The classically described benefit of RPC supplementation is a reduction in liver fat accumulation across the transition to lactation. A decrease in liver fat has been observed with peripartum RPC supplementation (14.4 to 15 g/day choline) in several (Cooke et al., 2007; Elek et al., 2008; Lima et al., 2012; Zom et al., 2011; Goselink et al., 2013) but not all (14.4 to 19 g/day choline) (Piepenenbrink and Overton, 2003; Zahra et al., 2006; Zhou et al., 2016c; Zenobi et al., 2018c) transition cow studies. When supplemented to dry, pregnant cows that were feed restricted to mimic the NEB aspect of the transition period, RPC supplementation lessened how much fat accumulated within the liver (Cooke et al., 2007; Zenobi et al., 2018d). When RPC was supplemented after fatty liver induction using the same model, supplementation reduced liver fat (Cooke et al., 2007), suggesting an ability of RPC to aid in recovery from fatty liver.

Choline is a key component of very low density lipoprotein (VLDL), particles that aid in transport of fat from the liver to other tissues. The mechanism of RPC action to reduce liver fat is thought to be through increased phosphatidylcholine (a component of cell membranes and VLDL) synthesis and thus increased VLDL package and export from the liver, as in nonruminants. It is very challenging to measure blood VLDL in ruminants because of the differences in lipid profile and because the mammary gland in dairy cows takes up more fat from the blood compared with the mammary gland of other species because of the greater extent of milk fat synthesis. Markers of VLDL secretion were increased in transition cows supplemented with RPC that showed reduced liver TG accumulation (Goselink et al., 2013). To narrow in on the effect of choline supplementation on VLDL export, bovine liver cells can be isolated and cultured in vitro, allowing for specific examination of many treatments and outcomes. Quantification of VLDL export from liver cells in culture by ELISA assay indicated an increase in VLDL export with increased choline supplementation (Chandler and White, 2017). In addition, recent advanced laboratory techniques have confirmed the ability of RPC supplementation to increase phosphatidylcholine concentrations in lipid-rich lipoproteins isolated from plasma of non-lactating cows (Myers et al., 2019).

Increases in milk fat yield may be reflective of increased VLDL export from the liver because the VLDL can subsequently be taken up and used by the mammary gland. Despite this, improvements in lipid metabolism may not fully explain production advantages observed with RPC supplementation because production responses have been seen without a decrease in liver fat (Zenobi et al., 2018c). Previously, it

was noted that decreased liver fat may allow for increased liver gluconeogenesis, the pathway by which the liver makes glucose (Drackley, 1999; Goselink et al., 2013). Gluconeogenesis produces glucose for release into circulation for immediate use, or as glycogen that is stored in the liver for quick release when needed. Increased liver glycogen has been observed with RPC supplementation in cows (Piepenbrink and Overton, 2003; Zenobi et al., 2018d) and liver cell culture (Chandler and White, 2019) and may reflect greater rates of gluconeogenesis. Just as supply of glucose to the mammary gland via increased hepatic glucose production can support increased milk yield, increased mammary gland lipid uptake may support improved milk or milk fat yield.

▪ Methionine

Methionine (Met) is an essential amino acid and often one of the first two limiting amino acids in dairy cow diets. It is critical to many pathways in the body and is involved in DNA methylation, creatine synthesis, and glutathione synthesis. During lactation, methionine demands increase because it is an essential amino acid for milk protein synthesis. Although dietary methionine is degraded during rumen fermentation, it is still supplied to the cow because it is a key component of microbial crude protein (protein produced by the rumen bacteria); however, high producing dairy cows likely need more methionine than microbial protein can provide.

Supplementation of Met has been through RP Met, a Met analogue 2-hydroxy-4-(methylthio)-butanoic acid (HMB), or the isopropyl ester of HMB (HMBi). Supplementing RP Met consistently results in increased milk protein yield and increased DMI (Zanton et al., 2014). This response is logical given the potentially limited supply and important role of essential amino acids for milk protein synthesis during the early postpartum period and throughout the entire lactation. Response of RP Met supplementation on milk yield is less consistent, especially during the transition period. For example, supplementation of HMBi or RP Met during the peripartum period did not affect milk yield but did increase milk protein percent in one study (Ordway et al., 2009); in another study, similar supplementation resulted in a 2.4 and 4.3 kg/day increase in milk yield for HMBi and RP Met, respectively (Osorio et al., 2013).

A key role of Met outside of amino acid function is as a methyl donor (a methyl group contains one carbon atom bonded to three hydrogen atoms; it is usually part of a larger molecule). Methionine is part of the transmethylation pathway that generates S-adenosylmethionine (SAM), the universal methyl donor of the body (Figure 1). The complexity of the figure indicates the intricate balance of methyl donation to SAM and the potential depletion of the methionine supply for other roles. After methyl group donation, Met becomes other intermediates unless it is regenerated by adding a methyl group back to the molecule via the transmethylation pathway. This regeneration requires a methyl group to be donated from another nutrient: folate, betaine, or choline (via betaine as an intermediate). Interestingly, when choline is provided in a cell culture model, expression of genes involved in transmethylation is increased, regardless of how much Met the cells are provided (Chandler and White, 2017). This highlights the priority of the cell for regenerating Met and the potential for other methyl donors to support the regeneration.

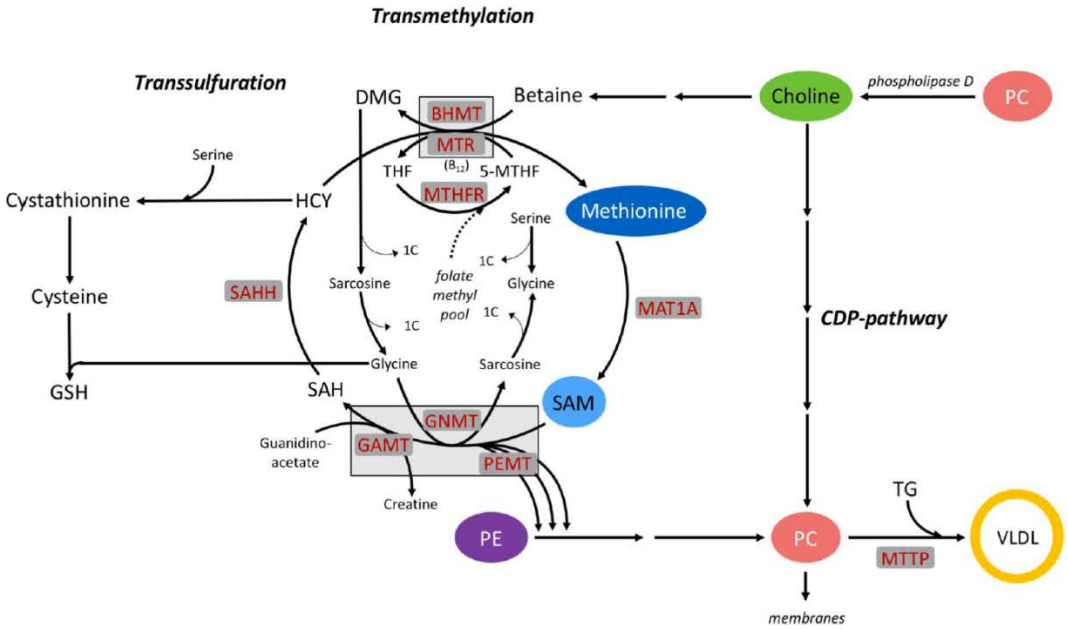

Figure 1. Intersection between pathways of choline and methionine metabolism in the transmethylation pathway. The abbreviations shown in red represent key enzymes that control methyl group transfer. Other abbreviations are: dimethylglycine (DMG), glutathione (GSH), homocysteine (HCY), S-adenosylmethionine (SAM), S-adenocylhomocysteine (SAH), tetrahydrofolate (THF), phosphatidylethanolamine (PE), phosphatidylcholine (PC), and very low-density lipoprotein (VLDL). (Chandler and White, 2017).

The methyl cycle also highlights two other potential roles for Met. In addition to generation of phosphatidylcholine from dietary choline to support VLDL synthesis, phosphatidylcholine can also be synthesized through three sequential methylations of phosphatidylethanolamine to phosphatidylcholine, known as the PEMT pathway. While both pathways are biochemically possible, the PEMT pathway is energetically expensive and relies heavily on SAM methyl-donation. Cell culture experiments measuring the key gene (*PEMT*) involved in the PEMT pathway demonstrated decreased gene expression with both Met and choline supplementation, despite increased VLDL export with choline supplementation (Chandler and White, 2017). Conversely, increased gene expression was observed with Met supplementation in one transition cow study; however, VLDL were not quantified and liver lipids did not change (Zhou et al., 2016c). Across four transition cow studies and one study involving feed restricted, non-lactating cows, Met supplementation either did not change (Bertics et al., 1999; Osorio et al., 2013; Piepenbrink et al., 2014; Zhou et al., 2016c) or increased liver lipid accumulation (Preynat et al., 2010).

Perhaps the most interesting role of Met is related to the generation of glutathione (Figure 1) and the role in inflammatory response. As a sulfur-containing amino acid, Met is the principal precursor for the synthesis of glutathione (Brosnan and Brosnan, 2006), which serves as an antioxidant. Liver concentrations of glutathione decrease postpartum and take nearly 3 weeks after calving to return to postpartum concentrations, but supplementation with RP Met increased liver glutathione concentrations (Osorio et al., 2014). Addition of Met in liver cell cultures experiments resulted in increased glutathione and decreased lipopolysaccharide-induced inflammatory response (Zhang and White, 2017). Supplementation of RP Met in transition cows also reduced markers of oxidative stress (Zhou et al., 2016a,b). These studies indicate an exciting role for Met in improving inflammatory status in transition dairy cows.

Potential Interactions between Choline and Methionine

The potential interactions between choline and Met are highlighted through the roles of each nutrient in VLDL synthesis and methyl donation. Limited transition cow studies have examined the effects of Met, choline, and the interaction of the two. In two transition cow studies where cows received either no treatment, choline, Met, or choline and Met (Sun et al., 2016; Zhou et al., 2016c), there were no significant interactions on production or markers of health. Consistently, cell culture models exposed to Met and choline across a range of treatment doses demonstrated no significant interactions on expression of key genes (either methyl donation pathways or gluconeogenesis) or metabolites (glycogen, cellular lipid, VLDL, etc.) (Chandler and White, 2017; Chandler and White, 2019). These data support separate biological priorities for choline and Met. Ultimately choline and Met both play a key role in transition cow liver health.

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