Choline and Methionine for Transition Cows: Separating Fact from Fiction

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Introduction

Research conducted on non-ruminant animals has clearly demonstrated an interrelationship between the nutrients choline and methionine, largely due to the common characteristic of them being methyl donors. In the field, there are many statements being made: e.g., choline can spare methionine, methionine can spare choline, if you feed methionine you don't need to feed choline, choline is a required nutrient for transition cows, choline is only needed for fat cows, and methionine can prevent fatty liver. These statements are largely based on research findings in non-ruminants. Is it correct to assume that these statements also hold true for transition dairy cows? The objective of this paper is to separate fact from fiction. That said, it is important to note that there is a paucity of data on the subject of choline-methionine interrelationships in ruminant animals.

Common Biology of Choline and Methionine

Dietary choline and methionine are extensively degraded in the rumen (Sharma and Erdman, 1988a), hence they must be fed in a form that minimizes ruminal degradation and maximizes flow to the small intestine. Both compounds contain methyl (**-CH_3**) groups which is the main basis for them being metabolically related. Choline is a constituent of phosphatidylcholine (**PC**) which is present in every cell membrane in the body and is a component of milk fat globule membranes. PC is also a component of lipoproteins that are responsible for transporting fat throughout the body. As a constituent of very low density lipoproteins (**VLDL**), PC is required for fat export out of the liver. Fatty liver is the classic deficiency symptom for choline deficiency, and the development of fatty liver in 50% of transition cows has been attributed to the lack of absorption of dietary choline during the transition period (Grummer, 2012).

Cows can synthesize PC endogenously, and clearly there is sufficient endogenous synthesis except during the transition period when fatty acid mobilization from adipose tissue is great and fatty acid uptake by the liver increases dramatically. Endogenous synthesis of PC occurs by methylation of phosphatidylethanolamine (**Figure 1**). The methyl groups for this can be derived from methionine. Hence the close metabolic relationship of the two compounds and the observation in non-ruminants that methionine can spare choline and choline can spare methionine.

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One of the exciting recent discoveries is that gene expression can be regulated by DNA methylation. Therefore, choline and methionine can potentially be involved in regulation of an infinite number of metabolic pathways. This area of investigation is in its infancy.

Compared to non-ruminants, very little is known about choline-methionine relationships. A classic study conducted by Emmanuel and Kennelly (1984) in lactating goats indicated that 28% of methionine was utilized for choline synthesis and 6% of the choline pool was derived from methionine. Interestingly, choline methyl groups were not used for synthesis of methionine. Sharma and Erdman (1988b) obtained greater milk production responses in dairy cattle to postruminal infusion of choline vs. methionine in the presence of a methylation inhibitor suggesting that methionine methyl groups can be used for the synthesis of choline.

Effects of Choline and Methionine on Fatty Liver

During the transition period, due to fatty acid mobilization, fatty acid uptake by the liver increases from 100 to approximately 1300 g/day (Overton, unpublished). If there is not sufficient PC to synthesize VLDL to export the fatty acids as triglyceride, fatty liver can result. Most (Cooke et al., 2007; Zom et al., 2011; Lima et al., 2012; Elek et al., 2013), but not all (Zahra et al., 2006; Zhou et al., 2016) studies indicate that feeding protected choline pre- and postpartum can reduce fat accumulation in the liver during periods of intense fatty acid mobilization. he same cannot be said for feeding protected methionine or methionine analogs. In six studies conducted thus far (Socha, 1994; Bertics et al., 1999; Piepenbrink et al., 2004; Preynat et al., 2010; Osario et al., 2013; Zhou et al., 2016), none have reported a reduction in liver fat due to methionine supplementation. Any claims that feeding protected methionine can replace feeding protected choline for prevention or treatment of fatty liver have not been substantiated. On a weight basis, choline has 4.3 times more methyl groups than methionine, therefore, it is possible that doses of methionine used in these studies were not sufficient enough to reduce fat accumulation in the liver. A second explanation may be that ruminants differ from non-ruminants in hepatic PC metabolism. More on this possibility below.

Effects of Choline and Methionine on Milk Production

A meta-analysis of thirteen studies (Grummer, 2012) in which protected choline supplementation had begun prepartum revealed increased postpartum dry matter intake (1.6 lb/day), milk yield (4.9 lb/day), fat yield (0.254 lb/day), and protein yield (0.167 lb/day). Termination of supplementation varied from calving day to 120 days postpartum, however, there was no difference in milk response for cows that were supplemented for less than thirty days postpartum versus those supplemented equal to or greater than thirty days postpartum. Interestingly, none of the studies monitored the performance of cows following supplementation. However, in a recent study (Zenobi et al., 2016) a carryover effect of feeding protected choline on milk production was observed following termination of supplementation.

A common misconception is that cows only respond to choline when diets are not "balanced" for methionine. This is clearly not true. In trials balanced for methionine (Piepenbrink and Overton, 2003; Ardalan et al., 2011; Lima et al., 2012; and Zenobi et al., 2016) the milk response has been consistent with the response derived from the meta- analysis.

A summary of trials monitoring production responses to feeding protected methionine or methionine analogs pre- and postpartum are in **Table 1** (Overton et al., 1996; Phillips et al., 2003; Piepenbrink et al., 2004; Ghorbani et al., 2007; Ordway et al., 2009; Preynat et al., 2009; Osorio et al., 2013; Zhou et al., 2016). Milk yield responses have been inconsistent. Increases in milk protein percentage have been the most consistent response seen. The most impressive responses have been in recent studies from the University of Illinois (Osorio et al., 2013; Zhou et al., 2016) in which supplemented diets have been formulated to contain metabolizable lysine:methionine ratios below 3.

Effects of Choline and Methionine on Reproduction

Several studies have observed large increases in first service conception rates when feeding protected choline (Oelrichs et al., 2004, 29 vs 58%; Shahsavari, 2012, 25 vs 40%; Zenobi et al., 2016, 24 vs 41%). However, these studies utilized few animal numbers (less than 50 per treatment) which limited statistical power. The Oelrichs study obtained a significant improvement and Zenobi study noted a tendency for improvement. Two larger studies on commercial farms observed either a nonsignificant numerical increase (Lima et al., 2012, 41 vs 48%; 165 cows per treatment) or a significant decrease (Amundson, 2014, 46 vs 40%; > 900 cows per treatment). The mechanism of action for an increase in conception rate is not known, but it may be related to a choline requirement for embryonic development.

Feeding protected methionine from calving to flushing altered gene expression in embryos; some of the changes were for genes related to embryo development and immune responses (Penagaricano et al., 2013). Embryos had greater lipid content when dams were fed protected methionine from three weeks prepartum to 30 days postpartum (Acosta et al., 2016). The researchers speculated that the improved energy status of embryos may facilitate superior embryo survival. Although first service conception rate was not affected, embryo loss following first service was reduced by feeding protected methionine from 31 to 127 days postpartum (0 vs 8.9% for control; Toledo et al., 2015). More studies are needed to evaluate the effects of supplementing methionine during the transition period on reproductive performance.

Head to Head Comparisons: Choline vs Methionine

There have been four studies that have utilized a factorial design (2 x 2; 4 treatments = control, methionine, choline, and methionine plus choline) to examine the effects of rumen protected choline and methionine on transition cows and to determine if there are any interactions between the two compounds. Ardalan et al. (2011) fed

treatments from 4 weeks prepartum to 10 weeks postpartum and observed increases in dry matter intake (3.0 and 6.9 lb/day for methionine and choline, respectively) but only choline increased milk yield (6.4 lb/day). Soltan et al. (2012) fed treatments from calving until 96 days postpartum and observed an increase in dry matter intake for choline which was greater (3.7 lb/day) when methionine was not fed than when it was fed (0.6 lb/day). Milk yield response to choline was also greater when methionine was not fed (4.2 vs 1.5 lb/day). Sun et al. (2016) did not observe interactions between feeding rumen-protected choline and methionine; choline increased dry matter intake, milk yield, and milk fat percentage while methionine increased dry matter intake, milk yield, and milk protein percentage. Finally, Zhou et al. (2016) observed no effects of choline but large effects of methionine on dry matter intake (4.6 lb/day), milk (8.8 lb/day), and milk protein percentage (0.18 units) when treatments were applied from 21 days prepartum until 30 days postpartum. The discrepancies between these studies are difficult to explain but may be related to differences in basal diets, amount and source of supplements, length of feeding, etc.

Wisconsin researchers (Chandler et al., 2015) have used liver cell cultures to study the effects of methionine and choline on metabolism. As expected, increasing concentrations of methionine in the media reduced expression of methionine synthase, an important gene controlling methionine formation. Choline had no effect. Interestingly, addition of methionine had no effect on expression of PEMT, an important gene in regulating methylation of phosphatidylethanolamine to form PC. This may be a reason why supplementing transition cows with methionine has not reduced fat accumulation in the liver. Consistent with this observation was that methionine did not enhance VLDL (i.e. fat) export from the cells (McCourt et al., 2015). These studies were the first to directly demonstrate that choline does enhance VLDL export from bovine liver cells which explains why supplementing rumen-protected choline to transition cows reduces fatty liver. Finally, oxidative stress of liver cells was reduced by choline but not by methionine.

Conclusions

Limited evidence does suggest that there are inter-relationships between choline and methionine in transition cows. Clearly, choline and methionine are both essential nutrients and both should be fed to transition cows in a rumen-protected form. Choline and methionine have unique roles and they can’t simply be substituted for one another in transition cow diets. For example, methionine increases milk protein percentage but choline apparently does not. Conversely, choline decreases liver fat but methionine, at levels tested, does not. Choline increases milk yield and methionine may as well, but initial evidence does not suggest that their effects are additive. Although more research is needed, there is sufficient evidence in the literature to clarify many of the misconceptions that are prevalent in the industry.

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Figure 1. Pathways for phosphatidylcholine synthesis.

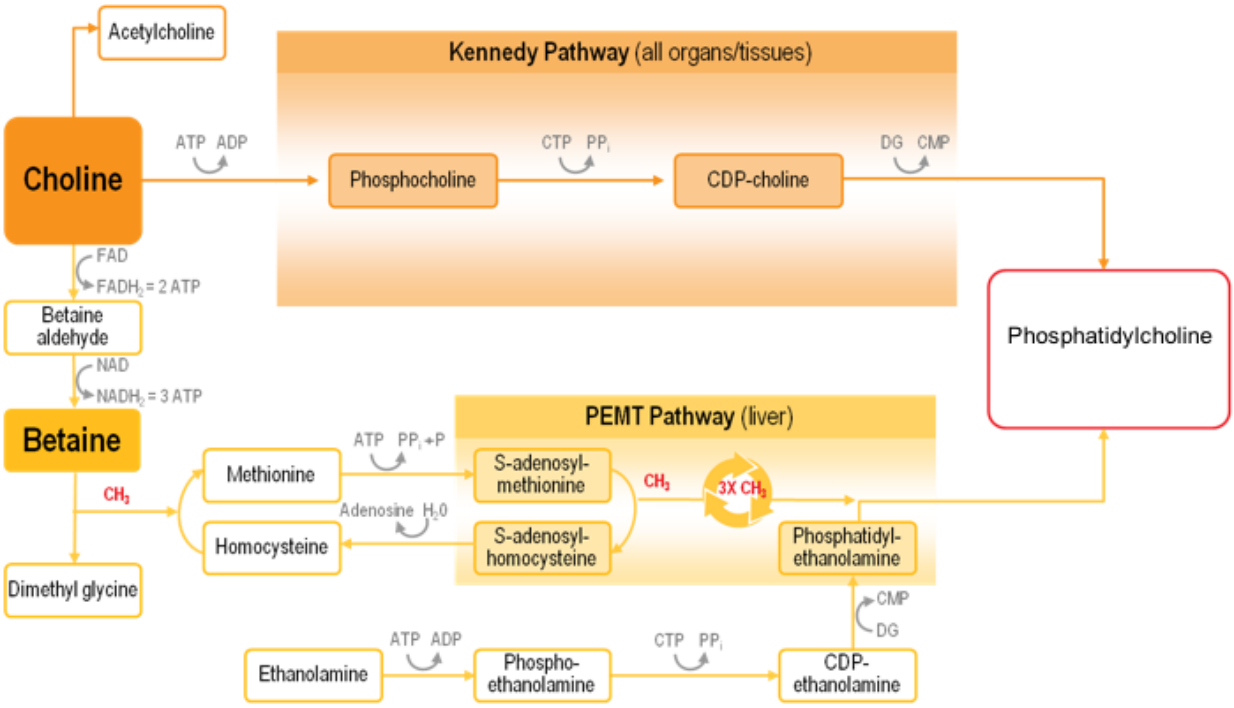

Table 1. Effects of feeding rumen-protected methionine or methionine analog during the transition period on milk yield, milk protein percentage, and protein yield.

Study	Source	Amount and duration	Milk yield, lb/d	Milk protein, %	Milk protein yield, kg/d
Overton et al., 1996	Mepron	0 vs 20 g of Met/d; -10 d to 18 wk	NS	NS	NS
Preynat et al, 2009	Mepron	Met 1.83 vs 2.23% of MP; -3 to +16 wk	NS	2.94 vs 3.04	1.106 vs 1.143
Ordway et al., 2009	Smartamine or Metasmart	SM (0.06\0.10) or MS (0.35\0.54) % of DM Pre/Post; -21 to +140 d	NS	2.72 vs 2.81 (MS) or 2.87 (SM)	NS
Ghorbani et al., 2007	Smartamine	12 (-2 to +2 wk) or 17 g of Met; +3 to +14 wk	NS	2.76 vs 2.93	NR
Osorio et al., 2013	Smartamine /Metasmart	3.4 vs 2.8:1 Lys:Met; -21d to +30d	78.6 vs 86.0 (pooled SM/MS)	3.04 vs 3.22	1.110 vs 1.235
Zhou et al., 2016	Smartamine	3.5 vs 2.9 Lys:Met; -21 d to +30 d	89.0 vs 97.4	3.14 vs 3.32	1.25 vs 1.43
Phillips et al., 2003	HMB	0 vs 20 (pre) or 50 (post) g/d; -21 to +120 d	NS	NS	NR
Piepenbrink et al., 2004	HMB	0 vs 0.09 or 0.18 (pre) or 0.13 or 0.20 (post) % of DM; -21 to +84 d	Inc. Quad 92.4, 99.0, 92.2	NS	NS

Met = methionine; Lys = lysine; MP = metabolizable protein; SM = Smartamine; MS = Metasmart; HMB = methionine hydroxy analog; NS = nonsignificant; NR = not reported; DM = dry matter; d = day; wk = week;

SESSION NOTES