Choline: A Limiting Nutrient for Transition Dairy Cows

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Introduction

Choline has been shown to be a required nutrient for many animals including rats, mice, dogs, pigs, guinea pigs, chickens, and trout. Choline is often referred to as a vitamin, however, it doesn't fit any of the classical definitions for a vitamin. It is not a co-factor in enzymatic reactions, it can be synthesized endogenously as phosphatidylcholine (PC), and it is required in larger amounts than vitamins. The ability to synthesize choline endogenously does not mean it is a dispensable or non-essential nutrient. Deficiency symptoms include suppressed growth rates, renal dysfunction, and development of fatty liver. Choline is crucial for normal function of all cells. The most common form of choline in biological systems is PC, a phospholipid that is a component of all cell membranes and lipoproteins that function to transport lipids through the circulatory system. Choline is a source of methyl groups, therefore, it can spare methionine and have interactions with other nutrients involved in one-carbon metabolism (e.g. folate). Choline is also a component of acetylcholine, an important neurotransmitter.

The NRC (2001) wrote: "The establishment of a choline requirement, either for lactating dairy cow, or a transition cow in the late dry period and in early lactation, will require more extensive feeding experiments than available at the time of this publication." It has now been 15 years since publication of the last NRC. Since publication of the last NRC, numerous studies have been conducted to examine the effects of feeding ruminally protected choline to dairy cows, particularly as they transition from the dry period to early lactation. In light of new research it seems appropriate to initiate discussion on whether choline should be considered a required nutrient in dairy diets.

Transition Cow And Choline Biology

Several studies have shown 50 to 60% of transition cows experience moderate to severe fatty liver (Bobe et al., 2004). These studies have been conducted in numerous countries across different genetic lines of cattle, different feedstuffs, and varying management systems and the data were not generated from a population of problem cows or herds . The consistency amongst these studies suggests that development of fatty liver is a "normal" part of the cow's biology. Because fatty liver is a classic deficiency symptom for choline, it is reasonable to question if transition cows are typically deficient in choline.

At calving there are hormonal changes that trigger an intense period of lipid mobilization from adipose tissue and as a result, blood nonesterified fatty acid (NEFA) concentrations typically increase 5- to 10-fold (Grummer, 1993). NEFA remain elevated, although to a lesser extent, during early lactation when cows experience negative energy balance. Blood flow to the liver doubles as a cow transitions from the dry period to lactation (Reynolds et al., 2003). NEFA concentration and blood flow are the two biggest factors affecting how much NEFA is taken up

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by the liver. As a result, daily fatty acid uptake by the liver increases and estimated 13-fold at calving, from approximately 100 to 1300 g/day (Overton, unpublished). Not all of the fatty acids taken up by the liver will be stored and contribute to fatty liver. However, Drackely (2001) estimated that during peak blood NEFA concentration, approximately 600 g might be deposited in 24 hours, which would correspond to an increase in liver fat of 6-7% by weight. As a reference, fat above 5% in the liver (wet basis) is considered by the veterinary community to be moderate to severe fatty liver. It is important to understand that this dramatic increase in NEFA uptake by the liver is part of the normal biology of transition cows and is not restricted to fat cows, poorly fed cows, or cows housed in suboptimal environments.

The most desirable fate of fatty acids entering the liver would be complete oxidation to provide energy to the liver or reesterification and export as triglyceride from the liver as part of a very low density lipoprotein (VLDL). Hepatic oxidation increases approximately 20% during the transition period (Drackley et al., 2001). This increase does not represent a strategic move by the cow's liver to cope with the sudden surge of NEFA uptake at calving. It occurs because the liver becomes metabolically more active. Unfortunately, the increase in oxidation is not sufficient to cope with the increased load of fatty acid being presented to the liver. Research conducted nearly 25 years ago at the University of Wisconsin (Kleppe et al., 1988) and Michigan State University (Pullen et al., 1990) revealed that ruminants have a low capacity to export triglyceride from the liver as very low density lipoprotein (VLDL) as compared to nonruminants. This and the inability to markedly increase fatty acid oxidation is why transition dairy cattle develop fatty liver when experiencing elevated blood NEFA.

It is now apparent that choline deficiency is a limiting factor for VLDL triglyceride export from the liver. It has been shown in many species, using a wide variety of experimental approaches, that rate of VLDL export is highly related to the rate of hepatic PC synthesis (Cole et al., 2012). Models include monograstrics fed choline deficient diets, isolated hepatocytes cultured in choline and methionine deficient media, and in knock out mice for genes involved in PC synthesis (Cole et al., 2012).
Interestingly, there is no evidence that synthesis of any other phospholipid is required for hepatic VLDL assembly and secretion. In addition to direct PC synthesis from dietary choline, there is endogenous hepatic synthesis of PC via methylation of phosphotidylethanolamine (PE). Sharma and Erdman (1988) demonstrated dietary choline is extensively degraded in the rumen of dairy cows and very little is available to the small intestine for absorption. Choline flow to the duodenum increased less than 2 g/day, even when free choline intake was increased to more than 300 g/d. Therefore, ruminants are more highly dependent than nonruminants on endogenous synthesis of PC from PE. Is endogenous synthesis of PC from PE sufficient during the transition period or do cows require choline supplementation? The high proportion of transition cows developing moderate to severe fatty liver during the transition period suggests that endogenous synthesis is not sufficient in many cows.

Evidence for a Choline Deficiency in Transition Dairy Dows

The first piece of evidence that transition cows are deficient in choline is the development of fatty liver during the periparturient period (Grummer, 1993; Bobe et al., 2004). More compelling evidence is the alleviation of fatty liver when supplying cows with choline that is protected from ruminal degradation (Cooke et al., 2007; Zom et al., 2011). Dutch researchers (Goselink et al., 2013) recently demonstrated greater gene expression for microsomal triglyceride transfer protein (MTTP) in liver of transition cows supplemented with rumen-protected choline (RPC). MTTP is an important protein required for hepatic VLDL synthesis. Recently, it was shown that choline, but not methionine, increases VLDL secretion from primary bovine (McCourt et al., 2015). This provided solid evidence that choline limitation is a causative factor for inadequate fat export out of the liver.

The reduction in liver fat content when feeding transition cows RPC is accompanied by improved health and production. Lima et al. (2012) observed reduced incidences of clinical ketosis, mastitis, and morbidity when feeding RPC from 25 days prepartum to 80 days postpartum. It has been known for years that elevated fat in the liver is associated with poor reproductive performance (Bobe et al., 2004). First service conception rate was increased by feeding RPC in one study (Oelrichs et al., 2004) but not another (Lima et al., 2012). I (Grummer, 2012) completed a meta-analysis for 13 studies that fed RPC to transition cows. Feed stability or evidence of bioavailability of choline source was not a criterion for study selection. Studies were not screened for "soundness" of research. Treatment means and sample size (standard error of the mean) had to be available for the analysis. Ten of the thirteen trials were published in peer-reviewed journals. For studies to be included in this analysis, RPC had to be fed ***prior*** to calving. Time when RPC supplementation was started varied between 28 to 7 days prior to expected calving. RPC supplementation was terminated anywhere from the day of calving (one study) to 120 days in milk. Response variables included DMI, milk yield, energy corrected milk yield, fat %, protein %, and fat and protein yield. Insufficient data was available for analysis of liver fat or energy-related blood parameters. Analysis revealed a significant increase of 4.9 lb milk/day and 1.6 lb of dry matter intake/day (Table 1). Milk fat and protein percentage were not significantly affected by treatment but yields were (Table 1). These studies were conducted in several countries under a variety of management conditions and they did not target problem herds or cows. This implies that benefits to supplementing protected choline can be realized by a wide variety of herds. Alleviating a choline deficiency not only reduces liver fat but also improves parameters that are economically important to dairy producers.

Table 1. A Meta-analysis of 13 studies examining the effects of feeding RPC to transition cows on dry matter intake and milk.

	Control	RPC	SEd	P =
DMI, lb/d	39.98	41.60	.46	.0042
Milk, lb/d	70.88	75.75	.75	<.0001
ECM, lb/d	76.87	82.78	1.33	.0038
Fat yield, lb/d	2.788	3.042	.086	.021
Protein yield, lb/d	2.300	2.467	.053	.010

Can Protected Methionine Substitute For Protected Choline?

Protected methionine has often been suggested as a possible alternative to protected choline for supplementation to transition dairy cows. Methionine and choline both serve as methyl donors. Methionine methyl groups can be used for endogenous synthesis of PC from PE. As an amino acid, methionine is needed for the synthesis of apolipoproteins. Therefore, there is a conceptual basis for methionine substitution for choline. Six feeding trials have been conducted to examine the effects of rumen-protected methionine or methionine analog on liver total lipid or triglyceride content and none of them showed a reduction (Socha, 1994; Bertics et al., 1997; Piepenbrink et al., 2004; Preynat et al., 2010; Osorio et al., 2013; Zhou et al., 2016).

The reason for methionine's failure to prevent fatty liver in transition cows is not known. One explanation may be that the studies cited above employed insufficient doses of protected methionine or methionine analog. Choline contains three methyl groups while methionine only contains one methyl group. When differences in molecular weight between choline and methionine are accounted for, choline by weight is 4.3 times more "potent" than methionine as a methyl donor. Therefore, assuming equal bioavailability of the rumen-protected products being fed, one could speculate that one would need to feed 64.5 g/d of methionine during the transition period to obtain a similar amount of methyl groups as when feeding 15 g/d of choline. As previously mentioned, choline, but not methionine, increases VLDL secretion from primary bovine hepatocytes (McCourt et al., 2015).

Conclusions

Since the last NRC (2001) publication, a significant body of evidence has accumulated to support choline being a required but limiting nutrient in transition cow diets. There is overwhelming evidence that feeding transition dairy cows 15 g choline/day in a form that is protected from ruminal degradation will alleviate choline's classic deficiency symptom and lead to improvements in health and performance.

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