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Effects of supplementing rumen-protected niacin on fiber composition and metabolism of skeletal muscle in dairy cows during early lactation

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ABSTRACT

Nicotinic acid (NA) has been shown to induce muscle fiber switching toward oxidative type I fibers and a muscle metabolic phenotype that favors fatty acid (FA) utilization in growing rats, pigs, and lambs. The hypothesis of the present study was that supplementation of NA in cows during the periparturient phase also induces muscle fiber switching from type II to type I fibers in skeletal muscle and increases the capacity of the muscle to use free FA, which may help to reduce nonesterified fatty acid (NEFA) flow to the liver, liver triglyceride (TG) accumulation, and ketogenesis. Thirty multiparous Holstein dairy cows were allocated to 2 groups and fed a total mixed ration without (control group) or with ∼55 g of rumen-protected NA per cow per day (NA group) from 21 d before expected calving until 3 wk postpartum (p.p.). Blood samples were collected on d −21, −14, −7, 7, 14, 21, 35, and 63 relative to parturition for analysis of TG, NEFA, and β-hydroxybutyrate. Muscle and liver biopsies were collected on d 7 and 21 for gene expression analysis and to determine muscle fiber composition in the musculus semitendinosus, semimembranosus, and longissimus lumborum by immunohistochemistry, and liver TG concentrations. Supplementation of NA did not affect the proportions of type I (oxidative) or the type II: type I ratio in the 3 muscles considered. A slight shift from glycolytic IIx fibers toward oxidative-glycolytic fast-twitch IIa fibers was found in the semitendinosus, and a tendency in the longissimus lumborum, but not in the semimembranosus. The transcript levels of the genes encoding the muscle fiber type isoforms and involved in FA uptake and oxidation, carnitine transport, tricarboxylic acid cycle, oxidative phosphorylation, and glucose utilization were largely unaffected by NA supplementation in all 3 muscles. Supplementation of NA had no effect on plasma TG and NEFA concentrations, liver TG concentrations, and hepatic expression of genes involved in hepatic FA utilization and lipogenesis. However, it reduced plasma β-hydroxybutyrate concentrations in wk 2 and 3 p.p. by 18 and 26% and reduced hepatic gene expression of fibroblast growth factor 21, a stress hormone involved in the regulation of ketogenesis, by 74 and 56%. In conclusion, a high dosage of rumen-protected NA reduced plasma β-hydroxybutyrate concentrations in cows during early lactation, but failed to cause an alteration in muscle fiber composition and muscle metabolic phenotype.

Key words: niacin, muscle fiber, lactating dairy cow, ketogenesis

INTRODUCTION

During the periparturient phase, high-yielding dairy cows are typically in a strong negative energy balance (**NEB**) as food intake capacity in this phase is limited and the amount of energy consumed does not meet the high requirement of maintenance and milk production. Negative energy balance leads to mobilization of nonesterified fatty acids (**NEFA**) from adipose tissue that are released into the blood. The major part of NEFA released from adipose tissue is taken up by the mammary gland and used for the synthesis of milk fat. Approximately 25% of the NEFA passing through hepatic circulation are taken up by the liver (White, 2015). Part of these NEFA is subjected to β-oxidation in the liver. However, as the capacity of β-oxidation in the liver is limited during the periparturient phase, a part of the NEFA is also incorporated into triglycerides (**TG**), which under physiological conditions are secreted into the blood via very low density lipoproteins (**VLDL**).

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However, as the capacity for synthesis and secretion of VLDL in the liver in dairy cows is also limited during this period, TG are accumulating in the liver. Consequently, liver TG concentrations increase after parturition, which can impair liver function and result in fatty liver development (Hocquette and Bauchart, 1999; White, 2015). The development of a fatty liver is of high clinical relevance in dairy cows because it not only impairs liver function but also increases the risk of other diseases such as ketosis (Bobe et al., 2004). It has been well established that concentrations of NEFA in plasma are directly linked with the development of fatty liver in dairy cows (Hocquette and Bauchart, 1999). Although NEFA are an important energy source in early lactation, an excessive NEFA supply to the liver will overburden its oxidative capacity, which is frequently found in early-lactating dairy cows (White, 2015). Therefore, nutritional strategies to counteract the development of a fatty liver in dairy cows should consider possibilities to lower plasma NEFA concentrations to a certain degree during the periparturient phase.

Nicotinic acid (**NA**) is a water-soluble vitamin that is involved in the metabolism of carbohydrates, fats, and proteins. However, NA in high dosages is also known to decrease concentrations of lipids, including TG and low-density lipoprotein, and to increase concentrations of high-density lipoprotein in the plasma of humans (Barter and Rye, 2016; Feingold and Grunfeld, 2017). It is known that NA, when binding to its receptor GPR109A, renamed hydroxy-carboxylic acid receptor 2 (**HCAR2**), inhibits adipose tissue lipolysis (Wise, 2003; Offermanns, 2006), which reduces the supply of NEFA for hepatic TG synthesis and hepatic VLDL assembly (Wang et al., 2001; Offermanns, 2006). A reduction in plasma NEFA concentrations has been confirmed in feed-restricted dairy cows when NA was infused postruminally, and the expected NEFA rebound occurred after NA infusion was terminated (Pires and Grummer, 2007). Although oral feeding of non-rumen-protected NA has yielded contradictory data concerning its effects on plasma NEFA concentrations, possibly because too low NA amounts were entering the bloodstream (Niehoff et al., 2009), feeding rumen-protected NA has been shown to reduce plasma NEFA concentrations in early-lactating dairy cows (Yuan et al., 2012). However, NA also has effects that are independent from activation of the HCAR2 receptor, such as, for example, its effect on plasma lipids (Feingold and Grunfeld, 2017). Therefore, the classic view that NA influences hepatic lipid metabolism mainly due to an inhibition of adipose tissue lipolysis has been put into question (Choi et al., 2011).

We have recently observed that high dosages of NA, resembling those required to achieve lipid lowering effects in humans, caused a shift from the glycolytic, fast-twitch type II fibers to oxidative slow-twitch type I fibers in various skeletal muscles of growing rats, pigs, and sheep (Khan et al., 2013a,b; Ringseis et al., 2013). In line with the fact that type I fibers are rich in mitochondria, exhibit high activities of oxidative enzymes, and mainly use fatty acids for energy production, the animals treated with NA showed an increased expression of genes involved in fatty acid uptake, mitochondrial fatty acid import, and oxidation and oxidative phosphorylation in skeletal muscles (Khan et al., 2013a,b; Ringseis et al., 2013). In parallel with the increased proportion of oxidative type I fibers, NA also induced an upregulation peroxisome proliferator-activated receptor δ (**PPARD**) and PPAR-γ coactivator-1-α (**PPARGC1A**), transcription factors that are key regulators of muscle fiber composition, mitochondrial biogenesis, fatty acid oxidation, oxidative phosphorylation, and angiogenesis (Wang et al., 2004; Schuler et al., 2006). This finding suggests that muscle fiber transition from type II to type I in animals treated with NA was caused by an induction of genes encoding critical regulators of muscle fiber composition, such as PPARD and PPARGC1A. In obese rats, NA treatment caused also a strong reduction of plasma NEFA concentration, associated with lower concentrations of TG in plasma and liver (Ringseis et al., 2013). It is likely that reduced plasma NEFA concentrations in the rats treated with NA were, at least in part, due to increased utilization of fatty acids in skeletal muscle, which significantly contributes to whole-body fatty acid utilization.

In the present study, we investigated the hypothesis that treatment of periparturient cows with high dosages of NA causes a muscle fiber switch in skeletal muscle similar to that observed in rats, pigs, and sheep (i.e., an increase of oxidative type I fibers at the expense of glycolytic type II fibers). Such an effect might be favorable in dairy cows as it is expected that an increase in type I fibers might enhance the uptake of NEFA released from adipose tissue into the skeletal muscle and the utilization of NEFA by β-oxidation. An increased uptake of NEFA into the skeletal muscle might lead to a reduction of plasma NEFA concentration and in turn to a reduced uptake of NEFA into the liver causing a decrease in TG accumulation and ketogenesis.

MATERIALS AND METHODS

The study was carried out at the Educational and Research Centre for Animal Husbandry Hofgut Neumühle (Münchweiler an der Alsenz, Germany). All