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Whole-body propionate and glucose metabolism of multiparous dairy cows receiving folic acid and vitamin B_{12} supplements

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ABSTRACT

This study was undertaken to evaluate the effect of supplementation of folic acid and vitamin B_{12} on glucose and propionate metabolism. Twenty-four multiparous cows were assigned according to a complete block design in a 2 × 2 factorial arrangement to one of the following treatments: (1) saline 0.9% NaCl, (2) 320 mg of folic acid, (3) 10 mg of vitamin B_{12}, or (4) 320 mg of folic acid and 10 mg of vitamin B_{12}. Intramuscular injections were given weekly from 3 wk before the expected calving date until 9 wk postpartum. At 63 d in milk, D-[6,6-$^{2}H_2$]-glucose (16.5 mmol/h; jugular vein) and [1-^{13}C]-sodium propionate (13.9 mmol/h; ruminal vein) were simultaneously infused for 4 h; blood samples were collected from 2 to 4 h of the infusion period. Liver biopsies were carried out the following day. Supplements of folic acid and vitamin B_{12} respectively increased folate and vitamin B_{12} concentrations, both in milk and liver. Although dry matter intake was unaffected by treatments, milk and milk lactose yields tended to be lower by 5.0 and by 0.25 kg/d, respectively, for cows receiving the folic acid supplement. Plasma β-hydroxybutyrate concentration with the folic acid supplement followed the same tendency. Hepatic gene expression of methylmalonyl-CoA mutase and S-adenosylhomocysteine hydrolase was higher for cows receiving the combined folic acid and vitamin B_{12} supplement compared with cows receiving only the supplement of folic acid, whereas no treatment effect was noted for cows not receiving the folic acid supplement. Whole-body glucose rate of appearance and the proportion of whole-body glucose rate of appearance secreted in milk lactose decreased by 229 g/d and 5%, respectively, for animals receiving the folic acid supplement, concomitant with the lower milk lactose synthesis in these cows, indicating that supplementary folic acid may alter energy partitioning in cows. The absence of treatment effect on plasma concentrations of methylmalonic acid as well as on the proportion of glucose synthesized from propionate, averaging 60%, supports the fact that vitamin B_{12} supply was sufficient in control cows in the current study. Our results suggest that the folic acid supplement reduced glucose-derived lactose synthesis by redirecting glucose for other metabolic activity in the mammary gland or in other tissues.
Key words: dairy cow, folic acid, vitamin B_{12}, propionate, glucose

INTRODUCTION

The transition from late gestation to early lactation represents a challenge for high-yielding dairy cows. Major metabolic, physiological, and nutritional changes occur at parturition and the onset of lactation (Goff and Horst, 1997). Detrimental health effects may be induced by excessive negative energy balance in dairy cows coping with this challenging period (McArt et al., 2013). Previous studies concluded that a combined supplement of folic acid and vitamin B_{12} seems to improve the efficiency of energy metabolism in early lactation (Girard and Matte, 2005; Graulet et al., 2007; Preynat et al., 2009b) as suggested by the enhancement of lactational performance without a DMI increase for cows receiving the combined vitamin supplement.

In lactating cows, approximately 20% of glucose supply is provided through glucose absorption into the hepatic portal vein following starch digestion, whereas the remaining originates from gluconeogenesis (Galindo et al., 2011). In fed cows, propionate is the major precursor of glucose and liver removal of propionate contributes up to 60% of glucose hepatic release (Reynolds, 2006; Larsen and Kristensen, 2013). Before entering into the Krebs cycle, propionate needs to be transformed into propionyl-CoA, then into methylmalonyl-CoA, and, finally, into succinyl-CoA (Scott, 1999; Preynat et al., 2010). The latter transformation is vitamin B_{12}-dependent, the vitamin playing a role of coenzyme for

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methylmalonyl-CoA mutase (EC 5.4.99.2). In case of a vitamin B_{12} deficiency, methylmalonyl-CoA accumulates and is instead converted into methylmalonic acid (Scott, 1999).

In a previous study, increased plasma glucose was observed for multiparous cows in early lactation receiving a combined dietary supplement of folic acid and vitamin B_{12}, whereas no effect was noted for cows receiving only a vitamin B_{12} supplement (Graulet et al., 2007). Moreover, in multiparous cows at 87 DIM, weekly intramuscular injections of a combined supplement of folic acid and vitamin B_{12} increased the rate of appearance (**Ra**) of glucose by 160 g/d (Preynat et al., 2009a). The glucose Ra represents the sum of glucose entry rates into the plasma pool from portal absorption, glycogenolysis, and gluconeogenesis. Preynat et al. (2009a) hypothesized that this increase was likely due to an enhanced gluconeogenesis caused by the combined vitamin supplement. Differences in glucose absorption and glycogenolysis were discarded as being the cause of the increased glucose Ra as DMI was similar between treatments and no study reports an effect of a combined supplement of folic acid and vitamin B_{12} on glycogen kinetics (Preynat et al., 2009a).

Vitamin B_{12} also acts as a coenzyme in the methylation cycle (Figure 1) and is closely interrelated with folate metabolism. Indeed, 5-methyl-tetrahydrofolate, the methylated form of folic acid, can give its methyl group to homocysteine (**Hcy**) to form Met using vitamin B_{12} as a coenzyme of Met synthase (EC 2.1.1.13). Methionine could be used to form proteins or could be transformed into S-adenosylmethionine, which is the major methyl donor in mammals (Scott, 1999). After its demethylation, tetrahydrofolate might be involved in purine and pyrimidine syntheses, both DNA components. Consequently, a lack of folic acid and vitamin B_{12} impedes cell division (Scott, 1999).

It was hypothesized that increasing folic acid and vitamin B_{12} supplies would facilitate propionate entering into the Krebs cycle and then would increase gluconeogenesis. This study was undertaken to evaluate whole-body (**WB**) kinetics of glucose and propionate and the proportion of glucose synthesized from propionate at 9 wk of lactation following a supplementation of

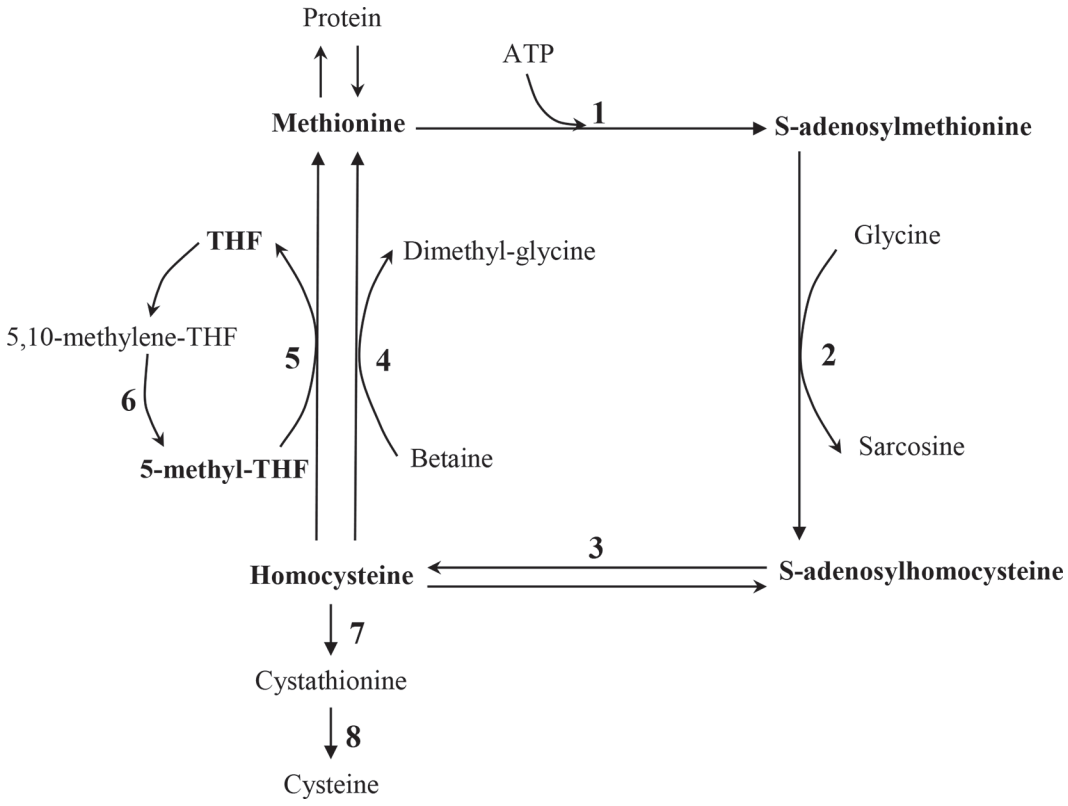

Figure 1. Simplified metabolic pathways involving folic acid and vitamin B_{12}. Enzymes: 1 = methionine adenosyltransferase; 2 = glycine *N*-methyltransferase; 3 = adenosylhomocysteinase; 4 = betaine homocysteine methyltransferase; 5 = methionine synthase and vitamin B_{12} as a coenzyme; 6 = 5,10-methylenetetrahydrofolate reductase; 7 = cystathionine β-synthase; and 8 = cystathionine β-lyase (adapted from Preynat et al., 2010). THF = tetrahydrofolate.