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Abstract

Creatine stores energy in muscles as high-energy phosphate bonds. Creatine is endogenously synthesized in the liver through the methylation of guanidinoacetic acid. We hypothesized that provision of guanidinoacetic acid, the precursor to creatine, would increase creatine supply to the body and improve animal production. Because increased synthesis of creatine will increase methyl group consumption, an adequate supply of methyl groups might improve the benefits of guanidinoacetic acid supplementation. This study was to determine whether guanidinoacetic acid supplementation could improve lean tissue deposition (growth) and whether an additional methyl group source (methionine) was required to optimize the response to guanidinoacetic acid. Ruminally-cannulated steers were housed in metabolism crates to allow complete collection of feces and urine for calculation of nitrogen retention. The experiment included six 10-day periods, and each animal received one of the 6 different treatments in each period. The 6 treatments were supplementation of 0, 7.5, or 15 g/day of guanidinoacetic acid each in the presence or absence of 6 g/day supplemental L-methionine. Supplementation of guanidinoacetic acid increased plasma creatine concentrations, demonstrating that the cattle converted guanidinoacetic acid to creatine. Responses to guanidinoacetic acid for lean tissue deposition were dependent on the methionine status of the steers. When methionine was supplemented to steers, there was an increase in nitrogen retention when 15 g/day of guanidinoacetic acid was provided. In contrast, supplemental guanidinoacetic acid did not improve nitrogen retention when no methionine was supplemented. The growth-enhancing effect of guanidinoacetic acid supplementation indicates a direct means of increasing beef production, although further research is required to confirm benefits.

Introduction

Creatine serves as an energy source for muscles by storing energy in high-energy phosphate bonds. Creatine is endogenously synthesized in the liver through the methylation of guanidinoacetic acid, the precursor to creatine that can be synthesized in the kidney. Both creatine and guanidinoacetic acid can also be absorbed from the diet. The requirement for creatine is considerable in growing animals, and its provision in the diet has the potential to increase performance. Production of guanidinoacetic acid is typically the rate-limiting step in the endogenous synthesis of creatine by the body; therefore,

supplementation of creatine or creatine precursors such as guanidinoacetic acid can be beneficial to increase creatine in the body. Previous studies have shown increases in growth and yield of breast meat in chickens and muscle mass in humans when creatine was supplemented to the diet. In recent years, creatine use as a dietary supplement has been widespread among athletes to maximize exercise performance.

Methionine acts as a methyl donor and typically is the most limiting amino acid for beef and dairy cows. Although cattle might benefit from increased creatine synthesis, the increased synthesis of creatine will increase methyl group consumption, which might lead to methyl group deficiency in the animal. Therefore, an adequate supply of methyl groups might improve the benefits of guanidinoacetic acid supplementation on growth, because methionine also has an important function in protein synthesis. However, to our knowledge, there are little data available about creatine utilization by cattle and no data are available regarding the ability of guanidinoacetic acid to increase the lean growth rate of cattle. In a preliminary study with guanidinoacetic acid using growing Holstein heifers, we observed that large doses of guanidinoacetic acid could be provided to cattle without any signs of toxicity under conditions where methionine was not likely to be limiting. This research evaluated the effects of guanidinoacetic acid supplementation under conditions where methionine was limiting. The purpose of this study was to determine whether guanidinoacetic acid supplementation could improve lean tissue deposition (growth) in a model where cattle were purposefully maintained under conditions of a methionine deficiency.

Experimental Procedures

Seven ruminally-cannulated Holstein steers (355-lb initial body weight) were housed in metabolism crates to allow complete collection of feces and urine for calculation of nitrogen retention. Cattle had free access to water and were limit-fed twice daily. All steers received 6 lb of dry matter daily of a diet designed to provide deficient amounts of methionine. The diet contained 82% soybean hulls, 8.5% wheat straw, 4.2% molasses, and 5.1% of a vitamin/mineral premix. The methionine deficiency was reinforced by supplementing energy via volatile fatty acid infusions into the rumen (0.66 lb/day) and glucose infusions into the abomasum (0.73 lb/day). Both infusions increase energy supply without increasing methionine supply. Additionally, all steers received an abomasal infusion of all essential amino acids except methionine to ensure that amino acids other than methionine did not limit performance.

The experiment included six 10-day periods, with 4 days for initial adaptation and 6 days for sample collection, and each animal received one of the 6 different treatments in each period. The 6 treatments were supplementation of 0, 7.5, or 15 g/day of guanidinoacetic acid each in the presence or absence of 6 g/day supplemental L-methionine. Methionine was included in the treatment structure because it provides the methyl group used for the conversion of guanidinoacetic acid to creatine. Urine and feces samples were collected daily from days 5 through 10 of each period to measure nitrogen retention, and blood samples were collected from the jugular vein from each steer on days 6, 8, and 10 of each period for analyses of creatine. On day 10 of each period, jugular catheters were placed for infusion of labeled methionine to allow measurement of whole body methionine methyl flux.

Results and Discussion

Nitrogen retention, a measure of lean tissue growth, was significantly elevated by methionine supplementation (Figure 1; $P < 0.01$); this response to methionine was expected because methionine was deficient by design. Responses to guanidinoacetic acid for lean tissue deposition were dependent on the methionine status of the steers. When methionine was supplemented to steers, there was an increase in nitrogen retention when 15 g/day of guanidinoacetic acid was provided. The lack of a nitrogen retention response to 7.5 g/day of guanidinoacetic acid might have been due to an offsetting decrease in endogenous production of guanidinoacetic acid, which was expected to be near 7.5 g/day. Therefore, at the supplementation level greater than endogenous production (i.e., 15 g/day), the increase in total guanidinoacetic acid/creatine availability seemed to improve animal production. In contrast, supplemental guanidinoacetic acid did not improve nitrogen retention when no methionine was supplemented (Figure 1). When methionine was not supplemented (i.e., methionine was deficient), the lack of response to guanidinoacetic acid might have been due to the guanidinoacetic acid consuming methionine for the production of creatine. Under conditions of a poor methionine status, increases in creatine production may not be able to improve cattle growth. These observations provide a starting point for further research on the effects of guanidinoacetic acid supplementation on increasing lean tissue deposition in growing cattle.

By increasing the supply of guanidinoacetic acid, plasma creatine concentrations increased linearly (Figure 2; $P < 0.01$). The increases in plasma creatine in response to guanidinoacetic acid supplementation can be attributed to conversion of guanidinoacetic acid to creatine in cattle. Steers supplemented with methionine had lower concentrations of plasma creatine. This may be attributable to enhanced tissue growth in response to methionine, which could lead to an increased uptake of creatine into muscle.

The consumption of methyl groups from methionine (Figure 3) was increased by guanidinoacetic acid supplementation when no supplemental methionine was provided, suggesting that the guanidinoacetic acid increased use of methionine to provide methyl groups for creatine synthesis. However, the flux of methionine methyl groups was not affected by guanidinoacetic acid supplementation when supplemental methionine was provided. This may be because the steers receiving supplemental methionine had enough readily available methyl groups from the supplemental methionine to prevent creatine synthesis from being a major drain on the body's methyl group supplies.

Implications

Supplementation of guanidinoacetic acid (15 g/day) in the presence of supplemental methyl groups (as methionine) tended to increase nitrogen retention, demonstrating that tissue growth was stimulated by post-ruminal guanidinoacetic acid supplementation. The growth-enhancing effect of guanidinoacetic acid supplementation indicates a direct means of increasing beef production, although further research is required to confirm benefits.

Supplementation of guanidinoacetic acid elevated plasma creatine concentration, demonstrating that guanidinoacetic acid supplementation can be an effective way to increase creatine supply to cattle. Supplementation of methionine decreased plasma creatine concentration, perhaps indicating that the greater tissue growth in response to methionine supplementation resulted in increased muscle creatine uptake.

In the absence of supplemental methyl groups, supplementation of guanidinoacetic acid increased methionine methyl group flux, suggesting that guanidinoacetic acid might increase methionine methyl group utilization for creatine synthesis. In contrast, when methionine was supplemented, methionine methyl group flux was not affected by supplementation with guanidinoacetic acid.

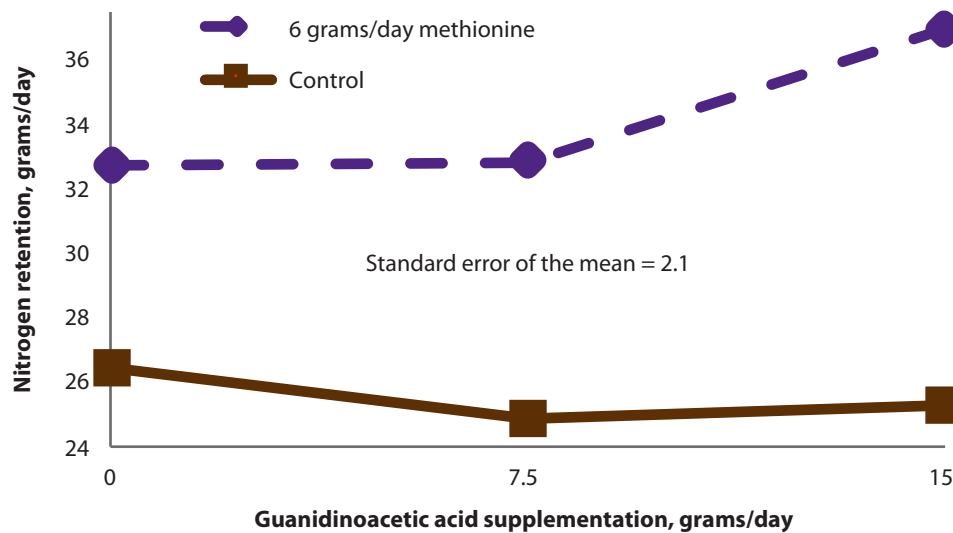


Figure 1. Effect of methionine and guanidinoacetic acid supplementation on nitrogen retention (effect of methionine, $P < 0.01$; interaction of guanidinoacetic acid $\times$ methionine, $P = 0.10$).

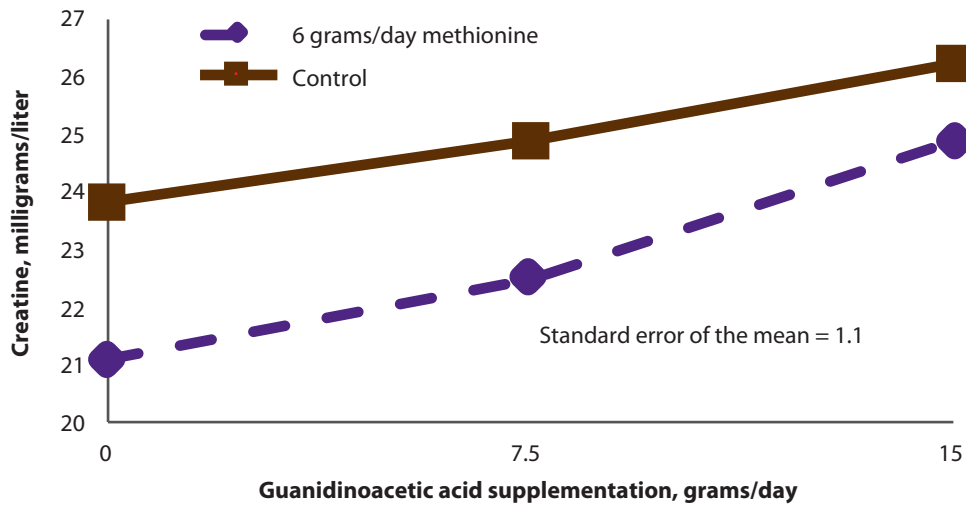


Figure 2. Effect of methionine and guanidinoacetic acid supplementation on plasma creatine concentrations (effect of methionine, $P < 0.01$; linear effect of guanidinoacetic acid, $P < 0.01$).

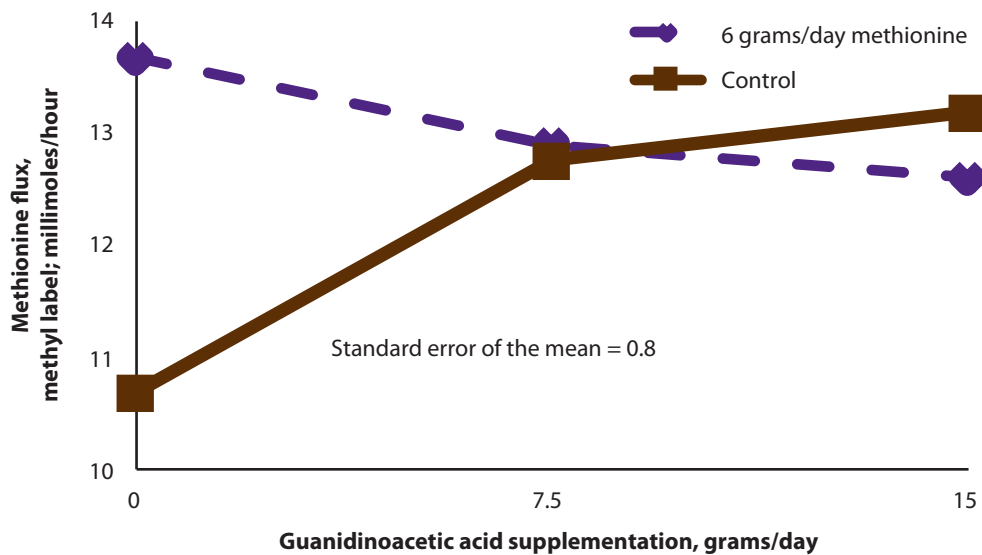


Figure 3. Effect of methionine and guanidinoacetic acid supplementation on methionine methyl flux (effect of methionine, $P = 0.17$; interaction of guanidinoacetic acid $\times$ methionine, $P = 0.03$).