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Copelin, J.E., J.L. Firkins, M.T. Socha, C. Lee. 2021. Effects of diet fermentability and supplementation of 2-hydroxy-4-(methylthio)-butanoic acid and isoacids on milk fat depression: 1. Production, milk fatty acid profile, and nutrient digestibility. J. Dairy Sci. 104: 1591-1603.
https://doi.org/10.3168/jds.2020-18949

Ten Holstein cows (194 ± 58 DIM, 691 ± 69 kg BW, 28 ± 5 kg milk yield) were used to determine the effects of increased diet fermentability and polyunsaturated fatty acids (FA) with or without supplemental 2-hydroxy-4-(methylthio)-butanoic acid (HMTBa; 0.1% of DM), isoacids (IA; 0.24% of DM) or the combination of these, on milk fat depression (MFD). Treatments included a high-forage (HF-C) and low-forage (LF-C) control diet. The LF-C diet decreased milk fat yield (0.87 vs. 0.98 kg/d) but increased protein yield compared with HF-C. HMTBa and IA were only compared to LF-C. **Compared to LF-C, HMTBa increased milk yield (30.6 vs 29.0 kg/d), milk fat percentage (3.27 vs 2.97%), energy corrected milk (ECM; 31.0 vs 28.5 kg/d) and feed efficiency (1.20 vs 1.12 ECM/DMI; kg/kg).** The mechanism by which HMTBa and IA alleviated MFD appears to be by different mechanisms.

Lee, C., J.E. Copelin, T. Park, J.L. Firkins, M.T. Socha, D. Luchini. 2021. Effects of diet fermentability and supplementation of 2-hydroxy-4-(methylthio)-butanoic acid and isoacids on milk fat depression: 2. Ruminal fermentation, fatty acid, and bacterial community structure. J. Dairy Sci. 104: 1604-1619.
https://doi.org/10.3168/jds.2020-18950

Ten Holstein cows (194 ± 58 DIM, 691 ± 69 kg BW, 28 ± 5 kg milk yield) were used to determine the effects of increased diet fermentability and polyunsaturated fatty acids (FA) with or without supplemental 2-hydroxy-4-(methylthio)-butanoic acid (HMTBa), isoacids (IA; isobutyrate, 2-methylbutyrate, isovalerate and valerate) or the combination of these on rumen dynamics and populations. Treatments included a high-forage control diet (HF-C), a low-forage control diet (LF-C), the LF-C diet supplemented with HMTBa at 0.11% (28 g/d), the LF-C diet supplemented with IA at 0.24% of dietary DM and the LF-C diet supplemented with HMTBa and IA. The α-diversity for LF-C was lower compared with HF-C, and β-diversity also differed between LF-C and HF-C. **Cows fed HMTBa had increased ratios of acetate to propionate and butyrate molar proportion. Ruminal saturated FA were increased, and unsaturated FA concentration were decreased by HMTBa, with minimal changes detected in ruminal bacterial diversity and community.** IA supplementation the percentage of trans-10 C18 isomers in total FA. **Supplementation of HMTBa increased biohydrogenation capacity** and supplemental IA increased bacterial diversity, possibly alleviating milk fat depression.

Jenkins, C.J.R., S.C. Fernando, C.L. Anderson, E. Castillo-Lopez, G.I. Zanton, P.J. Kononoff. 2020. The effects of 2-hydroxy-4-methylthio-butanoic acid supplementation on the rumen microbial population and duodenal flow of microbial nitrogen. J. Dairy Sci. 103: 10161-10174.
https://doi.org/10.3168/jds.2019-17664

Four multiparous, lactating Holstein cows (average DIM 169.5 ± 20.5 d) were used in a 4 × 4 Latin square with a 2 × 2 factorial arrangement of treatments to investigate the effects of 2-hydroxy-4-methylthio-butanoic acid (HMTBa) when fed with diets differing in metabolizable protein (MP) supply and equal levels of crude protein. Cows were assigned to 4 dietary treatments: low MP or high MP, supplemented with or without 25 g of HMTBa, which was top-dressed once daily at 0930 hours. Milk yield was not affected by treatment and averaged 23.8 ± 2.06 kg/d. **Rumen pH was lower in cows consuming high MP diets as well as in those consuming HMTBa. Rumen ammonia concentrations tended to be greater in cows consuming HMTBa, and volatile fatty acid concentrations were greater in cows consuming HMTBa. The bacterial community structure of cows receiving HMTBa was not affected at the phylum level.** The relative abundance of bacterial phyla in vivo differed when compared with in vitro conditions.

Pitta, D. W., N. Indugu, B. Vecchiarelli, M. Hennessy, M. Baldin, K.J. Harvatine. 2020. Effect of 2-hydroxy-4-(methylthio) butanoate (HMTBa) supplementation on rumen bacterial populations in dairy cows when exposed to diets with risk for milk fat depression. J. Dairy Science 103: 2718–2730.
https://doi.org/10.3168/jds.2019-17389

This study was undertaken to determine if the reduction in diet-induced milk fat depression (MFD) by HMTBa is due to changes in the rumen microbiota. Twenty-two high-producing, cannulated Holstein dairy cows were assigned to either Control or HMTBa supplementation (0.1% of diet DM), then exposed to 3 different diets with a low-, moderate- or high-risk for diet-induced MFD. Rumen samples were subjected to bacterial diversity analysis using the QIIME (machine used) pipeline. The α-diversity estimates (species richness and Shannon diversity) were decreased in the Control group compared with the HMTBa group. **Certain bacterial genera including Dialister, Megasphaera, Lachnospira and Sharpea were increased in the Control group compared with the HMTBa group. These genera were positively correlated with milk fat trans-10, cis-12 conjugated linoleic acid and trans-10 C18:1, fatty acid isomers associated with biohydrogenation-induced MFD. HMTBa supplementation reduces the microbial perturbations associated with diets that are at risk for MFD.**

Baldin, M., H.A. Tucker, K.J. Harvatine. 2019. Milk fat response and milk fat and urine biomarkers of microbial nitrogen flow during supplementation with 2-hydroxy-4-(methylthio)butanoate. J. Dairy Sci. 102: 6157-6166.
https://doi.org/10.3168/jds.2018-15031

Twenty-four multiparous cows (45.6 ± 8.5 kg of milk/d) and 12 primiparous cows (32.8 ± 3.1 kg of milk/d) were used to measure the effect of HMTBa on biohydrogenation-induced (BH) milk fat depression (MFD) and changes in milk fatty acids (FA) associated with altered rumen BH. Treatments were unsupplemented control and HMTBa fed at 0.1% of diet DMI. Diets were low and moderate-risk for MFD. Milk fat yield (1.43 ± 0.51 kg/d) and milk fat trans-10 C18:1 (0.42 ± 0.08 g/100 g of FA) did not differ during the low-risk phase. During the moderate-risk phase, HMTBa maintained higher milk fat concentration (3.91 vs. 3.79%), tended to maintain higher milk fat yield (1.44 vs. 1.38 kg/d) and decreased milk fat trans-10 C18:1 (0.61 vs. 0.93% FA) compared with Control. HMTBa increased milk fat concentration and secretion of odd- and branched-chain FA by 5.3 and 10.2%, respectively. **HMTBa decreased absorption of alternate BH intermediates and maintained higher milk fat when feeding a diet with moderate risk for MFD.**

Feng, X., R.R. White, H.A. Tucker, M.D. Hanigan. 2018. Meta-analysis of 2-hydroxy-4-methylthio-butanoic acid supplementation on ruminal fermentation, milk production, and nutrient digestibility. J. Dairy Sci. 101: 7182-7189.
https://doi.org/10.3168/jds.2017-13847

A meta-analysis was performed to quantitatively summarize the accumulated results of HMTBa supplementation on animal performance and nutrient digestibility. Data pertaining to HMTBa dose, dietary composition and major performance variables (rumen volatile fatty acid composition, milk production, nutrient digestibility) were collected from 39 articles containing 169 treatment means. Publications were from scientific journals published from 1970 to 2018; 1 internal report from Novus was also included. The HMTBa effects on response variables were analyzed using linear mixed models with random study effects. Other explanatory variables tested included neutral detergent fiber and crude protein percent as well as days in milk. HMTBa supplementation increased blood methionine concentration and milk fat yield. **HMTBa increased rumen microbial protein synthesis (MPS). For every gram of HMTBa fed, an additional 5 grams of MPS were produced with no effect on nutrient digestibility.**

Baldin, M. G.I. Zanton, K.J. Harvatine. 2018. Effect of 2-hydroxy-4-(methylthio)butanoate (HMTBa) on risk of biohydrogenation-induced milk fat depression. J. Dairy Science 101: 376–385.
https://doi.org/10.3168/jds.2017-13446

High-producing (44.1 ± 4.5 kg of milk/d) and low-producing (31.4 ± 4.3 kg of milk/d) cows were used to evaluate the effect of HMTBa supplementation on milk fat synthesis in fed diets with increasing risk of biohydrogenation-induced milk fat depression (MFD). Treatments were unsupplemented Control and HMTBa fed at 0.1% of diet dry matter (25 g/d at 25 kg DMI) fed in diets with increasing risk of MFD was achieved by reducing NDF (neutral detergent fiber) and increasing levels of corn oil. Low-producing cows neither experienced substantial biohydrogenation-induced MFD nor a response in milk fat to HMTBa supplementation. In high-producing cows, HMTBa maintained higher milk fat concentration during the moderate- (2.94 vs. 3.49%) and high-risk (2.38 vs. 3.11%) phases. **High-producing cows receiving HMTBa had greater milk fat yield (0.94 vs. 1.16 kg/d) and lower trans-10 C18:1 (6.11 vs. 1.50) during the high-risk phase. HMTBa increased milk fat in situations with a high risk of biohydrogenation-induced MFD by decreasing absorption of alternate biohydrogenation intermediates.**

Lee, C., J. Oh, A.N. Hristov, K. Harvatine, M. Vázquez-Añón, G.I. Zanton. 2015. Effect of 2-hydroxy-4-methylthio-butanoic acid on ruminal fermentation, bacterial distribution, digestibility, and performance of lactating dairy cows. J. Dairy Sci. 98: 1234-1247.
https://doi.org/10.3168/jds.2014-8904

Eight multiparous lactating Holstein dairy cows were to determine the effect of HMTBa on ruminal fermentation and microbial protein synthesis, nutrient digestibility, urinary N losses and performance of dairy cows. Cows were assigned to 4 levels of HMTBa [0 (Control), 0.05, 0.10 and 0.15% (DM basis)] in a replicated 4x4 Latin square trial. Treatment had no effect on dry matter intake (28.4 to 29.8 kg/d), milk yield (44.1 to 45.3 kg/d), feed efficiency and milk composition. Total-tract digestibility of crude protein and starch decreased quadratically with HMTBa supplementation. Fecal, but not urinary and total excreta N losses were increased quadratically by HMTBa. Ruminal pH, ammonia concentration, protozoal counts and the major volatile fatty acids were not affected by treatment. **Microbial N outflow from the rumen was linearly increased by HMTBa.** The proportion of Fecalibacterium increased linearly and the proportion of Eubacterium quadratically decreased in ruminal contents. HMTBa increased or tended to increase Prevotella loescheii and Prevotella oralis. **The concentration (and yield) of 15:0 in milk fat increased with level of HMTBa and may be a biomarker for microbial protein synthesis.**

Zanton, G.I., G.R. Bowman, M. Vázquez-Añón, L.M. Rode. 2014. Meta-analysis of lactation performance in dairy cows receiving supplemental dietary methionine sources or postruminal infusion of methionine. J. Dairy Sci. 97: 7085-7101.

https://doi.org/10.3168/jds.2014-8220

A meta-analysis was conducted to evaluate the productive response to methionine (Met) supplementation in lactating dairy cows and to define a relationship between metabolizable Met (MP Met) intake and production. A database of 64 papers meeting the selection criteria was developed evaluating postruminally infused dl-methionine (9 papers with 18 Control diets and 35 treatment comparisons), HMTBa (17 papers with 34 Control diets and 46 treatment comparisons), Mepron (18 papers with 35 Control diets and 42 treatment comparisons) and Smartamine (20 papers with 30 Control diets and 39 treatment comparisons). Dietary ingredients were entered into the Cornell-Penn-Miner software to model the diets and predict nutrients that were not reported in the original publication. Cows supplemented with Smartamine consumed more, whereas cows supplemented with Mepron consumed less DM (dry matter) compared with controls. Milk yield tended to increase for cows supplemented with HMTBa and Mepron and decrease for cows fed Smartamine. **All Met sources increased milk protein yield by 2.23 g of protein/g of MP Met. Response of milk fat yield to Met supplementation was not different for infused dl-Met, Mepron and Smartamine (1.87 g of fat/g of MP Met), whereas the response to HMTBa was significantly greater at 5.38 g of fat/g of MP Met.**

Lapierre, H., M. Vázquez-Añón, D. Parker, P. Dubreuil, G. Holtrop, G.E. Lobley. 2011. Metabolism of 2-hydroxy-4-(methylthio)butanoate (HMTBa) in lactating dairy cows. J. Dairy Science 94: 1526–1535.

https://doi.org/10.3168/jds.2010-3914

The fate and contribution to methionine (Met) kinetics of 2-hydroxy-4-(methylthio) butanoate (HMTBa) at the whole-body, splanchnic and mammary levels was determined in multicatheterized cows (31.3 kg of milk/d; 17.7 kg of DMI/d). The jugular-infused HMTBa increased whole-body plasma flux of Met by 36% and accounted for between 43 to 74% of the HMTBa infused, contributing to increased whole-body Met availability. The portal-drained viscera, liver and mammary gland extracted 11, 37 and 3.4%, respectively, of the infused HMTBa. **The HMTBa provided directly 15% of the Met required for milk protein secretion. Absorbed HMTBa, therefore, both produces and spares Met for use by the mammary gland.**

Lobley, G.E., T.J. Wester, G. Holtrop, J.J. Dibner, D.S. Parker, M. Vázquez-Añón. 2006. Absorption and Digestive Tract Metabolism of 2-Hydroxy-4-Methylthiobutanoic Acid in Lambs. J. Dairy Sci. 89: 3508-3521.

https://www.journalofdairyscience.org/article/S0022-0302(06)72391-8/

Anabolic availability of HMTBa given as oral doses to lambs, was quantified both directly as appearance in the portal vein and as synthesis to methionine (Met) by digestive tract tissues. Eight lambs, prepared with vascular catheters in the mesenteric and portal veins plus the aorta, received [1-13C] HMTBa was supplied as an oral dose while [methyl-2H3] Met was infused into the jugular vein. **Peak absorption as HMTBa occurred 70 to 90 minutes after the oral dose. All digestive tract tissues converted HMTBa to Met, equivalent to 24% of the Met provided by the diet for the larger HMTBa dose. Total availability of HMTBa averaged 17.9% of the dose of which 70% appeared as absorbed HMTBa and the remainder as Met synthesized by digestive tract tissues.** Release of 13CO2 into the portal vein accounted for another 23% of the dose.

Lobley, G.E., T.J. Wester, A.G. Calder, D.S. Parker, J.J. Dibner, M. Vázquez-Añón. 2006. Absorption of 2-Hydroxy-4-Methylthiobutyrate and Conversion to Methionine in Lambs. J. Dairy Sci. 89: 1072-1080.
https://www.journalofdairyscience.org/article/S0022-0302(06)72175-0/

Absorption and metabolism of the methionine (Met) hydroxy analogue 2-hydroxy-4-methylthiobutyrate (HMTBa) was examined using stable isotopes. In the first trial, dl [1-13C] HMTBa was infused for 6 hours (7.4 μmol/min) into the abomasum, and [2H3] Met was infused into the mesenteric vein, of lambs prepared with vascular catheters across the splanchnic bed. **Recovery of HMTBa at the portal vein was 87%, and of this, 63% bypassed the liver. In contrast, hepatic extraction of Met equaled or exceeded net absorption.** Only small quantities of Met synthesized from HMTBa were exported from either the digestive tract or liver, but there was substantial and significant input from posthepatic tissues. In a second experiment, lambs were killed following 4 hours infusions of dl [1-13C] HMTBa and [2H3] Met with enrichments monitored in 15 tissues. Only the kidney showed [1-13C] Met enrichment higher than plasma, which suggests that it must be a primary source of plasma Met derived from HMTBa. All tissues synthesized Met from HMTBa but to significantly different extents. The lowest values were for muscle, skin, brain and lung; intermediate conversions occurred in rumen, omasum, abomasum, duodenum, jejunum, ileum and cecum. **The greatest synthesis, equivalent to 22 to 24% of Met entry into cells, was observed for the liver and kidney. The liver and kidney both converted HMTBa to Met, and was retained by the liver and exported by the kidney.** Under these experimental conditions, **synthesis of Met from HMTBa completely eliminated use of dietary Met.**

Piepenbrink, M. S., A. L. Marr, M. R. Waldron, W. R. Butler, T. R. Overton, M. Vázquez-Añón, and M. D. Holt. 2004. Feeding 2-hydroxy-4-(methylthio)-butanoic acid to periparturient dairy cows improves milk production but not hepatic metabolism. J. Dairy Sci. 87:1071–1084.
https://www.journalofdairyscience.org/article/S0022-0302(04)73253-1/

Forty-eight Holstein cows, entering second or later lactation, were utilized to determine the effects of 2-hydroxy-4-(methylthio)-butanoic acid (HMB) on milk production, hepatic lipid metabolism, and gluconeogenesis during the periparturient period. Cows were fed one of 3 diets as TMR starting 21 d before expected calving. These diets contained 0 (the basal diet), 0.09 (+HMB), or 0.18 (++HMB)% HMB. From parturition to 84 DIM. Cows were fed diets that contained 0, 0.13, or 0.20% HMB. Prepartum and postpartum DMI were similar among cows fed the basal diet, +HMB and ++HMB. There was a quadratic effect on milk yield such that cows fed +HMB had the greatest milk yield; yields of milk by cows fed the basal diet and ++HMB were similar. This led to trends for increased yields of 3.5% fat-corrected milk and total solids when cows were fed +HMB. Percentages of fat, protein, and total solids in milk were not affected by treatment. Despite differences in milk yield, calculated energy balance was not affected by treatment. Plasma concentrations of NEFA, β-**hydroxybutyrate, and glucose were not different among treatments. Liver triglyceride content was similar among treatments on d 1 postpartum and was increased for cows consuming +HMB on d 21 postpartum compared with the other dietary treatments. Capacities for metabolism of [1-14C]palmitate by liver slices in vitro were not affected by treatment; however, conversion of [1-14C]propionate to CO2 and glucose decreased as the amount of HMB consumed by cows increased on d 21 postpartum. Cows consuming +HMB had greater days to first ovulation compared with cows consuming the basal diet and ++HMB as measured by plasma progesterone concentrations. These data suggest that adding HMB to low Met diets to achieve a predicted Met supply of approximately 2.3% of metabolizable protein supply is beneficial for increasing milk production but does not appear to benefit hepatic energy metabolism during early lactation.**