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Effect of chromium on bioenergetics and leukocyte dynamics following immunoactivation in lactating Holstein cows

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ABSTRACT

Activated immune cells are insulin sensitive and utilize copious amounts of glucose. Because chromium (Cr) increases insulin sensitivity and may be immunomodulatory, our objective was to evaluate the effect of supplemental Cr (KemTrace Cr propionate, 20 g/d; Kemin Industries Inc., Des Moines, IA) on immune system glucose utilization and immune system dynamics following an intravenous endotoxin challenge in lactating Holstein cows. Twenty cows (320 ± 18 d in milk) were randomly assigned to 1 of 4 treatments: (1) pair-fed (PF) control (PF-CON; 5 mL of saline; n = 5), (2) PF and Cr supplemented (PF-Cr; 5 mL of saline; n = 5), (3) lipopolysaccharide (LPS)-euglycemic clamp and control supplemented (LPS-CON; 0.375 μg/kg of body weight LPS; n = 5), and (4) LPS-euglycemic clamp and Cr supplemented (LPS-Cr; 0.375 μg/kg of body weight LPS; n = 5). The experiment was conducted serially in 3 periods (P). During P1 (3 d), cows received their respective dietary treatments and baseline values were obtained. At the initiation of P2 (2 d), either a 12-h LPS-euglycemic clamp was conducted or cows were PF to their respective dietary counterparts. During P3 (3 d), cows consumed feed ad libitum and continued to receive their respective dietary treatment. During P2, LPS administration decreased dry matter intake (DMI; 40%) similarly among diets, and by experimental design the pattern and magnitude of reduced DMI were similar in the PF cohorts. During P3, LPS-Cr cows tended to have decreased DMI (6%) relative to LPS-CON cows. Relative to controls, milk yield from LPS-challenged cows decreased (58%) during P2 and LPS-Cr cows produced less (16%) milk than LPS-CON cows. During P3, milk yield progressively increased similarly in LPS-administered cows, but overall milk yield remained decreased (24%) compared with PF controls. There were no dietary treatment differences in milk yield during P3. Circulating insulin increased 9- and 15-fold in LPS-administered cows at 6 and 12 h postbolus, respectively, compared with PF controls. Compared with LPS-CON cows, circulating insulin in LPS-Cr cows was decreased (48%) at 6 h postbolus. Relative to PF cows, circulating LPS binding protein and serum amyloid A from LPS-administered cows increased 2- and 5-fold, respectively. Compared with PF cows, blood neutrophil counts in LPS-infused cows initially decreased, then gradually increased 163%. Between 18 and 48 h postbolus, the number of neutrophils was increased (12%) in LPS-Cr versus LPS-CON cows. The 12-h total glucose deficit was 220 and 1,777 g for the PF and LPS treatments, respectively, but glucose utilization following immune activation was not influenced by Cr. In summary, supplemental Cr reduced the insulin response and increased circulating neutrophils following an LPS challenge but did not appear to alter the immune system's glucose requirement following acute and intense activation.

Key words: chromium, lipopolysaccharide, insulin, neutrophil

INTRODUCTION

Dairy cows employ homeorhetic mechanisms to support dominant physiological states (i.e., growth, reproduction, lactation; Bauman and Currie, 1980), and during lactation this is in large part characterized by decreased circulating insulin coupled with reduced insulin sensitivity in adipose tissue and skeletal muscle (De Koster and Opsomer, 2013; Baumgard et al., 2017). However, immunoactivation markedly reprioritizes the hierarchy of coordinated nutrient trafficking (Bradford et al., 2015) at the expense of milk synthesis. Inflammation is caused by multiple pathologies, including mastitis, metritis, heat stress, intestinal barrier dysfunction, and feed restriction (Lambert et al., 2002; Sheldon et al., 2008; Ballou, 2012; Zhang et al., 2013; Kvidera et al., 2017a,d). Although these insults have

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differing etiologies, inflammation and suboptimal production are common outcomes; therefore, identifying strategies amenable to dietary manipulation that could facilitate the immune response or ameliorate production loses during immunoactivation would largely affect animal health and farm profitability.

Upon activation, immune cells become obligate glucose utilizers and shift ATP production from oxidative phosphorylation to aerobic glycolysis, a process known as the "Warburg effect" (Palsson-McDermott and O'Neill, 2013). During an immune challenge circulating insulin increases, likely because insulin facilitates immune cell glucose uptake and improves function (Walrand et al., 2004). In an attempt to spare glucose for the immune system, muscle and adipose tissue become insulin resistant (Lang et al., 1990) and milk synthesis is reduced (Kvidera et al., 2017b). However, the ubiquitous nature of leukocytes makes quantifying the immune system's in vivo glucose consumption difficult. By using an LPS-euglycemic clamp technique, we recently demonstrated that an activated immune system utilizes >1 kg of glucose within 12 h in the lactating cow model (Kvidera et al., 2017b). Thus, mounting an immune response is energetically expensive, and strategies that divert glucose toward activated leukocytes may allow for a more efficient immune response.

Chromium (Cr) potentiates insulin action (Chen et al., 2006), and although the exact mechanism is not fully understood, it appears to work intimately with chromodulin (or low-molecular-weight Cr-binding substance; Vincent, 2015). In response to insulin, Cr enters insulin-sensitive cells and, in combination with chromodulin, binds to the insulin receptor, which amplifies downstream signaling cascades (Vincent, 2015). Subsequently, GLUT-4 translocation to the plasma membrane is improved and glucose uptake is increased (Chen et al., 2006), a potential benefit to insulin-sensitive immune cells upon activation. Therefore, study objectives were to evaluate effects of supplemental Cr on glucose consumption and circulating leukocyte dynamics in an acute and intensely activated immune system via the LPS-euglycemic clamp technique.

MATERIALS AND METHODS

Animals and Experimental Design

All procedures were approved by the Iowa State University Institutional Animal Care and Use Committee. Twenty nonpregnant lactating Holstein cows (781 ± 21 kg of BW; 320 ± 18 DIM; parity 3 ± 0.3) were used in an experiment conducted in 2 replications (10 cows/replicate). Cows were housed in individual boxstalls (4.57 × 4.57 m) at the Iowa State University Dairy Farm. Cows were allowed 4 d to acclimate to housing and feeding conditions; during this time, they were implanted with bilateral jugular catheters. Beginning on d 1 of acclimation and through study completion, cows received 1 of 2 dietary treatments: (1) a control supplement (20 g/d of calcium carbonate) or (2) a Cr supplement (KemTrace Cr propionate, 20 g/d to deliver 8 mg of Cr/d; Kemin Industries Inc., Des Moines, IA). Supplements were provided as a top-dress premixed with ground corn at a rate of 200 g/d. Period 1 (**P1**) lasted 3 d and served as the baseline (data generated for covariate analysis) for periods 2 (**P2**) and 3 (**P3**). At the initiation of P2, which lasted 48 h, animals either experienced a 12-h LPS-euglycemic clamp as previously described (Kvidera et al., 2017b) or were pair fed (**PF**) to their respective dietary counterparts for the entire 48 h to eliminate the confounding effects of dissimilar nutrient intake. Dietary and challenge combinations resulted in 4 treatments: (1) PF and control supplemented (**PF-CON**; 5 mL of sterile saline with control supplement; n = 5), (2) PF and Cr supplemented (**PF-Cr**; 5 mL of sterile saline with Cr propionate supplement; n = 5), (3) LPS-euglycemic clamp and control supplemented (**LPS-CON**; 0.375 μg/kg of BW LPS with control supplement; n = 5), and (4) LPS-euglycemic clamp and Cr supplemented (**LPS-Cr**; 0.375 μg/kg of BW LPS with Cr propionate supplement; n = 5). Period 3 lasted 3 d, during which all animals continued to receive their dietary treatment but were allowed to consume feed ad libitum.

All cows were fed a diet formulated to meet or exceed the predicted requirements (NRC, 2001; Table 1) of energy, protein, minerals, and vitamins. Reduced feed intake in LPS-treated cows during P2 was determined as a percentage of their mean daily ad libitum intake during P1. Throughout the experiment, PF cows lagged 1 d behind LPS-infused cows to allow for pair-feeding calculations as previously described (Baumgard et al., 2011).

Cows were milked 4 times daily (0000, 0600, 1200, and 1800 h) during P1 and P2 and twice daily (0600 and 1800 h) during P3. Milk yield was recorded, and a sample for composition analysis was obtained at each milking. Samples were stored at 4°C with a preservative (bronopol tablet; D & F Control System, San Ramon, CA) until analysis by Dairy Lab Services (Dubuque, IA) using infrared analysis equipment and procedures approved by AOAC International (1995). Rectal temperature (**Tr**), respiration rate (**RR**), and heart rate (**HR**) were recorded after each milking. Heart rate and RR were measured as beats or flank movements during a 15-s interval and later transformed to beats per minute and breaths per minute, respectively. Rectal temperature was measured using a digital thermometer