Effects of an intravenous endotoxin challenge on glucose and insulin dynamics in horses

Ferenc Tóth, DVM; Nicholas Frank, DVM, PhD; Sarah B. Elliott, BSc; Raymond J. Geor, BVSc, PhD; Raymond C. Boston, PhD

Objective—To evaluate the effects of endotoxin administered IV on glucose and insulin dynamics in horses.

Animals—16 healthy adult mares.

Procedures—Each week of a 2-week randomized crossover study, each horse received an IV injection (duration, 30 minutes) of Escherichia coli O55:B5 lipopolysaccharide (LPS) in 60 mL of sterile saline (0.9% NaCl) solution (20 ng/kg) or sterile saline solution alone (control treatment). Frequently sampled IV glucose tolerance test procedures were performed at 24 hours before (baseline) and 24 and 48 hours after injection; glucose and insulin dynamics were assessed via minimal model analysis.

Results—13 of 16 horses had a clinical response to LPS, which was characterized by mild colic and leukopenia. Before treatment, mean ± SD insulin sensitivity was 2.9 ± 1.9 × 10⁻⁴ L min⁻¹ • mU⁻¹; this significantly decreased to 0.9 ± 0.9 × 10⁻⁴ L min⁻¹ • mU⁻¹ 24 hours after treatment (69% reduction) and was 1.5 ± 0.9 × 10⁻⁴ L min⁻¹ • mU⁻¹ 48 hours after treatment. At baseline, mean ± SD acute insulin response to glucose was 520 ± 196 mU min⁻¹ L⁻¹; this significantly increased to 938 ± 620 mU min⁻¹ L⁻¹ (80% increase) and 755 ± 400 mU min⁻¹ L⁻¹ (45% increase) at 24 and 48 hours after LPS treatment, respectively.

Conclusions and Clinical Relevance—Compared with baseline values, insulin sensitivity decreased for 24 hours after IV injection of LPS, and affected horses had a compensatory pancreatic response. These disturbances in glucose and insulin dynamics may contribute to development of laminitis in horses. (Am J Vet Res 2008;69:82–88)

Endotoxin is a heat-stable LPS located within the outer membrane of gram-negative bacteria that can be released as a result of rapid bacterial growth or cell death.1,2 In healthy animals, endotoxin is located within the intestines and is contained there by the mucosal barrier and mucus layer.2 If endotoxin enters the portal blood system via active transport or passive diffusion from the intestinal tract, LPS molecules are removed from circulation by the Kupffer cells of the liver.3 Clinical signs of endotoxemia develop when body defenses are compromised and blood endotoxin concentration increases. In horses, endotoxia is most commonly associated with gastrointestinal tract disturbances such as colic and colitis that involve bacterial overgrowth and increased intestinal wall permeability.3,4 Endotoxia develops when the mucosal barrier is compromised and there is movement of endotoxin into the blood and lymphatic system or when endotoxin passes through the serosa into the peritoneal cavity.3,5 Horses that have retained fetal membranes or that develop pleuropneumonia, wound infections, or gram-negative bacteremia are also at risk for endotoxemia.1,2

Insulin resistance is a state in which normal concentrations of insulin fail to elicit a normal physiologic response,6 and it develops as a consequence of endotoxemia in humans7 and rats.8 This disturbance in glucose metabolism in horses is a concern because of its putative link with laminitis. Administration of a high dose of LPS (125 µg/kg) to ponies induces hyperglycemia within the first hour, followed by significant hyperglycemia, compared with blood glucose concentrations before endotoxin administration; however, plasma insulin concentrations remained unchanged.9,10 Effects of endotoxia on sensitivity to insulin are relevant because IR is a risk factor for pasture-associated lamini-

Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>LPS</td>
<td>Lipopolysaccharide</td>
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<td>IR</td>
<td>Insulin resistance</td>
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<td>FSIGT</td>
<td>Frequently sampled IV glucose tolerance</td>
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<td>Sg</td>
<td>Glucose effectiveness</td>
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<td>SI</td>
<td>Insulin sensitivity</td>
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<td>AIRg</td>
<td>Acute insulin response to glucose</td>
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<td>DI</td>
<td>Disposition index</td>
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<td>TNF-α</td>
<td>Tumor necrosis factor-α</td>
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<td>EHC</td>
<td>Euglycemic hyperinsulinemic clamp</td>
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<td>IRS-1</td>
<td>Insulin receptor substrate-1</td>
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From the Department of Large Animal Clinical Sciences, College of Veterinary Medicine, University of Tennessee, Knoxville, TN 37996 (Toth, Frank, Elliott); the Middleburg Agricultural Research and Extension Center, Virginia Polytechnic and State University, Middleburg, VA 20117 (Geor); and the Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania, Kennett Square, PA 19348 (Boston).
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Address correspondence to Dr. Frank.
tis in ponies, and there is in vitro evidence that hoof laminar tissues require an adequate supply of glucose to maintain structural integrity. If IR is an important risk factor for laminitis, then endotoxemia may exacerbate this disturbance in glucose metabolism and further increase the risk of disease.

Administration of exogenous LPS is used to experimentally induce endotoxemia but does not represent development of the disease clinically, which may be why laminitis has not developed in LPS-treated horses. However, endotoxemia may still play a role in the development of laminitis, and this method allows physiologic responses to LPS administration to be isolated and studied. Endotoxemia has been associated with acute laminitis in 2 studies, although a causal relationship has not been established. Parsons et al retrospectively evaluated horses that had developed acute laminitis during hospitalization and determined that preceding the development of laminitis, those horses were 5 times as likely to have endotoxemia as horses with no clinical signs or evidence of endotoxemia detectable via routine clinicopathologic testing. However, endotoxemia was only inferred from clinical signs and not confirmed via endotoxin assay. Sprouse et al also reported that plasma endotoxin concentrations significantly increased in 11 of 13 horses that developed Obel grade 3 laminitis after alimentary carbohydrate overload.

Clinical signs consistent with endotoxemia have been observed in horses that developed laminitis after administration of oligofructose. Horses that received 10 g of oligofructose/kg via intraesophageal administration developed diarrhea within 12 hours and had signs of depression, inappetence, fever, and tachycardia within the 48-hour period following treatment. Mean WBC and neutrophil counts initially decreased but then increased within 48 hours of oligofructose administration. These findings suggest that endotoxemia contributes to the development of laminitis associated with carbohydrate overload in horses. Carbohydrate overload causes an overgrowth of intestinal bacteria that lowers the intraluminal pH and increases intestinal wall permeability. Endotoxemia detected during the development of carbohydrate-induced laminitis may reflect this increase in intestinal wall permeability.

The purpose of the study reported here was to evaluate the effects of endotoxin administered IV on glucose and insulin dynamics in horses. We hypothesized that endotoxemia would induce alterations in glucose and insulin dynamics in horses. The FSIGT test was selected to evaluate this hypothesis because FSIGT test data can be assessed via minimal model analysis. The minimal model of glucose and insulin dynamics is a nonlinear model that uses data obtained from the FSIGT test to partition the glucose disposal into glucose and insulin-mediated fractions. It provides values for $S_g$, $S_i$, and $AIR_g$. Glucose effectiveness describes the capacity of glucose to mediate its own disposal, whereas SI represents the ability of insulin to promote glucose disposal. The acute insulin response to glucose is a measure of initial-phase endogenous insulin secretion in response to exogenous glucose. The ability of pancreatic beta cells to increase insulin secretion in response to decreased insulin sensitivity is represented by the DI.

### Materials and Methods

**Horses**—Sixteen healthy mares from the University of Tennessee teaching and research herd were evaluated during the study period (February to June 2006). Horses were admitted to the University of Tennessee Large Animal Hospital in pairs, and each pair of horses remained hospitalized for 14 days. Only mares were selected to eliminate differences attributable to sex. The horses were 4 to 12 years old (mean age, 9.1 years; median, 9.5 years); breeds included mixed (n = 8), Quarter Horse (3), Tennessee Walking Horse (1), Appaloosa (1), and Paint (3). Horses were weighed at the time of admission; weights ranged from 436 to 563 kg (mean weight, 493.6 kg; median, 498.6 kg). Body condition score (on a scale of 1 to 9) ranged from 4 to 6. The study protocol was approved by the University of Tennessee Institutional Animal Care and Use Committee.

**Experimental design**—A randomized crossover study design with repeated measures was used; each horse received the LPS and control treatments. Eight horses were randomly selected to receive an injection of LPS during the first of the 2-week period and then an injection of sterile saline (0.9% NaCl) solution (control treatment) alone during the second week; the remaining 8 horses received the LPS and control treatments in the reverse order. Horses were weighed and performed physical examinations were performed on the first day (Friday), and then each horse was housed separately in 3.7 × 3.7-m stalls within the veterinary teaching hospital. Grass hay and water were provided ad libitum, and each horse was acclimated to its new environment for approximately 72 hours. Horses were evaluated during each of the 2 study weeks; each week, procedures were performed according to the same schedule. On the first day of the week (Monday), an IV catheter was placed and a sham FSIGT test was performed. An FSIGT test was performed 24 hours before treatment (Tuesday; baseline [–24 hours]), and the infusion of LPS or saline solution was administered between 12:00 and 12:30 PM on Wednesday (designated time = 0). Frequent sampled IV glucose tolerance test procedures were performed 24 (Thursday) and 48 hours (Friday) after treatment. All FSIGT tests were performed between 12:00 and 3:00 PM. Intravenous catheters were removed at the end of each study week. After the completion of the study, horses were returned to the University of Tennessee teaching and research herd.

**Lipopolysaccharide administration**—Escherichia coli O55:B5 LPS was mixed with 60 mL of sterile saline solution under a fume hood by a person (SBE) who wore gloves and used a respirator to minimize exposure. The LPS solution (20 ng/kg) or 60 mL of saline solution was infused via the IV catheter during a 30-minute period. Horses were observed for signs of colic and physical examination variables, including rectal temperature, heart rate, respiratory rate, mucous membrane color, and capillary refill time, were recorded every 15 minutes for the first 3 hours, then every...
30 minutes for the following 3 hours, and then every 2 hours for 18 hours.

CBC analysis—Blood was collected from the indwelling jugular catheter into tubes containing EDTA before the LPS or saline solution infusion was initiated (commenced at time = 0) and 3 hours later (ie, 2.5 hours after completing the LPS infusion). Samples were immediately transported to the clinical pathology laboratory for CBC analysis.

FSIGT test procedure—On the first day of each study week, each horse was weighed and a 14-gauge polypropylene catheter was inserted into the left jugular vein. During tests, the horse was allowed access to grass hay and water ad libitum. Patency of the IV catheter was maintained between tests by injection of 5 mL of saline solution containing heparin into the catheter every 6 hours. An injection cap and infusion set (length, 30 cm; internal diameter, 0.014 cm) were attached to the catheter. The FSIGT test procedure first described for use in horses by Hoffman et al27 was used. Briefly, a bolus (300 mg of glucose/kg) of a 50% (wt/vol) dextrose solution was administered to each horse via the infusion line and catheter, followed by injection of saline solution containing heparin. Blood samples were collected via the catheter immediately before and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 19 minutes after infusion of dextrose. At 20 minutes, regular insulin (30 mU/kg) was administered followed by another infusion of saline solution containing heparin. Blood samples were subsequently collected via the catheter at 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 150, and 180 minutes after the dextrose infusion. At each time point, 3 mL of blood was withdrawn from the infusion line and discarded. A 6-mL blood sample was then collected, followed by infusion of 5 mL of saline solution containing heparin. Half the volume of the blood sample was transferred to a tube containing sodium heparin, which was immediately cooled on ice and then refrigerated. The remaining blood volume was transferred to a tube containing no anticoagulant. Those samples were allowed to clot at 22°C for 1 hour, and then serum was harvested via low-speed (1,000 X g) centrifugation. Plasma and serum samples were stored at –20°C until further analyzed.

Plasma glucose and serum insulin concentrations—Plasma glucose concentrations were measured by use of a colorimetric assay31 on an automated discrete analyzer.1 Serum insulin concentrations were determined by use of a radioimmunoassay5 that has been validated for use in horses.31 Each sample was assayed in duplicate, and intra-assay coefficients of variation < 5% or < 10% were required for acceptance of glucose and insulin assay results, respectively.

Interpretation of FSIGT test data by use of the minimal model—Values of SI, Sg, AIRg, and DI were calculated for each FSIGT test in accordance with the minimal model22 by use of commercially available software and previously described methods.27,33 Disposition index was calculated via multiplication of AIRg by SI.

Statistical analysis—Horses were classified as responders or nonresponders according to their response to endotoxin, and groups were compared by use of the nonparametric Mann-Whitney U test. Mixed-model ANOVA for repeated measures was performed by use of statistical software to determine the effects of treatment (LPS vs saline solution) and time (–24, 24, or 48 hours) on Sg, SI, AIRg, and DI. When a significant treatment-time effect was detected, the Bonferroni test for multiple comparisons was used to identify significant differences between least squares means. Significance was defined at a value of P < 0.05.

Results

The response to endotoxin was determined via observation of signs of colic and detection of leukopenia, which was defined as WBC count < 5.6 X 103 WBCs/µL,31 at 3 hours after LPS administration. Compared with horses that were classified as nonresponders (n = 3), rectal temperature, heart rate, WBC count, percentage decrease (from baseline) in WBC count, and neutrophil count differed significantly in horses that were identified as responders (n = 13; Table 1). In responders, signs of colic detected within 3 hours of LPS administration included pawing, rolling, and stretching. Nonresponders did not develop signs of colic. Frequently sampled intravenous glucose tolerance tests were successfully performed, and mean ± SE plasma glucose and serum insulin concentrations were calculated (Figures 1 and 2). Data from a single FSIGT test performed 48 hours after LPS administration in 1 horse were excluded from the statistical analysis because the DI value was clearly an outlier and had a studentized residual (adjusted by dividing it by an estimate of its SD) of 7.44.

Compared with the control treatment, injection of LPS significantly decreased SI (time X treatment; P = 0.04) and increased AIRg (time X treatment; P = 0.006) over time (Table 2). Mean ± SD SI significantly decreased from 2.9 ± 1.9 X 10–4 L/min•mU–1 at baseline (ie, prior to LPS administration) to 0.9 ± 0.9 X 10–4 L/min•mU–1 after 24 hours (69% reduction); however, the value at 48 hours did not differ significantly from the pretreatment value. Mean AIRg significantly decreased from 27 ± 32 WBCs/µL to 23 ± 19 WBCs/µL; however, the value at 48 hours did not differ significantly from the pretreatment value. Period effects were detected (time X treatment); compared with the pretreatment value, the value at 48 hours did not differ significantly from the pretreatment value. Period effects were detected (time X treatment); compared with the pretreatment value, the value at 48 hours did not differ significantly from the pretreatment value.

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Table 1—Mean ± SD physical examination variable and WBC count data in 16 horses that received Escherichia coli O55:B5 LPS in 60 mL of sterile physiologic saline (0.9% NaCl) solution (20 ng/kg) administered IV and developed signs of colic and leukopenia (responders) or did not respond to treatment (nonresponders).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonresponder group (n = 3)</th>
<th>Responder group (n = 13)</th>
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<tr>
<td>Maximal heart rate (beats/min)</td>
<td>49 ± 7</td>
<td>67 ± 17*</td>
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<tr>
<td>Maximal rectal temperature (°C)</td>
<td>38.2 ± 0.6</td>
<td>39.1 ± 0.5*</td>
</tr>
<tr>
<td>Decrease in WBC count at 3 hours after treatment, compared with pretreatment value (%)</td>
<td>9.4 ± 5.1</td>
<td>45.1 ± 11.1*</td>
</tr>
<tr>
<td>WBC count at 3 hours after treatment (X 10^3 cells/µL)</td>
<td>7.4 ± 1.4</td>
<td>4.0 ± 0.9*</td>
</tr>
<tr>
<td>Neutrophil count (X 10^3 cells/µL)</td>
<td>5.5 ± 0.7</td>
<td>2.3 ± 0.8*</td>
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Leukopenia was defined as WBC count < 5.6 X 10^3 WBCs/µL. Reference range for heart rate = 28 to 40 beats/min. Reference range for rectal temperature = 37.6°C to 38.5°C. Reference range for neutrophil count = 2.9 to 8.5 X 10^3 cells/µL.

*For this variable, value was significantly (Mann-Whitney U test; P < 0.05) different from that of the nonresponder group.
increased from 520 ± 196 mU·min⁻¹·L⁻¹ at -24 hours to 938 ± 620 mU·min⁻¹·L⁻¹ and 712 ± 400 mU·min⁻¹·L⁻¹ at 24 and 48 hours after LPS treatment, respectively. After LPS treatment, mean DI significantly (time X treatment; P = 0.024) decreased from the baseline value of 1.4 ± 1.0 × 10⁻² to 0.6 ± 0.5 × 10⁻² at 24 hours after endotoxin administration. No significant treatment-time effects were detected for values of Sg.

In the 3 horses that did not develop a clinical response to endotoxin administration, mean SI increased...
by 12% and then decreased by 27% at 24 and 48 hours following LPS infusion, respectively, compared with the value before treatment. Compared with the pretreatment value, mean AIRg was decreased by 2% and increased by 7% at 24 and 48 hours after injection, respectively; mean Sg was decreased by 36% and increased by 14% at 24 and 48 hours after injection, respectively. The DI values did not increase or decrease from baseline by > 1% after LPS administration.

**Discussion**

In the present study, 13 of 16 healthy horses that received *E coli* O55:B5 LPS via IV infusion at a dose of 20 ng/kg developed signs of mild colic and leukopenia (ie, WBC count < 5.6 × 10^4 WBCs/µL). At 24 hours after LPS administration, insulin sensitivity was significantly lower than the value prior to treatment and AIRg increased to compensate for this alteration in glucose dynamics. Signs of colic, fever, tachycardia, and leukopenia were detected in the horses that responded to LPS in the present study, and these findings are consistent with those of previous reports. In a study, IV administration of *E coli* O55:B5 LPS at a dose of 30 ng/kg decreased the WBC count, compared with baseline values, and the nadir occurred 2 hours after infusion. Horses developed mild restlessness, sweating, increased respiratory effort, and tachypnea in response to LPS; mean rectal temperature increased over time, and a peak value > 39°C was detected 4 hours after initiation of the endotoxin infusion. Plasma interleukin-6 and TNF-α activities were also increased in treated horses. In another study, *E coli* O26:B5 LPS was administered to horses at the dose used in the present study (20 ng/kg). In those horses, mean rectal temperature was approximately 39°C at 3 hours after initiation of the LPS infusion; mean heart rate also increased significantly from baseline values and peaked at approximately 50 beats/min after 1.5 hours. In that same study, neutrophil counts were assessed every 30 minutes and the lowest mean value (< 3,000 cells/µL) was detected 1 hour after LPS infusion. However, similar to the finding in the responder group of the present study, the mean neutrophil count remained less than the pretreatment value for 3 hours after LPS was infused.

In the study reported here, 3 horses failed to develop signs of colic or leukopenia. This lack of response may be attributable to circulating anti-endotoxin antibodies or genetic polymorphism within intracellular LPS signal transduction pathways. Toll-like receptor-4, myeloid differentiation factor-2, and cluster differentiation factor-14 can be affected. In humans, mis- sense mutations affecting the extracellular domain of the toll-like receptor-4 are associated with a diminished response to inhaled LPS. However, a common mutation was not identified when this hypothesis was tested in horses that had blunted responses to LPS.

Glucose and insulin dynamics were assessed in horses by use of FSGT test and minimal model analysis procedures in the present study. These methods have been previously used in horses and are preferred over the EHC technique, which is an alternative method of quantifying SI. One advantage of the minimal model is that it provides measures of the pancreatic response (AIRg) and ability of glucose to mediate its own disposal (Sg), as well as SI. The DI, which represents the ability of pancreatic beta cells to compensate for decreased insulin sensitivity, can also be calculated. Measures of AIRg, Sg, and DI are not provided by use of the EHC technique. The EHC technique is also more difficult to perform from a technical standpoint because an infusion line must remain connected to each horse throughout the 2- to 3-hour study period, which provides more opportunity for equipment failure and stress.

Insulin sensitivity values prior to LPS infusion and those determined in horses during the week that they received the control treatment compared favorably with results of previous studies. A mean SI value of 1.9 × 10^{-4} L·min^{-1}·mU^{-1} was reported for nonobese Thoroughbred geldings, and the mean value for a group of 46 horses was 2.1 × 10^{-4} L·min^{-1}·mU^{-1}. In contrast, lower mean SI values of 0.39 × 10^{-4} L·min^{-1}·mU^{-1} and 0.08 × 10^{-4} L·min^{-1}·mU^{-1} have been detected in healthy ponies and ponies that had previously had laminitis, which suggests that insulin sensitivity is generally lower in ponies than in horses. Mean SI significantly decreased following LPS administration in the horses of the present study. At 24 hours after treatment, mean SI was significantly lower than the mean value before LPS infusion; at 48 hours after treatment, mean SI was still lower than the mean value before LPS infusion, but this difference was not significant. A biphasic glucose response has been detected after LPS administration in humans.

Glucose infusion rates during EHC procedures were significantly higher 120 minutes after LPS was administered, compared with rates in persons receiving saline solution, but then progressively decreased and were significantly lower than rates in persons receiving saline solution at 420 minutes after LPS administration. Endotoxemia also induces IR in rats, as evidenced by a 37% decrease in glucose disposal following LPS administration. At the tissue level, continuous LPS infusion significantly decreased insulin receptor abundance, inhibited insulin-stimulated tyrosine phosphorylation of insulin receptors, and decreased the number of IRS-1 molecules within liver tissues collected from treated rats. In contrast, only tyrosine phosphorylation of IRS-1 molecules was significantly affected in rat skeletal muscle tissue. Results of those studies suggest that IR can be rapidly induced through interference with tissue insulin signaling pathways; however, in those experiments, rats received markedly larger doses of LPS than those administered to horses in the study reported here.

Increases in serum TNF-α activity have been detected in the plasma of horses following the experimental induction of endotoxemia, and this cytokine may mediate the development of IR in equids. Results of a study involving rodents indicated that TNF-α induces serine phosphorylation of IRS-1, which disrupts the interaction of IRS-1 with the catalytic domain of the insulin receptor and inhibits insulin-stimulated activation of the phosphatidylinositol 3-kinase cascade. Alternatively, IR may develop in horses after LPS administration because of increases in circulating cortisol.
concentrations. Administration of LPS significantly increases cortisol concentrations in ponies, and pretreatment of rat adipocytes with glucocorticoids inhibits insulin-mediated glucose uptake in vitro. Increased catecholamine concentrations have also been detected in humans after injection of LPS, and this response may lower S1. In an in vitro study of isolated rat muscle, physiologic concentrations of epinephrine inhibited insulin-mediated glucose uptake into tissues by modulating activation of IRS-1-associated phosphatidylinositol 3-kinase. Intravenous administration of epinephrine has also been shown to delay the ability of insulin to inhibit endogenous glucose production in humans.

Glucose effectiveness in horses was not altered by LPS administration in the present study, and values were consistent with those previously reported. In nonobese and moderately obese Thoroughbred geldings, mean ± SE Sg values of 1.43 ± 0.16 × 10⁻⁶ min⁻¹ and 1.59 ± 0.19 × 10⁻⁶ min⁻¹ have been detected, respectively, and for 46 healthy horses, a 95% confidence interval for Sg of 0.12 to 2.95 × 10⁻⁷ min⁻¹ has been reported. In the study reported here, mean AIRg was 83% and 45% higher than the pretreatment value at 24 and 48 hours after LPS administration, respectively. Before LPS infusion and during the week that horses received the control treatment, AIRg values were higher than the mean value of 270 mU min⁻¹ L⁻¹ detected in 46 healthy horses, but were within the 95% reference interval of 67 to 805 mU min⁻¹ L⁻¹ previously reported for this variable. Minimal model analysis values may vary between study populations because of differences in evaluation techniques and breed, sex, age, or diet of the study horses.

The results of our study have indicated that pancreatic beta cells of horses respond to endotoxin-induced IR by secreting more insulin. Compensated IR has been previously described in ponies and is recognized by the presence of hyperinsulinemia in chronically insulin-resistant animals. However, in the horses of the present study, mean DI decreased by 57% over 24 hours in response to LPS, which suggests that this compensatory response was inadequate. More time may be required for the pancreatic beta cells to fully respond to the decrease in SI, or alternatively, endotoxin may directly inhibit pancreatic function.

The data obtained in the present study may be relevant to the pathogenesis of laminitis because laminar keratinocytes appear to have a high requirement for glucose. Insulin-sensitive glucose transporter 4 protein within equine hoof tissues suggests that insulin plays an important role in glucose uptake. In vitro experiments performed with freshly isolated hoof explants have also revealed that laminae separate at the dermoepidermal junction when glucose concentrations are decreased within the tissue culture medium. Insulin resistance might also predispose horses to laminitis by inducing endothelial cell dysfunction. This may increase endothelin-1 synthesis and cause a concurrent decrease in nitric oxide production in the endothelium, resulting in vasoconstriction. It has previously been shown that endothelin-1 concentrations are higher in laminar connective tissues from horses with laminitis. In a recent study in horses, Eades et al determined that digital venous blood endothelin-1 concentrations were significantly higher than baseline values at 11 hours after carbohydrate was administered to induce laminitis.

In the present study, administration of 20 ng of E. coli O55:B5 LPS/kg decreased insulin sensitivity while enhancing the acute insulin response to glucose and did not alter glucose effectiveness in horses. Results suggest that endotoxemia will further compromise glucose and insulin dynamics in chronically insulin-resistant horses, which may place them at higher risk for development of laminitis.

References


