Increased responsiveness to intravenous lipopolysaccharide challenge in steers grazing endophyte-infected tall fescue compared with steers grazing endophyte-free tall fescue

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Abstract

Fescue toxicosis in cattle occurs as a result of consumption of ergot alkaloids in endophyte-infected (E+, Neotyphodium coenophialum) tall fescue (Festuca arundinacea). The condition is characterized by pyrexia, decreased weight gains, rough hair coats, and decreased calving rates. The objective of this experiment was to investigate whether steers grazing E+ fescue have altered host response to lipopolysaccharide (endotoxin, LPS) challenge compared with steers grazing endophyte-free (E−) fescue. Angus steers (n = 8) had continuously grazed either E+ (n = 4) or E− (n = 4) tall fescue grass for 8 months prior to the experiment. The E+ steers had lower body weight, depressed average daily gain, and decreased basal serum prolactin compared with the E− steers prior to LPS administration. Each steer received a single bolus i.v. injection of LPS (0.2 µg/kg body weight; Escherichia coli; 026:B6) dissolved in sterile saline, and blood was serially collected every 30 min for 4 h and at 24 h post LPS administration. LPS increased serum tumor necrosis factor-α (TNF-α), cortisol, and haptoglobin but decreased plasma glucose and IGF-I. Importantly, however, TNF-α, cortisol, and IGF-I responses to LPS were greater in E+ compared with E− steers. These results indicated that animals grazing E+ fescue had altered integrated metabolic host response compared with animals grazing E− fescue. Potentially, combined exposure to E+ fescue and a bacterial LPS could have greater deleterious effects on the animal compared with exposure to only one of the two and would likely lead to increased catabolism.


Introduction

Consumption of endophyte-infected (E+, Neotyphodium coenophialum; Glenn et al., 1996) tall fescue (Festuca arundinacea Schreb) is associated with fescue toxicosis in cattle (Thompson & Stuedemann 1993, Oliver 1997). Numerous ergot alkaloids found in E+ fescue are implicated as toxic agents (Porter 1995). Rough hair coats, increased body temperature, decreased intake, weight gains and reproductive efficiency, and alteration in secretion of various pituitary hormones are associated with ingestion of E+ fescue (Thompson & Stuedemann 1993). Among a variety of clinical chemistry changes such as depressed serum alkaline phosphatase (Oliver 1997) associated with fescue toxicosis, circulating prolactin (PRL) is generally decreased (Lipham et al. 1989, Aldrich et al. 1993).

An emerging body of literature indicates that an immune challenge leads to metabolic and endocrine shifts, which ultimately lead to decreased growth (Elsasser et al. 1995b, Spurlock 1997). An immune challenge may be bacterial or viral infection, acute stress, or other non-pathogenic challenge. Typically, an immune challenge results in an increase of one or, more often, all of the proinflammatory cytokines (interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α)). Once increased, these cytokines may invoke other immune modulators such as cortisol. The effects of TNF-α, for example, are consistent with the pathophysiology of fescue toxicosis (Thompson & Stuedemann 1993). Lipopolysaccharide (endotoxin, LPS) is a potent inducer of the proinflammatory cytokines, and these bring about the acute phase response. For example, marked increases of plasma TNF-α...
and cortisol were observed following LPS administration in cattle (Elsasser et al. 1994). Similarly, Webel et al. (1997) demonstrated in swine that intraperitoneal injection of LPS leads to increase of TNF-α, IL-6, and cortisol, followed by an increase in urea nitrogen, an indicator of induced protein catabolism. In cattle, haptoglobin (Hp) is one of the major acute phase proteins synthesized in the liver during inflammation (Godson et al. 1995, Young et al. 1996), and there have not been reports as to whether Hp is affected in fescue toxicosis.

Purdy et al. (1989) reported that steers grazing E+ fescue pastures that are moved to feedlots have increased morbidity and mortality and a decreased resistance to transportation stress. Moreover, there are speculations that consumption of E+ fescue results in a decreased pathogen resistance. Therefore, measurement of the host response to an inflammatory challenge was regarded as being potentially helpful to further the understanding of the fescue toxicosis condition.

Thus, the objective of this study was to determine if consumption of E+ fescue alters the host response to LPS challenge. We hypothesized that grazing E+ fescue forage would result in greater host response to LPS challenge compared with consumption of endophyte-free (E−) fescue forage and that may result in increased catabolism.

Materials and Methods

Animals

Angus steers (n=8) continuously grazed either E+ (n=4) or E− (n=4) tall fescue grass pastures from 22 April to 9 December 1997 (USDA/ARS, Natural Resource Conservation Center, Watkinsville, GA, USA). Before random assignment to E+/E− pastures, animals were weighed (16 h off-water weight) and blood was collected for serum PRL determination. Steer weight before beginning of grazing was 213.5 ± 3.3 kg (means ± s.d.) and serum PRL was 132.4 ± 41.27 ng/ml (means ± s.e.m.). Neither body weight nor serum PRL were different between E+ and E− steers. The E+/E− pastures were tested for the endophyte using tissue immunoblot kits (Agrinotics, Watkinsville, GA, USA). E+ pastures were >90% infected, whereas the E− pastures tested 0% endophyte infection. Additionally, total ergot alkaloid concentration was monitored throughout the grazing season using enzyme-linked immunosorbent assay (ELISA) according to Hill & Agee (1994). Ergot alkaloid concentration varied during the grazing season from 1 to 3.3 mg/kg for E+ fescue whereas it was always less than 0.03 mg/kg for E− fescue grass. The day before the experiment, E+ steer weights (358.4 ± 11.8 kg, mean ± s.d.) were decreased (P<0.01) compared with E− steers (393 ± 19.3 kg). Similarly, average daily gain (22 April to 9 December 1997) was depressed (P<0.02) in the E+ group (0.63 ± 0.06 kg, mean ± s.d.) compared with E− (0.77 ± 0.08 kg). After weighing, an indwelling cannula (Tygon; 1.02 mm internal diameter, 1.78 mm outside diameter) was surgically placed into each steer’s jugular vein for administration of LPS and for blood collection according to Hill et al. (1994). Endotoxin challenge was performed on the following day. Animals were tethered in individual stalls and provided with water ad libitum. Ambient temperature on the day of the endotoxin challenge (10 December 1997) averaged 11 °C.

Treatment and data collection Prior to LPS administration, two sham blood samples (10 ml/sample) were collected and discarded to accustom animals to blood collection. Blood samples were then collected into sterile tubes (Vacutainer; Becton Dickinson, Rutherford, NJ, USA) at times −30 and 0 min for determination of basal levels. At time 0, each steer received a single i.v. bolus of LPS (0.2 µg/kg body weight; Escherichia coli; 026:B6; Sigma, St Louis, MO, USA) dissolved in sterile saline (5 ml). Following LPS administration, blood samples were collected at 30-min intervals for 4 h, and steers were not fed. All animals were then returned to pastures and brought back the next morning to the sampling stalls for an additional blood collection at 24 h post LPS. After each blood collection and LPS administration, sterile 3.5% sodium citrate was placed in the cannulas to maintain patency and prevent blood clotting. Serum was then harvested, aliquotted, and stored at −70 °C until assayed for the compounds of interest.

Assay procedures

Prolactin Serum concentrations of PRL were determined by RIA procedures as in Mizinga et al. (1992) with reagents supplied by the USDA Hormone Distribution Program (Beltsville, MD, USA). The intra- and interassay coefficients of variation (C.V.) were 3-7% and 7-3% respectively.

Growth hormone Serum concentrations of growth hormone (GH) were measured by RIA as described previously (Elsasser et al. 1986) using reagents and protocol supplied by the USDA Hormone Distribution Program and the National Pituitary Agency, Bethesda, MD, USA. All samples were assayed together with an intra-assay C.V. of 8.5%.

Cortisol Serum cortisol was determined with a commercially available solid-phase RIA kit (Diagnostic Products Corp., Los Angeles, CA, USA) which has a 2 ng/ml limit of detection. All samples were assayed together with an intra-assay C.V. of 7-9%.

Tumor necrosis factor-α Serum immunoreactive TNF-α was measured by a specific RIA for the bovine as
Serum urea nitrogen
Serum urea nitrogen (SUN) was determined using a commercially available kit based on colorimetric endpoint ultraviolet method (Sigma Diagnostics, St Louis, MO, USA).

Insulin-like growth factor-I (IGF-I) was determined by RIA according to Elsasser et al. (1988). All samples were assayed together with an intra-assay C.V. of 8.1%.

Haptoglobin
Serum concentration of Hp was determined by an ELISA according to Young et al. (1995) using plates coated with hemoglobin for capture and anti-haptoglobin monoclonal antibody for detection of serum Hp.

Statistical analysis
Analysis was performed using the Statistix software (Statistix Analytical Software, Tallahassee, FL, USA). All data were subjected to analysis of variance (ANOVA) with the following terms in the statistical model: steer, treatment, time, treatment × time. If significant effect of time within treatment, or treatment × time occurred (P<0.05) means were separated by Fisher’s PLSD post hoc test. Response over time areas under the curve were calculated for TNF-α and SUN responses. Calculations were performed using trapezoidal summation of individual areas according to Elsasser et al. (1996).

Results
Steers grazing E+ fescue exhibited signs of fescue toxicosis (Thompson & Stuedemann 1993, Oliver 1997) including rough hair coats and decreased body weight gains. Basal circulating PRL was also reduced (P<0.001) in the E+ group (0.36 ± 0.02 vs 14.11 ± 3.33 ng/ml, mean ± s.e.m. for E+ vs E− respectively) prior to LPS administration. While LPS administration itself resulted in insignificant changes of circulating PRL in both the E+ and E− groups, serum PRL in the E+ group remained reduced compared with E− during the entire LPS challenge (data not shown).

Prior to LPS challenge, serum TNF-α concentrations were low and not different between groups. However, serum TNF-α rapidly increased in both E+ and E− groups following LPS (Fig. 1a). Across groups, comparison of the increases in TNF-α revealed that the TNF-α response was of greater magnitude and duration in the E+ group (P<0.001). Consequently, the integrated area under the curve (AUC) TNF-α response in the E+ group was greater (P<0.05) compared with E− (Fig. 1b). In both E+ and E− groups, serum TNF-α returned to baseline by 4 h and was not different thereafter (values at 24 h not shown).

Serum Hp concentrations were not different between groups prior to LPS (Table 1). Following LPS challenge, Hp gradually increased in both groups and was greater (P<0.01) within both treatments at 24 h.

Serum cortisol was not different prior to LPS but rapidly increased following LPS in both groups (P<0.0001), and remained elevated for 240 min (Fig. 2). Serum cortisol was greater (P<0.05) in E+ compared with E− at 180 min and tended to be greater at 210 (P=0.09) and 240 (P=0.07) min respectively. At 240 min post LPS treatment, E− serum cortisol was not different from pre-LPS values, whereas E+ serum cortisol remained elevated. Therefore, serum cortisol response to LPS in the E+ group was greater compared with the E− group.
There were no treatment differences in serum GH prior to LPS and the GH response to LPS was similar in both groups (Fig. 3). Circulating GH increased ($P<0.05$) at 60 min in both groups compared with pretreatment values and similarly GH was increased in E+ at 120 min ($P<0.01$). Serum GH was again increased ($P<0.01$) in both groups at 24 h compared with respective pretreatment GH concentrations.

Serum IGF-I concentrations in the E+ group were decreased ($P<0.05$) compared with E− both before and after LPS (Fig. 4). Following LPS, serum IGF-I decreased in both groups. The magnitude of this decrease was 22% and 18% for E− and E+ respectively at 24 h. Within the E− treatment, the decrement in serum IGF-I with time (0 vs 24 h) was significant ($P<0.05$).

Serum glucose concentration was decreased ($P<0.05$) in the E+ compared with E− group prior to LPS challenge (Fig. 5). A hypoglycemic response to LPS was apparent in both groups by the third hour; however, across treatments serum glucose was lowered ($P<0.05$) in the E+ group at 180 and 210 min. The maximal decrease in serum glucose was 29% and 28% for the E+ and E− groups respectively. At 24 h post LPS, there were no treatment differences (78.1 ± 2.7 and 90 ± 4.9 mg/dl, means ± s.e.m. for E+ and E− respectively).

Mean SUN values were 13.74 ± 0.32 and 13.95 ± 0.38 mg/dl (means ± s.e.m.) for E+ and E− respectively, and were not different. However, LPS challenge resulted in SUN AUC (0–24 h) response of 23.4 ± 3.8 AUC units (mean ± s.e.m.) that was upward (net increase) in the E+ group. On the other hand, the E− the SUN response (47.4 ± 12.3 AUC units) was downward (net decrease) and different ($P<0.01$) from E+ SUN AUC response to LPS.

**Discussion**

The decreased weight gain, signs the animals exhibited, and the decreased serum PRL in the E+ group indicated

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**Table 1** Serum Hp concentrations (mean ± s.e.m., mg/dl) and Hp AUC in steers (n=4/group) grazing E+ or E− tall fescue challenged with 0.2 µg/kg body weight LPS i.v. bolus at time 0

<table>
<thead>
<tr>
<th>Time</th>
<th>0*</th>
<th>30 min–4 h</th>
<th>24 h</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E+</td>
<td>1 0</td>
<td>1·25 ± 0·067</td>
<td>1·61 ± 0·21***</td>
<td>9·18 ± 2·64</td>
</tr>
<tr>
<td>E−</td>
<td>1 0</td>
<td>1·17 ± 0·065</td>
<td>1·31 ± 0·067**</td>
<td>7·01 ± 1·44</td>
</tr>
</tbody>
</table>

*Time 0 is the average of ~30 min and 0 bleeding times. For statistical purposes samples with Hp values of <1 mg/dl (below assay sensitivity) were assigned a value of 1 mg/dl.

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**Figure 2** Serum cortisol concentration (mean ± s.e.m.) in steers (n=4/group) grazing E+ or E− tall fescue challenged with 0.2 µg/kg body weight LPS i.v. bolus at time 0. *Cortisol values were greater in E+ compared with E− ($P<0.05$) at 180 min and tended to be greater ($P=0.09$, $P=0.07$) at times 210 and 240 min after LPS treatment respectively. *$P<0.05$, **$P<0.01$, ***$P<0.001$ vs time 0 within treatment.

**Figure 3** Serum GH concentration (mean ± s.e.m.) in steers (n=4/group) grazing E+ or E− tall fescue challenged with 0.2 µg/kg body weight LPS i.v. bolus at time 0. There was no treatment or treatment × time effect ($P>0.05$). At 24 h (data not shown) GH was increased compared with pretreatment values in both E+ and E−. *$P<0.05$, **$P<0.01$ vs time 0 within treatment.
that this group was affected by the endophyte-infected forage. It is surmised that the ergot alkaloids present in the E+ forage were the reason for this difference. The decrease in PRL is a widely used marker for ergot alkaloid ingestion and perhaps lethargy and both the coughing and the lethargy were not apparent after the first four hours of the experiment.

The magnitude and duration of the TNF-α increase following LPS challenge was similar to cattle (Kahl et al. 1997) and sheep (Coleman et al. 1993). The augmented TNF-α response in the E+ steers may have been an effect of decreased feed intake, the effects of the ergot alkaloids in the E+ forage, or both. Intake is decreased in cattle grazing E+ fescue (Thompson & Studemann 1993). In this regard, chronic decrease in intake in humans was reflected by enhanced TNF-α production by monocytes stimulated in vitro (Vaisman et al. 1989). Alternatively, ergot alkaloids in E+ forage can themselves induce a variety of host responses in cattle, including increased levels of thromboxane B₂, von Willibrand factor, and angiotensin-converting enzyme (Oliver 1997). The significance of this difference would appear to be that animals grazing E+ fescue would have greater muscle catabolism in response to an inflammatory challenge because increased circulating TNF-α is associated with increased muscle protein catabolism (Zamir et al. 1992).

The increased Hp in both groups in response to LPS is indicative of an inflammatory response. Hp is one of the major acute phase proteins in cattle (Godson et al. 1995, Young et al. 1996). The sampling duration here following LPS may not have been sufficiently long to observe an effect across treatment groups. For example, cattle challenged with the proinflammatory cytokine IL-1 (Godson et al. 1995) had elevated serum Hp within 24 h, and it remained elevated for 72 h. Moreover, Cheryk et al. (1998) reported increased Hp values in cattle within 24 h, and peak values 72 h post bacterial challenge with Pasteurella haemolytica A1. Nevertheless, the lack of initial difference between E+ and E− indicates acute phase protein synthesis, such as Hp in the liver, is not likely to be stimulated by a chronic exposure to ergot alkaloids.

Previously, plasma cortisol in steers was not affected by consumption of E+ fescue (Aldrich et al. 1993). Acute administration of ergotamine, however, promptly increased plasma cortisol levels in cattle (Browning et al. 1998). The increased cortisol response to LPS in the E+ steers observed here indicates that ergot alkaloids sensitized the pituitary-adrenal axis for cortisol secretion. The kinetics of the cortisol response to LPS here were similar to previous reports in cattle (Giri et al. 1990, Elsasser et al. 1994) and sheep (Coleman et al. 1993, Briard et al. 1998). The general mechanism for the cortisol response to LPS appears to be both increased adrenocorticotropin (ACTH) and hypothalamic corticotropin-releasing hormone (Dadoun et al. 1998). The mechanism for the increased cortisol response to LPS in the E+ group may well have been secondary to increased TNF-α considering that

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**Figure 4** Concentration of IGF-I (mean ± S.E.M.) in steers (n=4/group) grazing E+ or E− tall fescue challenged with 0.2 µg/kg body weight LPS i.v. bolus at time 0. *IGF-I values were decreased (P<0.05) in E+ compared with E− for the entire period. *P<0.05 vs time 0 within treatment.

**Figure 5** Serum glucose concentration (mean ± S.E.M.) in steers (n=4/group) grazing E+ or E− tall fescue challenged with 0.2 µg/kg body weight LPS i.v. bolus at time 0. *Glucose values for E+ were lower (P<0.05) compared with E− before LPS treatment and for most of the 240-min sampling period, but not at 24 h (data not shown). *P<0.05, **P<0.01 vs time 0 within treatment.
TNF-α is capable of increasing ACTH secretion (Sharp et al. 1989). Increased cortisol is associated with progressive muscle protein loss (Kaplan 1988). Together, the increased TNF-α and cortisol observed in the E+ group indicate that exposure of animals to both E+ fescue and infectious agents would result in decreased weight gains and muscle mass.

The lack of treatment effect on serum GH before and after LPS challenge indicates that grazing E+ forage did not affect pituitary GH secretion and the observed increases in both E+ and E− groups at particular time-points may be due to normal GH pulsatility. It has been previously reported that steers grazing E+ fescue had elevated basal but not thyrotropin-stimulated serum GH (Thompson et al. 1987). Plasma GH was also elevated in steers administered ergotamine intravenously (Browning et al. 1989). The effects of LPS on GH secretion are minor. Previously, LPS challenge resulted in decreased plasma GH in cattle (Kenison et al. 1991), but in increased circulating GH in sheep (Coleman et al. 1993, Briard et al. 1998). It is expected that the lower dose of LPS used in the present experiment may have been insufficient to modulate GH secretion, but more frequent blood sampling regimen may be necessary to confirm that. Overall, circulating GH appears to be less sensitive to LPS challenge compared with TNF-α and cortisol.

In contrast to the lack of effect of E+ fescue consumption and LPS upon GH values, basal serum IGF-I values were reduced in the E+ group. The consistently reduced serum IGF-I in E+ agrees with Hazlett et al. (1998) where serum IGF-I was reduced in heifers on E+ fescue compared with controls fed oats. Diet composition and intake modulated circulating IGF-I concentrations in steers (Elsasser et al. 1989). Undernutrition not only leads to decreased circulating IGF-I but also to uncoupling of the IGF-I regulation by GH. IGF-I is synthesized predominantly in the liver (Hosnser et al. 1997) and perhaps the apparent uncoupling of IGF-I from GH here is a function of decreased hepatic function. Hepatic function appears compromised in cattle grazing E+ fescue as evidenced by a reduction in circulating concentration of several hepatic enzymes (Oliver 1997). Because IGF-I is anabolic (Hosnser et al. 1997), the decreased IGF-I values in the E+ group appear to be contributory to the decreased growth observed in fescue toxicosis (Thompson & Suedemann 1993). Intake in the present study was not measured, but body weights clearly reflect depressed average daily gain and, perhaps, intake. A decreased intake would explain both decreased IGF-I and lack of effect on GH upon IGF-I secretion. Moreover, undernutrition can lead to a reduction in IGF-I but an increase in circulating GH due to the loss of negative feedback from IGF-I (Vance et al. 1992). Administration of LPS decreased plasma IGF-I in cattle and the decrease was not dependent on feed intake (Elsasser et al. 1995a). Reduced basal IGF-I values and the further reduction in serum IGF-I in the present experiment in response to LPS suggest that animals grazing E+ fescue and exposed to pathogens would have a greater decrease in growth rates compared with animals independently exposed to only E+ fescue or pathogens.

The decreased serum glucose in the E+ group prior to LPS compared with E− differs from other reports. J W Oliver, R D Linnabary, J R Strickland, A E Schultz, J C Waller, H A Fribourg, L K Abney, E M Bailey & M A Barnhill (personal communication) observed increased serum glucose in steers grazing E+ fescue, whereas Lipham et al. (1989) found no difference in a similar experiment. A biphasic circulating glucose response to LPS in cattle has been reported with an initial hyperglycemia followed by a sustained hypoglycemia (Elsasser et al. 1996). The hyperglycemic phase may not be observed at low LPS doses (Giri et al. 1990). The hypoglycemic phase following LPS is considered detrimental (Elsasser et al. 1996) because it has considerable duration. LPS-induced hypoglycemia is a function of increased glucose utilization, increased glucose oxidation, and decreased gluconeogenesis (Johnson et al. 1997). Because there was no difference in the magnitude of the decrease in serum glucose following LPS in both the E+ and E− groups, it appears as though the hypoglycemic effect was LPS driven. Moreover, the prevalence of hypoglycemia in spite of a substantial increase in serum cortisol further supports the notion that serum glucose control was a function of LPS. The fact that serum cortisol was elevated prior to an appreciable decrease in serum glucose indicates also that the cortisol response was not mediated by the decrease in serum glucose.

The increased SUN response to LPS as measured by the AUC response in the E+ group compared with E− indicates that increased nitrogen metabolism occurred as a function of grazing E+ fescue. Circulating urea nitrogen in steers has either been unaltered following E+ fescue consumption (Lipham et al. 1989) or increased (Oliver 1997), possibly due to mild dehydration. The increased circulating urea nitrogen after LPS is a function of decreased protein synthesis, lowered capacity for nitrogen retention, and increased mobilization of skeletal muscle amino acids (Zamir et al. 1992, Elsasser et al. 1996, Webel et al. 1997). Temporally, urea nitrogen increased at 8 and 12 h post LPS treatment in pigs (Webel et al. 1997), whereas in cattle the greatest increase was from 6 to 12 h post LPS treatment (Elsasser et al. 1996). The increased AUC response for SUN by E+ here may be an integrated response to the decreased IGF-I and the increased serum cortisol and TNF-α which all favor protein degradation with perhaps a direct effect of LPS as well. Therefore, again the metabolic response to LPS in the E+ group is balanced towards catabolism such that contact with pathogens or perhaps another inflammatory agent would lead to increased tissue loss.
In summary, the hypothesis that chronic exposure to ergot alkaloids in cattle grazing E+ tall fescue results in a greater host response to LPS is supported. Therefore, chronic exposure to ergot alkaloids in E+ fescue sensitizes the animal to inflammatory agents such as LPS. Roth et al. (1997) suggest that concomitant exposure to LPS and certain toxicants increases the toxicity of the toxic agent. In the case here, chronic exposure to ergot alkaloids results in a greater host response to LPS that potentially would increase susceptibility to disease or another stress.

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