The response of the hepatic insulin-like growth factor system to growth hormone and dexamethasone in calves

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Abstract

Glucocorticoids inhibit postnatal growth and yet can stimulate the somatotropic axis around birth. The aim of the present study was to investigate the effects of dexamethasone on the somatotropic axis and on the responses of the insulin-like growth factor (IGF) system to growth hormone treatment in calves. Calves (n=24) were randomly divided into four groups. Group DX was injected with dexamethasone (30 µg/kg body weight per day), group GH was injected with 500 mg slow-release bovine growth hormone at 14-day intervals, group GHDX was injected with dexamethasone and bovine growth hormone, and group CNTRL (serving as control) was injected with saline from day 3 to day 42 of life. Blood samples were taken on day 3 and blood and liver samples were obtained on days 7, 14, 28 and 42. Body weight increased in the CNTRL and GH groups up to the end of the study and in the DX and GHDX groups up to the fourth week. Dexamethasone treatment decreased (P,0·05) plasma IGF binding protein (IGFBP)-1 on days 7 and 14, but increased (P,0·05) plasma IGFBP-1, decreased (P,0·05) plasma IGF-I and IGFBP-3, and decreased hepatic mRNA for growth hormone receptor (GHR) and IGF-I on day 42. Growth hormone treatment increased (P<0·05) plasma growth hormone concentrations on days 7 and 14, tended to increase (P<0·1) plasma IGF-I concentrations on day 42, and increased (P<0·05) hepatic mRNA levels of GHR on day 14 and IGF-I mRNA levels on days 7 and 14. The combined dexamethasone and growth hormone treatment increased plasma growth hormone concentrations on day 7 and resulted in the highest plasma concentrations of IGF-I and IGFBP-3 (day 7 to day 28) as well as the greatest abundance of hepatic GHR (day 14) and IGF-I (days 7 and 14) mRNA. Plasma IGFBP-1 concentrations in the GHDX group behaved in a similar manner as in the DX group. In conclusion, the response of the somatotropic axis to growth hormone treatment could be greatly enhanced by dexamethasone treatment during the neonatal and early postnatal period, but body weight gain was not improved. Dexamethasone alone inhibited the somatotropic axis and postnatal growth after the first month of life.


Introduction

Although several hormones regulate postnatal growth, the somatotropic axis becomes the dominant endocrine system (Spencer 1985, Etherton & Bauman 1998, Breier et al. 2000). Glucocorticoids inhibit prenatal (Newnham & Moss 2001) and postnatal growth, in part by direct interaction with the somatotropic axis (Spencer 1985, Unterman & Phillips 1985, Bloomfield et al. 2001, Butler & LeRoith 2001, Renaville et al. 2002). However, in the perinatal period glucocorticoids are supposed to enhance the maturation of the somatotropic axis. The prepartum cortisol surge plays an important role in initiating the perinatal switch of the somatotropic axis from the fetal to the postnatal status and function (Gluckman et al. 1999, Breier et al. 2000). Thus, cortisol stimulates hepatic growth hormone receptor (GHR) and insulin-like growth factor-I (IGF-I) mRNA levels in the sheep fetus (Li et al. 1996) and studies with hepatocytes indicated an increase in GHR and IGF-I expression and enhanced IGF-I response to growth hormone if combined with dexamethasone administration (Brameld et al. 1995). Recent studies in neonatal pigs report even enhanced postnatal growth and stimulation of the growth hormone (GH)–IGF system after dexamethasone treatment, lasting in part for the whole growth period (Carroll 2001, Gaines et al. 2002).
In addition, our own investigations in neonatal calves indicated a similar effect of dexamethasone on the somatotropic axis (Sauter et al. 2003). In contrast, dexamethasone reduced IGF-I levels in adult cattle (Elsasser et al. 1997, Maciel et al. 2001). Therefore, the effects of glucocorticoids on the somatotropic axis are inconsistent and may depend on the developmental stage.

Little is known of how glucocorticoids interfere with the somatotropic axis in the early growth period of calves. Furthermore, the effects of glucocorticoid treatment on growth in fetal animals and preterm infants are inconsistent (Newnham & Moss 2001). Plasma cortisol concentrations in calves were high around birth and then rapidly decreased with postnatal growth, whereas IGF-I concentrations decreased during the first week of life, but then increased (Kerr et al. 1991, Hammon & Blum 1997, 1998, Nussbaum et al. 2002). The present study was carried out to clarify the influence of dexamethasone on the somatotropic axis during the first 6 weeks of life. We have tested the hypothesis that dexamethasone treatment modifies the somatotropic axis and the response of the hepatic IGF system to growth hormone treatment in calves. Therefore, we have treated calves for 40 days with either dexamethasone or growth hormone alone or in combination.

Materials and Methods

Animals, husbandry, feeding and experimental procedures

All animal handling procedures were approved by the Purdue Animal Care and Use Committee. Twenty-four male Holstein calves, aged 1–2 days, were purchased from a single large commercial dairy farm and transported to the Purdue University Dairy Research and Education Center. Calves were born spontaneously, separated from their dams at birth, fed colostrum and housed individually. Calves were weighed upon receipt, blocked by initial body weight and randomly assigned within each block to one of four treatment groups (n=6 per group). The following treatments were initiated on day 3 of life: dexamethasone was administered subcutaneously (Azium, Schering-Plough, Terre Haute, IN, USA) at 30 μg/kg body weight per day (group DX); growth hormone, as 500 mg slow-release recombinant bovine somatotropin (Posilac, Monsanto, St Louis, MO, USA), was administered subcutaneously at 14-day intervals (on days 3, 17 and 31 of age; group GH); dexamethasone and Posilac (group GHDX) were administered in combination at the same concentrations as for the DX and GH groups and were injected subcutaneously; saline treatment acted as a control (group CNTRL). Treatments continued until 42 days of age. The dose of dexamethasone was chosen according to previous studies with neonatal calves (Sauter et al. 2003). The dose of bovine somatotropin is based on Holzer et al. (2000) and previous studies using neonatal calves (Hammon & Blum 1997). A constant rate of growth hormone release during the 14-day period was assumed to provide 0.5 to 0.9 mg/kg body weight per day, which is comparable to the effective daily injection of growth hormone used in previous studies (Hammon & Blum 1997).

Calves were fed a milk replacer diet (Milk Specialties Company, Dundee, IL, USA), which contained 29% crude protein, 15% crude fat and less than 0.15% crude fiber at a rate of 2% of body weight on a dry milk replacer basis. Milk replacer was diluted with warm water to 15% solids and was fed in buckets twice daily at 0700 and at 1600 h. Calves were weighed weekly, and the amount fed was adjusted according to body weight. Fresh water was available at all times. Calves that failed voluntarily to consume milk replacer within 45 min were fed their scheduled allotment of milk replacer via stomach tube.

To protect against bacterial infections all calves were injected intramuscularly with 1.5 mg/kg body weight ampicillin twice daily (Polyflex; Wyeth, Fort Dodge Animal Health, Overland Park, KA, USA) and 1500 U/kg body weight penicillin G procaine daily (Penicillin G Procaine, G.C. Hanford, Syracuse, NY, USA) upon receipt and for the following 2 days. The health status was evaluated weekly based on the following clinical traits: rectal temperature, heart rate, respiratory rate, behavior, nasal discharge, respiratory sounds, appetite, fecal consistency and navel adhesion. Calves with symptoms of respiratory or gastrointestinal infections were treated as per instructions of the Veterinary School at Purdue University.

Blood sampling and analyses

Blood was taken from the jugular vein with evacuated tubes on days 3, 7, 14, 28 and 42 of life. Tubes were put on crushed ice until centrifuged at 550 g for 15 min. Supematants were aliquoted and stored at −20 °C. Tubes containing dipotassium-EDTA (1.8 g/l blood) were used for the determination of plasma concentrations of GH, IGF-I, IGF binding protein (IGFBP)-1 and IGFBP-3 four to five hours after food intake. Plasma IGF-I, GH and IGFBP-1 concentrations were measured by radio-immunoassays as described previously (Hammon & Blum 1997, Kaufhold et al. 2000). Plasma concentrations of IGFBP-3 were measured by enzyme immunoassay (EIA) as described by Hennies and Sauerwein (2003).

Analyses in liver

Liver biopsy samples (about 500 mg) were obtained on days 7, 14, 28 and 42 of life, 2 to 3 h after food intake for analysis of IGF-I and GH receptor mRNA. The biopsy technique was adapted from Greenfield et al. (2000). Calves were restrained using a small animal squeeze chute and tilt table combination and were placed on their left side. The area above the 11th and 12th intercostal space on a line...
from the hip joint to the elbow was clipped, scrubbed with Betadine (Purdue Pharma L.P., Stamford, CT, USA) and swabbed with 70% ethanol. Lidocaine (10 ml; 2% lidocaine hydrochloride; Phoenix Pharmaceutical, St Joseph, MO, USA) was injected subcutaneously. Liver biopsy samples were obtained percutaneously. Samples were rinsed in saline and transferred to a fresh tube containing a guanidinium thiocyanate solution (4 M guanidinium thiocyanate, 25 mM sodium citrate (pH 7.4), 0.5% sarkosyl and 0.1 M β-mercaptoethanol) and frozen in liquid nitrogen. All samples were stored at −80 °C until analysis.

Isolation of RNA and Northern blotting

Total RNA was extracted from biopsy samples and 20 µg were separated by electrophoresis through a 1% agarose gel and transferred to a Genescreen membrane (NEN Life Science Products, Boston, MA, USA) and prehybridized as described (Donkin et al. 1996). The cDNA probes for GHR (total GHR) and IGF-I were kindly provided by Dr Matt Lucy (University of Missouri, MO, USA) and have been described recently (Kobayashi et al. 1999). The 32P-labeled cDNA probes were prepared using [dC-32P]TP and the Ready-to-Go DNA labeling beads dCTP random oligonucleotide priming kit (Pharmacia, Piscataway, NY, USA) to a specific activity of approximately 109 c.p.m./µg DNA. Membranes were probed sequentially for IGF-I, GHR, and 18S rRNA. Membranes were exposed to Kodak X-Omat film for 1 to 3 days at −80 °C. Labeled probes were stripped by boiling for 60 min in a buffer containing 1% sodium dodecyl sulfate, 15 mM sodium chloride and 1.5 mM sodium citrate. The removal of labeled probes from membranes was verified using a Geiger counter. Abundance of mRNA for each transcript was quantified from digital scans of autoradiographic images using Kodak Digital Science 1D Image Analysis software (Eastman Kodak Co, Rochester, NY, USA). Dexamethasone, growth hormone treatment and time were fixed effects and the individual calves were considered random effects. For the evaluation of differences in time-dependent changes within dexamethasone or growth hormone treatments, interactions (dexamethasone × time; growth hormone × time) were included in the model. Treatment and time effects were localized by Bonferroni t-test (P<0.05). Due to heteroscedasticity of IGFBP-1, the data were transformed to log values prior to analysis, and the reported values reflect the untransformed means.

Results

Food intake, body weight and health status

Body weight (Fig. 1) increased (P<0.05) in the CNTRL and GH groups up to week 6 and in the DX and GHDX groups up to week 5. Different treatments affected (P<0.05) body weight with time. Calves of the DX and GHDX groups ceased growing after week 4 of life, and in week 6 body weight was higher (P<0.05) in the CNTRL and GH groups than in the DX and GHDX groups. Food intake increased in accordance with body weight in all groups from 5.3 ± 0.3 to 8.6 ± 0.4 kg milk per day from week 1 to week 6. Food intake was influenced differently (P<0.05) by different treatments during the experimental period and was reduced (P<0.05) in week 6 by dexamethasone treatment (8 ± 0.5 and 9.2 ± 0.3 kg milk per day for dexamethasone-treated and non-dexamethasone-treated calves respectively). Two calves from the DX and GHDX groups respectively were excluded from the study.
after day 28 because of health problems. All other calves were healthy up to the end of the study.

**Blood parameters**

Plasma growth hormone concentrations (Fig. 2) increased \( (P < 0.05) \) in the GH and GHDX groups from day 3 to day 7 and then decreased \( (P < 0.05) \) up to day 28. Different treatments had different effects \( (P < 0.001) \) on growth hormone concentrations with time; concentrations on day 7 were highest \( (P < 0.01) \) in the GH group and were higher \( (P < 0.01) \) in the GHDX group than in the CNTRL and DX groups. On day 14, concentrations were highest \( (P < 0.01) \) in the GH group.

Plasma IGF-I concentrations (Fig. 3) increased \( (P < 0.05) \) in the CNTRL group from day 14 to day 42, increased \( (P < 0.05) \) in the GH group from day 3 to day 42, and increased in the GHDX group \( (P < 0.05) \) from day 3 to day 28 but thereafter decreased \( (P < 0.05) \) to day 42. Different treatments changed \( (P < 0.001) \) IGF-I concentrations during the experimental period. Plasma IGF-I concentrations on days 7 and 14 were higher \( (P < 0.05) \) in the GHDX group than in the CNTRL and DX groups, and on day 14 tended to be higher \( (P < 0.01) \) in the GHDX group than in the GH group. On day 28, IGF-I concentrations were higher \( (P < 0.05) \) in the GHDX group than in all other groups and were lower \( (P < 0.05) \) in the DX than in the GH group. On day 42, concentrations were lowest \( (P < 0.05) \) in the DX group and tended to be higher \( (P < 0.01) \) in the GH DX group.

Plasma IGFBP-1 concentrations (Fig. 4) increased \( (P < 0.01) \) in the CNTRL and GH groups from day 3 to day 7 and then decreased \( (P < 0.01) \) up to day 42. Concentrations increased \( (P < 0.05) \) in the DX and GHDX groups from day 28 to day 42. Different treatments changed \( (P < 0.001) \) IGFBP-1 concentrations with time. Dexamethasone decreased IGFBP-1 concentrations \( (P < 0.05) \) on days 7 and 14 and increased IGFBP-1 concentrations \( (P < 0.05) \) from day 28 to day 42. Different treatments had different effects \( (P < 0.05) \) at the specific time points.

Plasma IGFBP-3 (Fig. 5) concentrations increased \( (P < 0.05) \) in the CNTRL and GH groups up to day 42.

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**Figure 2** Plasma growth hormone (GH) concentrations on days 3, 7, 14, 28, 42 of life in control calves (CNTRL), calves treated with dexamethasone (30 µg/kg body weight/day; DX), calves treated with growth hormone (500 mg/14 days; GH), and calves treated with dexamethasone and growth hormone (GHDX) in the same amounts as the DX and GH groups. Arrows indicate the times of growth hormone treatment. Means with different uppercase letters (A, B, C) are significantly different \( (P < 0.05) \) at the specific time points.

**Figure 3** Plasma IGF-I concentrations on days 3, 7, 14, 28, 42 of life in control calves (CNTRL), calves treated with dexamethasone (30 µg/kg body weight/day; DX), calves treated with growth hormone (500 mg/14 days; GH), and calves treated with dexamethasone and growth hormone (GHDX) in the same amounts as the DX and GH groups. Arrows indicate the times of growth hormone treatment. Means with different uppercase letters (A, B, C) are significantly different \( (P < 0.05) \) at the specific time points.

**Figure 4** Plasma IGFBP-1 concentrations on days 3, 7, 14, 28, 42 of life in control calves (CNTRL), calves treated with dexamethasone (30 µg/kg body weight/day; DX), calves treated with growth hormone (500 mg/14 days; GH), and calves treated with dexamethasone and growth hormone (GHDX) in the same amounts as the DX and GH groups. Arrows indicate the times of growth hormone treatment. Means with different uppercase letters (A, B, C) are significantly different \( (P < 0.05) \) at the specific time points.

**Figure 5** Plasma IGFBP-3 concentrations on days 3, 7, 14, 28, 42 of life in control calves (CNTRL), calves treated with dexamethasone (30 µg/kg body weight/day; DX), calves treated with growth hormone (500 mg/14 days; GH), and calves treated with dexamethasone and growth hormone (GHDX) in the same amounts as the DX and GH groups. Arrows indicate the times of growth hormone treatment. Means with different uppercase letters (A, B, C) are significantly different \( (P < 0.05) \) at the specific time points.
Dexamethasone decreased (P<0.05) IGF-I mRNA levels on day 42.

Correlations between tissue and blood parameters

During the experimental period body weight correlated with hepatic mRNA abundance of IGF-I (r=0.56; P<0.001) and GHR (r=0.44; P<0.001) and with plasma concentrations of IGF-I (r=0.52; P<0.001), growth hormone (r= -0.29; P<0.01), IGFBP-1 (r= -0.28; P<0.01) and IGFBP-3 (r= -0.56; P<0.001). Levels of IGF-I mRNA in liver correlated with GHR mRNA levels (r=0.73; P<0.001) and with plasma concentrations of IGFBP-1 (r=0.62; P<0.001), IGFBP-1 (r= -0.28; P<0.01) and IGFBP-3 (r=0.49; P<0.01). Levels of GHR mRNA in liver correlated with plasma concentrations of IGFBP-1 (r=0.41; P<0.001), IGFBP-1 (r= -0.29; P<0.01) and IGFBP-3 (r=0.29; P<0.01). Plasma concentrations of IGF-I correlated with plasma concentrations of IGFBP-1 (r= -0.31; P<0.01) and IGFBP-3 (r= -0.85; P<0.01). Plasma concentrations of IGFBP-1 correlated with plasma concentrations of IGFBP-3 (r= -0.29; P<0.01). Almost the same pattern of correlations was seen in the CNTRL and GH group calves, whereas the number of correlations in the DX and GHDX groups were smaller (data not shown).

Discussion

The present study was performed to clarify the influence of dexamethasone on the somatotropic axis and the response of the hepatic IGF system to growth hormone treatment during the neonatal and early postnatal period in calves. We observed that the developmental increase in body weight in CNTRL calves was associated with an increase in plasma IGF-I and IGFBP-3 concentrations and with hepatic GHR and IGF-I mRNA levels, whereas plasma IGFBP-1 concentrations decreased. These findings support the general concept that the somatotropic axis is basically associated with growth performance during the early postnatal period (Kerr et al. 1991, Etherton & Bauman 1998, Breier et al. 2000, Renaville et al. 2000). However, plasma IGF-I and IGFBP-3 concentrations as well as hepatic mRNA levels of GHR, and IGF-I in CNTRL calves did not start to increase before day 14, indicating a delayed response of the somatotropic axis in postnatal growth regulation. Our findings in calves support the view that the somatotropic axis in neonatal calves is not fully competent at birth and that the postnatal rise in IGF-I levels is delayed (Hammon & Blum 1997, Nussbaum et al. 2002). The reasons for the low plasma concentrations of IGFBP-1 in all groups on day 3 are not known. The interval between feeding and blood sampling was the same for all groups and across sampling days. In addition,

Figure 5 Plasma IGFBP-3 concentrations on days 3, 7, 14, 28, 42 of life in control calves (CNTRL), calves treated with dexamethasone (30 μg/kg body weight/day; DX), calves treated with growth hormone (500 mg/14 days; GH), and calves treated with dexamethasone and growth hormone (GHDX) in the same amounts as the DX and GH groups. Arrows indicate the times of growth hormone administration. Means with different uppercase letters (A, B, C) are significantly different (P<0.05) at the specific time points.

Abundance of IGF-I and GHR mRNA in the liver (Table 1)

Abundance of GHR mRNA in liver tended to increase (P<0.1) in the CNTRL and GH groups from day 7 to day 42. Different treatments changed (P<0.001) GHR mRNA levels with time. On day 14 growth hormone and the combined dexamethasone and growth hormone treatment increased (P<0.05) GHR mRNA levels. On day 42, dexamethasone and the combined dexamethasone and growth hormone treatment decreased (P<0.05) GHR mRNA levels.

Abundance of IGF-I mRNA levels in liver increased (P<0.05) in the CNTRL and GH groups from day 14 to day 42 and in the DX group from day 14 to day 28. Different treatments tended to change (P<0.1) IGF-I mRNA levels with time. On days 7 and 14 growth hormone increased (P<0.01) IGF-I mRNA levels and mRNA levels on day 14 were higher (P<0.05) in the GHDX group than in the CNTRL and DX groups.
the order of sampling was uniformly balanced across treatments, therefore differences in IGFBP-1 are not attributable to short term nutritional status. Despite the lower IGFBP-1 in all groups on day 3, the plasma concentrations in the range of 5 to 50 mg/l, measured in the present study, correspond to postprandial plasma concentrations in neonatal calves (Sauter et al. 2003).

Dexamethasone treatment depressed plasma concentrations of IGFBP-1 in the neonatal period, but did not depress mRNA levels of GHR and IGF-I and plasma concentrations of IGF-I and IGFBP-3 before day 42. In the present study, chronic dexamethasone treatment failed to stimulate the somatotropic axis in the neonatal and early postnatal period, in contrast to recent findings in neonatal calves and pigs (Carroll 2001, Sauter et al. 2003). However, in these studies dexamethasone was injected immediately after birth and was administered only once (pigs; Carroll 2001) or for 4 days only (calves; Sauer et al. 2003). Obviously, the response of the somatotropic axis to dexamethasone treatment depends on age, dose, and duration of the administration (Bloomfield et al. 2001, Butler & LeRoith 2001). In human hepatocytes short-term dexamethasone treatment stimulated, whereas long-term treatment inhibited GHR gene expression (Vottero et al. 2003). The depression of the hepatic IGF system by dexamethasone on day 42 corresponds with findings in preterm infants (Bloomfield et al. 2001), during postnatal growth and in adults (Unterman & Phillips 1985, Burrin et al. 1999), including cattle (Elsasser et al. 1997, Maciel et al. 2001). Dexamethasone treatment may also affect growth hormone clearance (plasma growth hormone concentrations were lower in the GHDX group than in the GH group on days 7 and 14) possibly by interfering with growth hormone binding proteins (Gabrielsson et al. 1995).

Plasma growth hormone concentrations increased in the GH group at the beginning of the study, but concentrations did not remain elevated after day 14 of life. Although the blood sampling protocol did not permit a detailed evaluation of growth hormone status, the lack of plasma growth hormone responses in the GH and GHDX groups from day 28 onwards was unexpected (Holzer et al. 2000). The clearance rate of growth hormone may increase with age, because plasma growth hormone concentrations were elevated on day 14 of life (11 days after the first injection of growth hormone), but not on days 28 and 42 (11 days after the second and third injections of growth hormone respectively). The postnatal maturation of the somatotropic axis greatly depends on the competency of hepatic GHRs, which are low during fetal development and gradually increase after birth (Badinga et al. 1991, Min et al. 1999, Sauter et al. 2003). Growth hormone treatment up-regulates hepatic growth hormone binding sites in sheep, but not in lambs (Sauerwein et al. 1991, Min et al. 1999). Although growth hormone stimulated hepatic IGF-I mRNA levels up to day 14 in our study, plasma concentrations of IGF-I in the GH group did not increase before day 42 in our study, as is known for cattle (Elkasser et al. 1989, Holzer et al. 2000, Smith et al. 2002). Because hepatic IGF-I is the main source for circulating IGF-I in cattle (Pfaffl et al. 1998, Cordano et al. 2000), it may take some time before the mature IGF-I peptide is delivered to the circulation.

Most impressively, the combined growth hormone and dexamethasone treatment markedly stimulated the somatotropic axis up to day 28 of life. The IGF-I response to growth hormone treatment depends on the degree of maturation of the somatotropic axis and increases with age and nutrient intake (Breier et al. 2000; Holzer et al. 2000). Our findings suggest that dexamethasone greatly increases the hepatic IGF-I response to growth hormone treatment in the neonatal period. Studies with porcine hepatocytes, too, showed increased responsiveness of IGF-I mRNA to growth hormone after dexamethasone treatment.

Table 1 Hepatic mRNA levels (arbitrary units) of GHR and IGF-I in calves treated with 0.9% NaCl (CNTRL), 30 μg/kg body weight dexamethasone (DX), 500 mg/14 days growth hormone (GH), and 30 μg/kg body weight dexamethasone and 500 mg/14 days growth hormone (GHDX). Values are means ± S.E.M. (pooled standard error). Main effects of dexamethasone (δ), growth hormone (ϕ) and dexamethasone × growth hormone (δ × ϕ) are shown.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Main effects (P-values)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day</td>
<td>CNTRL</td>
</tr>
<tr>
<td>GHR</td>
<td>7</td>
<td>0.98 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>0.73 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>1.7 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>2.0 ± 0.31</td>
</tr>
<tr>
<td>IGF-I</td>
<td>7</td>
<td>0.39 ± 0.11</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>0.19 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>1.91 ± 0.42</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>2.27 ± 0.42</td>
</tr>
</tbody>
</table>

NS, not significant.
(Brameld et al. 1995), but in rats dexamethasone inhibited the IGF-I response to growth hormone (Luo & Murphy 1989, Beauloye et al. 1999). Because plasma insulin concentrations were elevated in the GHDX group (Hammon et al. 2003), insulin might, in part, have stimulated hepatic IGF-I production, as seen in rats and cows (Böni-Schnetzler et al. 1991, McGuire et al. 1995). Furthermore, elevated plasma IGF-I may result from reduced clearance rates due to increased IGFBP-3 and decreased IGFBP-1 plasma concentrations, which are closely associated with IGF-I and insulin concentrations. The IGFBP-3 retains IGF-I in the circulation by binding with the acid-labile subunit, whereas IGFBP-1 is able to leave the circulation (Clemmons 1997). The enhanced response of the somatotropic axis to growth hormone following dexamethasone treatment was abolished at the end of the study on day 42. Therefore, the enhanced growth hormone effects on the hepatic IGF system due to dexamethasone treatment might be age-dependent or might be a consequence of the chronic dexamethasone treatment.

Most parameters of the somatotropic axis measured in this study were closely related to body weight, as expected. However, contrary to chronic dexamethasone treatment in preterm infants and during postnatal growth, dexamethasone treatment in our study did not affect body weight gain before day 28 after birth (Spencer 1985, Bloomfield et al. 2001, Newnham & Moss 2001, Renaville et al. 2002). The lack of effects on growth performance during the first month of life in the DX group was associated with unresponsiveness of the somatotropic axis to dexamethasone. In neonatal pigs, a single dose of dexamethasone treatment after birth improved postnatal growth performance (Carroll 2001, Gaines et al. 2002), whereas chronic dexamethasone administration reduced growth rates (Burrin et al. 1999). Based on this information, the effects of glucocorticoids on growth performance in the neonatal period seem to depend on dose and duration of glucocorticoid administration, in accordance with studies in preterm infants (Bloomfield et al. 2001). Growth hormone treatment had no significant effect on body weight up to 6 weeks, but average daily gain was improved in the GH group when calves were studied during the first 2 months of life (Hammon & Donkin 2002). Previous studies in veal calves that were administered growth hormone daily up to the time of slaughter (age about 140 days) could not demonstrate any marked growth enhancement either (Ceppi & Blum 1994), indicating that it takes a long period of time before growing cattle become fully responsive to growth hormone. Administration of slow-release growth hormone to about 180-day-old calves resulted in a more distinct growth stimulation (Holzer et al. 2000). The enhanced hepatic IGF response to growth hormone treatment by dexamethasone failed to stimulate growth performance during the first month of life. Furthermore, the disappearance of stimulatory effects on the somatotropic axis after day 28 in the GHDX group was combined with a cessation of body weight gain.

In conclusion, dexamethasone administration improved the response of the IGF system to growth hormone treatment during the first month of life, but neither growth hormone nor dexamethasone alone or in combination stimulated postnatal growth during this time period. Dexamethasone and the growth hormone/dexamethasone combination depressed body weight gain and the somatotropic axis after day 28 of life, indicating that the response of the somatotropic axis to dexamethasone treatment in calves depends on age or at least on the duration of dexamethasone treatment.

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