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## Effect of progressive cachectic parasitism and growth hormone treatment on hepatic 5'-deiodinase activity in calves<sup>☆</sup>

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### Abstract

Thyroid status is compromised in a variety of acute and chronic infections. Conversion of thyroxine (T<sub>4</sub>) into the metabolically active hormone, triiodothyronine (T<sub>3</sub>), is catalyzed by 5'-deiodinase (5'D) mainly in extrathyroidal tissues. The objective of this study was to examine the effect of protozoan parasitic infection (*Sarcocystis cruzi*) on hepatic 5'D (type I) activity and plasma concentrations of T<sub>3</sub> and T<sub>4</sub> in placebo- or bovine GH (bGH)-injected calves. Holstein bull calves (127.5 ± 2.0 kg BW) were assigned to control (C, *ad libitum* fed), infected (I, 250,000 *S. cruzi* sporocysts per os, *ad libitum* fed), and pair-fed (PF, non-infected, fed to intake of I treatment) groups placebo-injected, and three similar groups injected daily with pituitary-derived bGH (USDA-B-1, 0.1 mg/kg, i.m.) designated as C<sub>GH</sub>, I<sub>GH</sub> and PF<sub>GH</sub>. GH injections were initiated on day 20 post-infection (PI), 3–4 days prior to the onset of clinical signs of the acute phase response (APR), and were continued to day 56 PI at which time calves were euthanized for liver collection. Blood samples were collected on day 0, 28, and 55 PI. Alterations in nutritional intake did not affect type I 5'D in liver. Treatment with bGH increased ( $P < 0.05$ ) 5'D activity in C (24.6%) and PF (25.5%) but not in I calves. Compared to PF calves, infection with *S. cruzi* reduced 5'D activity 25% ( $P < 0.05$ ) and 47.8% ( $P < 0.01$ )

<sup>☆</sup> Mention of a trade name, proprietary product, or specific equipment does not constitute a guarantee or warranty by the US Department of Agriculture and does not imply its approval to the exclusion of other products that may be suitable.

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in placebo- and bGH-injected calves, respectively. Neither nutrition nor bGH treatment significantly affected plasma concentrations of  $T_4$  and  $T_3$  on day 28 and 55 PI. However, plasma thyroid hormones were reduced by infection. On day 28 PI, the average plasma concentrations of  $T_3$  and  $T_4$  were reduced in infected calves (I and  $I_{GH}$ ) 36.4% ( $P < 0.01$ ) and 29.4% ( $P < 0.05$ ), respectively, compared to pair-fed calves (PF and  $PF_{GH}$ ). On day 55 PI, plasma  $T_3$  still remained lower (23.7%,  $P < 0.01$  versus PF) in infected calves while plasma  $T_4$  returned to control values. The data suggest that parasitic infection in growing calves inhibits both thyroidal secretion and extrathyroidal  $T_4$  to  $T_3$  conversion during the APR. After recovery from the APR, thyroidal secretion returns to normal but basal and bGH-stimulated generation of  $T_3$  in liver remains impaired. © 2002 Elsevier Science Inc. All rights reserved.

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## 1. Introduction

Thyroid status of growing animals is an important determinant of metabolic rate [1] and affects the amount of nutrients partitioned towards maintenance or growth [2]. A number of infectious and inflammatory illnesses are associated with profound changes in thyroid status in humans [3,4] and in laboratory [5] and domestic [6,7] animals. These changes are collectively known as euthyroid sick syndrome or non-thyroidal illness (NTI) and they include a decrease in serum concentration of triiodothyronine ( $T_3$ ), an increase in serum reverse- $T_3$  ( $rT_3$ ) and, in severe cases, a decrease in thyroxine ( $T_4$ ) and thyrotropin (TSH) concentrations. Most of these alterations are caused by a lower  $T_3$  production rate and a decreased  $rT_3$  metabolic clearance rate due to diminished extrathyroidal 5'-deiodination of  $T_4$  and  $rT_3$  [3,8].

Although  $T_4$  is the predominant thyroid hormone in the circulation, it has little inherent biological activity [3]. While  $T_4$  is synthesized only in the thyroid, the most metabolically active thyroid hormone,  $T_3$ , is produced by enzymatic 5'-deiodination of the  $T_4$  within the thyroid gland and in extrathyroidal tissues [9,10]. The extrathyroidal activity of iodothyronine 5'-deiodinase (5'D) is an important control point for regulating the thyroid status of animal tissues in various physiological and pathological situations [3,11,12].

Model systems of parasitism have demonstrated that a cachectic condition during the protracted acute phase response (APR) in calves infected with the protozoan *Sarcocystis cruzi* (chronic stunting, depletion of fat stores and severe skeletal muscle wasting) was accompanied by decreased activity of somatotropic and thyroid axes [6,13]. In infected calves, circulating plasma concentrations of  $T_4$ ,  $T_3$  and insulin-like growth factor-1 (IGF-1) were significantly reduced during APR on day 28 post-infection. Furthermore, plasma IGF-1 remained low for an extended period of time after the disappearance of clinical signs of APR. More recently, we have demonstrated that daily bGH administration to *S. cruzi* infected calves during APR and post-APR recovery period did not prevent reductions in lean tissue accretion of young animals or plasma concentration of IGF-1 associated with the cachexia of parasitic infection [14]. Accumulated data indicate that  $T_3$  is involved in the regulation of GH and IGF-1 gene expressions [2] and could be essential for GH to stimulate IGF-1 production [15]. On the other hand, GH has been demonstrated to stimulate type I 5'D activity in cattle [16], to have beneficial effects in regard to slowing nitrogen loss during low nutritional intake [17] and, in short-term use, to reduce the severity of physiological response to endotoxin [18].

The purpose of the present study was to investigate how GH regulation of thyroid status in growing calves is affected by mild systemic parasitism modeled with *S. cruzi*.

## 2. Materials and methods

### 2.1. Animals and experimental design

This experiment was performed in accordance with approval of the Animal Care and Use Committee at the USDA Agricultural Research Service (Beltsville, MD). The animals, diets, experimental protocol and design were described in detail earlier [14]. Briefly, Holstein bull calves, approximately 4 months old ( $127.5 \pm 2.0$  kg BW;  $n = 4\text{--}5/\text{group}$ ), were assigned to one of six treatment groups: control (C, *ad libitum* fed, non-infected); infected (I, 250,000 *S. cruzi* sporocysts per os, *ad libitum* fed); pair-fed (PF, non-infected, fed to previous day's intake of I treatment); GH-treated ( $C_{GH}$ , 12.5 mg/day pituitary-derived USDA-bGH-B1, i.m., *ad libitum* fed); GH-infected ( $I_{GH}$ , 12.5 mg/day bGH, 250,000 *S. cruzi* sporocysts per os, *ad libitum* fed) and pair-fed GH-treated ( $PF_{GH}$ , 12.5 mg/day bGH, non-infected, fed to previous day's intake of  $I_{GH}$  treatment). The day of oral dosing with the organism *S. cruzi* in I and  $I_{GH}$  calves was designated as day 0 of infection. Bovine GH or placebo injections were initiated on day 20 post-infection (PI), approximately 3–4 days prior to the onset of the APR, and were continued through 56 days PI. The APR of infected calves occurs between 24 and 35 days PI and is characterized by fever, shivering, inappetence, muscle tremors, physical discomfort, muscle wasting and lethargy [13]. Control, PF and I calves were injected daily with the bGH diluent, 0.05 M bicarbonate/carbonate buffer, pH 8.8. The experimental diet consisted of a pelleted feed providing 18.7% crude protein/kg DM (8.8% moisture) and 2.86 Mcal/kg fed *ad libitum* and an additional 200 g dry hay to facilitate digestion. Jugular blood samples were obtained on day 0, 28, and 55 PI and liver samples were collected after the calves were euthanized on day 56 PI. Liver samples were immediately frozen in liquid nitrogen. Blood plasma samples were stored at  $-20^{\circ}\text{C}$  and liver samples at  $-80^{\circ}\text{C}$  until assayed. All plasma and liver samples were analyzed within 4 months after the completion of the experiment. Growth performance, body composition data and plasma bGH and IGF-1 data for these calves were reported previously [14].

### 2.2. Hormone determination

Plasma  $T_4$  and  $T_3$  concentrations were determined in duplicate using RIA kits (ICN Biomedicals, Inc., Carson, CA) validated for bovine plasma [19]. For both hormones, intra-assay and inter-assay coefficients of variation were less than 6%.

### 2.3. 5'-Deiodinase determination (type I)

Outer-ring deiodinating activity (5'D) was determined by quantifying the  $^{125}\text{I}^-$  released from 3,3',5'-[ $^{125}\text{I}$ ]- $T_3$  ( $rT_3$ ) as previously described [19]. In brief, tissue samples of liver were homogenized in 0.01 M HEPES buffer (pH 7.0, 0.25 M sucrose, 5 mM EDTA) using a Polytron homogenizer (Brinkman Instruments Inc., Westbury, NY). After centrifugation (30 min

at  $2000 \times g$ ), the supernatant was incubated for 5 min in 0.1 M phosphate buffer (pH 7.0, 1 mM EDTA) in the presence of 5 mM dithiothreitol at  $37^\circ\text{C}$  with approximately 80,000 cpm of [ $^{125}\text{I}$ ]- $\text{rT}_3$  (DuPont-New England Nuclear, Boston, MA) and 500 nM of unlabeled  $\text{rT}_3$  (Calbiochem, La Jolla, CA). The released  $^{125}\text{I}^-$  was isolated as trichloroacetic acid (TCA)-soluble radioactivity. The 5'D activity was expressed as nmol of  $\text{I}^-$  produced per mg protein/h. Protein concentration in homogenates was determined with bicinchoninic acid reagent and BSA as a standard (Pierce Chemical Co., Rockford, IL).

#### 2.4. Statistical analysis

Data are presented as least squares means (LSM)  $\pm$  appropriate SE. Data were analyzed by the GLM procedure of SAS [20] using a  $3 \times 2$  factorial model. Infection, bGH and pair-feeding were set as main effects within the model. Plasma concentrations of  $\text{T}_4$  and  $\text{T}_3$  and plasma  $\text{T}_3:\text{T}_4$  molar ratio were analyzed separately for each collection time. When main effects were significant ( $P < 0.05$ ), the least significant difference was used to separate appropriate group means.

### 3. Results

Clinical signs of the APR appeared abruptly in infected calves between days 23 and 25 PI and persisted, in the most dramatic form, for the next 10–13 days. During that time infected calves displayed lethargy, decreased voluntary food intake, increased rectal temperature and plasma concentration of urea nitrogen [14]. Peak rectal temperatures of infected calves were recorded on days 27 and 28 PI. Compared with *ad libitum* fed C and  $\text{C}_{\text{GH}}$  calves, total voluntary food intake between onset of APR and day 56 PI was depressed 25% ( $P < 0.05$ ) in I and 37% ( $P < 0.01$ ) in  $\text{I}_{\text{GH}}$  calves. During the same period of time, the average daily body weight gain decreased ( $P < 0.01$ ) 31.6 and 47.7% in I and  $\text{I}_{\text{GH}}$  calves, and 23.7 and 51.6% in PF and  $\text{PF}_{\text{GH}}$  calves, respectively [14].

Plasma concentrations of  $\text{T}_4$  and  $\text{T}_3$  before infection (day 0), during APR (day 28) and after recovery from APR (day 55) are presented in Fig. 1. Because plasma concentrations of  $\text{T}_4$  and  $\text{T}_3$  and plasma  $\text{T}_3:\text{T}_4$  molar ratios were not affected by bGH treatment at any time during the experimental period, the results presented in this figure were the averaged responses of C, PF and I calves regardless of bGH or placebo treatment. Decreased food intake in PF calves (C versus PF) did not significantly affect plasma  $\text{T}_4$  and  $\text{T}_3$  on days 28 and 55 PI. Before the infection and onset of APR (day 0), plasma  $\text{T}_4$  and  $\text{T}_3$  did not differ between groups. During the peak of APR on day 28 PI, the average plasma concentration of  $\text{T}_3$  and  $\text{T}_4$  in infected calves decreased, respectively, 44.3% ( $P < 0.01$ ) and 24.4% ( $P < 0.05$ ) compared to C group and 36.4% ( $P < 0.01$ ) and 29.4% ( $P < 0.05$ ) compared to PF group. Therefore, the plasma  $\text{T}_3:\text{T}_4$  ratios on day 28 PI in infected calves decreased 22.2% ( $P < 0.05$ ) as compared to C group. However, there was also a tendency for a lower plasma  $\text{T}_3:\text{T}_4$  ratio in PF calves ( $P < 0.1$  versus C). On day 55 PI, when infected calves recovered from APR, plasma  $\text{T}_4$  concentrations returned to control values (Fig. 1, top panel). At the same time, plasma  $\text{T}_3$  concentrations in infected calves still remained lower ( $P < 0.01$ ) compared to C (–25.2%)

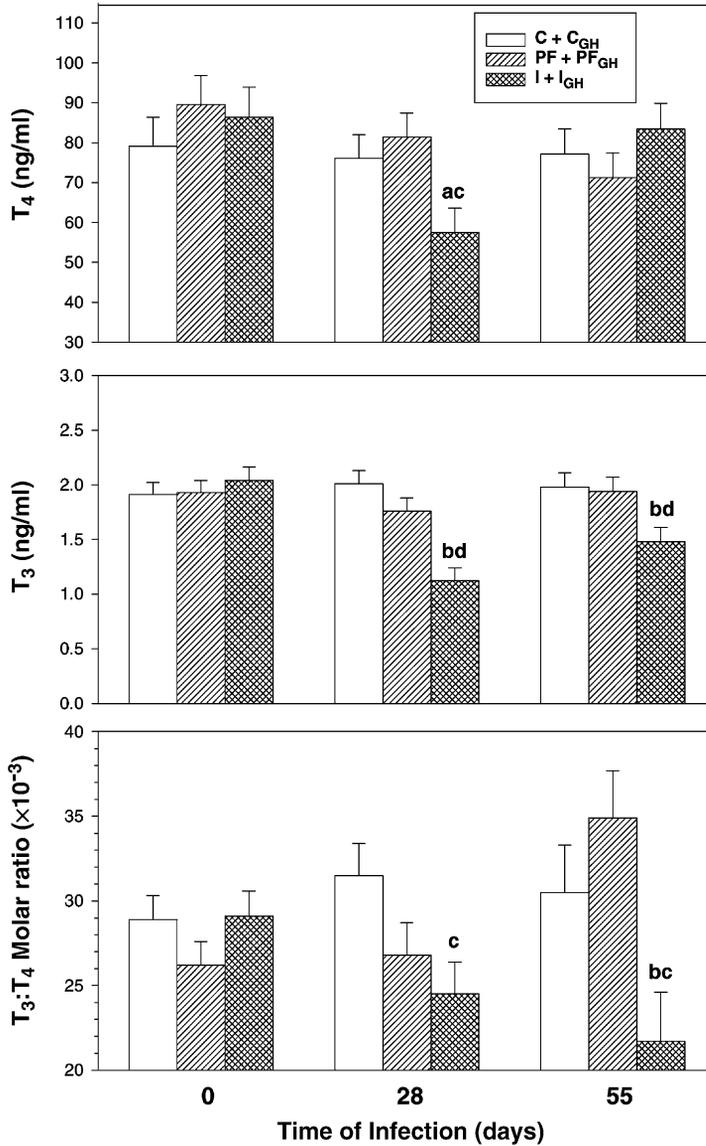


Fig. 1. Plasma concentration of thyroxine (T<sub>4</sub>, upper panel), triiodothyronine (T<sub>3</sub>, middle panel), and T<sub>3</sub>:T<sub>4</sub> molar ratio (bottom panel) in control (C), pair-fed (PF) and *S. cruzi* infected calves (I) injected daily with placebo or bovine GH for 35 days (C<sub>GH</sub>, PF<sub>GH</sub> and I<sub>GH</sub>, respectively; 12.5 mg/day, i.m., starting on day 20 post-infection). Because concentrations of T<sub>4</sub> and T<sub>3</sub> were not affected by GH treatment at any time during the experimental period, the results were averaged over ±GH treatment for each time in C, PF and I calves. Values represent LSMs ± appropriate SE of 8–9 calves/group. (a)  $P < 0.05$ , (b)  $P < 0.01$  between I and PF at the same time; (c)  $P < 0.05$ , (d)  $P < 0.01$  between I and C at the same time.

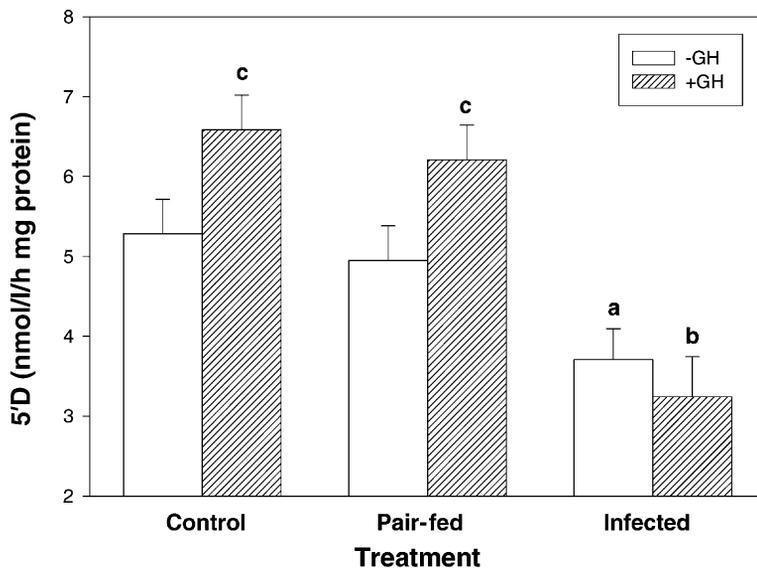


Fig. 2. Hepatic activity of type I 5'-deiodinase (5'D) in control (C), pair-fed (PF) and *S. cruzi* infected calves (I) injected daily with placebo (-GH) or bovine GH (+GH) for 35 days (12.5 mg/day, i.m., starting on day 20 post-infection). Values represent LSMs  $\pm$  appropriate SE of 4–5 calves/group. (a)  $P < 0.05$ , (b)  $P < 0.01$  between I and respective C and PF; (c)  $P < 0.05$  between +GH and -GH within respective treatment.

or PF (-23.7%) animals (Fig. 1, middle panel). Consequently, plasma  $T_3:T_4$  ratio in infected calves on day 55 PI (Fig. 1, bottom panel) was significantly lower than in the C ( $P < 0.05$ ) or PF ( $P < 0.01$ ) groups.

Hepatic activities of type I 5'D in experimental calves are presented in Fig. 2. Decreased food intake during APR and recovery period did not affect 5'D activity in liver on day 56 PI. In both placebo- and bGH-injected calves no differences were found ( $P > 0.05$ ) in 5'D activity between C and PF group. Treatment with bGH increased ( $P < 0.05$ ) 5'D activity in C (24.6%) and PF (25.2%) calves. Compared to PF calves, infection with *S. cruzi* reduced hepatic 5'D activity 25.0% ( $P < 0.05$ ) and 47.8% ( $P < 0.01$ ), respectively, in placebo- and bGH-injected calves. Also, in infected calves, bGH treatment did not stimulate 5'D activity in liver.

#### 4. Discussion

The data presented here support our previous observations that infection with *S. cruzi* in growing calves significantly reduces circulating concentrations of  $T_4$  and  $T_3$  during the peak of APR [6]. In addition, decreased plasma  $T_3:T_4$  molar ratio, observed in the present experiment during APR, reflects a greater decrease in plasma  $T_3$  than  $T_4$  in infected animals. These changes in thyroid hormone concentrations were not simply related to decreased feed intake during APR. In non-infected, pair-fed calves, no changes in plasma thyroid hormones were observed except for a trend toward a lower  $T_3:T_4$  molar ratio as a result of non-significant but numerically opposite changes in  $T_3$  and  $T_4$  concentrations. It has been shown in cattle that

starvation [21] or dietary restriction [22] reduced  $T_4$  and  $T_3$  plasma concentration. However, as reported previously [14], pair-fed calves in the present study cannot truly be considered in a state of nutritional stress because the rates of live weight gain exceeded 1 kg/day. Thus, the decreased concentrations of plasma  $T_3$  and  $T_4$  in infected calves appear to be related to infection *per se* and may represent an adaptive mechanism to conserve energy by reducing metabolic expenditure during the febrile state of APR.

Parasitic infections are known to induce euthyroid sick syndrome at the peak of APR. Decreased plasma  $T_4$  concentrations were also reported in cattle [7] and goats [23] infected with *Trypanosoma congolense*. In goats, the decrease in plasma  $T_4$  was related to severity of clinical symptoms of infection. In camels, infection with *Trypanosoma evansi* decreased plasma concentrations of thyroid hormones ( $T_4$  and  $T_3$ ) and TSH [24]. Alterations in plasma concentrations of thyroid hormones (decreased  $T_3$  and  $T_4$  without changes in TSH) in humans infected with *Trypanosoma brucei gambiense* [25] or *Plasmodium falciparum* [26] indicate that infected patients were also suffering from euthyroid sick syndrome or NTI.

In the present study, we estimated the total concentrations of  $T_4$  and  $T_3$  which may not directly reflect the changes in the concentrations of free  $T_4$  and  $T_3$  constituting the physiologically active hormones. NTI, including infection and inflammation, is generally associated with a decrease in binding of  $T_4$  to thyroxine-binding proteins (TBP). The mechanisms underlying this phenomenon are complex and species specific [5,8]. In humans infected with *T. brucei gambiense*, decreases in plasma total concentrations of  $T_4$  and  $T_3$  were accompanied by decreases in plasma concentrations of free  $T_4$  and  $T_3$  [25]. However, in dogs, acute challenge with endotoxin did not affect total  $T_4$  concentration but increased free  $T_4$  fraction [27]. Further studies are required to elucidate the relationship between circulating concentrations of total and free thyroid hormones during infection in cattle.

The overall decrease in plasma concentration of  $T_4$  and  $T_3$  accompanied by decreased  $T_3:T_4$  ratio observed in the present study during APR to *S. cruzi* infection could be caused by (a) down-regulation of pituitary TSH secretion, (b) diminished thyroid sensitivity to TSH stimulation, (c) suppression of synthesis and secretion of thyroid hormones, and (d) decrease in extrathyroidal 5'-deiodinating activity resulting in reduced  $T_3$  generation. In the present experiment, we did not measure TSH concentration in experimental calves. However, in a similar calf-sarcocystosis-pair feeding experimental model [28], no changes were observed in plasma basal and thyrotropin releasing hormone (TRH)-stimulated TSH concentrations in infected calves during APR or in pair-fed controls. These observations suggest that the depression in circulating concentrations of  $T_4$ ,  $T_3$ , and the plasma  $T_3:T_4$  ratio during APR in the present experiment was not related to reduced pituitary secretion of TSH but rather to decreased thyroidal activity and extrathyroidal 5'-deiodination.

On day 55 PI, when infected calves recovered from APR, the thyroidal secretion returned to normal as indicated by normal plasma  $T_4$  concentrations (Fig. 1, top panel). However, significantly decreased plasma  $T_3$  concentration and plasma  $T_3:T_4$  molar ratio at that time suggest that peripheral 5'-deiodination remained impaired, resulting in decreased extrathyroidal production of  $T_3$ . Indeed, hepatic type I 5'D, responsible for the production of most of the circulating  $T_3$ , was substantially suppressed in *S. cruzi* infected calves (Fig. 2). Moreover, suppressed 5'D activity could not be stimulated by treatment with GH. Growth hormone administration has been reported to increase extrathyroidal 5'-deiodination in fish [29], birds [30], and mammals

[31] including cattle [16]. In cattle, both long-term (3 weeks) and acute (2 days) treatment with pituitary-derived bovine GH increased type I 5'D activity in liver and kidney without significantly changing circulating concentrations of T<sub>4</sub> or T<sub>3</sub> [16]. Also, increased hepatic 5'D activity was reported in fed and fasted dwarf goats after administration of ovine GH [32]. As expected, GH treatment for 35 days in the present experiment increased hepatic type I 5'D activity in control and pair-fed calves. However, it failed to stimulate this enzyme in infected animals. These results clearly show that prolonged impairment of hepatic T<sub>3</sub> generation after recovery from APR is not simply related to decreased feed consumption.

As reported previously for the same model of infection [6], the feed intake in infected calves around day 60 PI approached 80% of the intake in the control group but the rate of weight gain was much lower in infected compared to pair-fed calves. The hormonal data from the above [6] and present [14] experiments also indicate that infection with *S. cruzi* in calves impaired GH regulation of IGF-I production and resulted in a long-term (i.e., beyond recovery from APR) decrease in plasma IGF-I concentrations despite normal or increased plasma GH concentrations. Furthermore, treatment of infected calves with GH did not increase reduced concentration of plasma IGF-I and hepatic content of mRNA for IGF-I and GH receptor [14]. We suggest, or at least do not exclude, the possibility that uncoupling of IGF-I regulation from GH in infected animals after recovery from APR is related to decreased availability of T<sub>3</sub> as a result of reduced activity of extrathyroidal 5'-deiodination.

As reviewed by Cabello and Wrutniak [15], dissociation between GH and IGF-I regulation was observed in several physiological (fetal life, food restriction) or pathological (sex-linked dwarfism, hypothyroidism) situations associated with reduced T<sub>3</sub> production. Accumulated data indicate that T<sub>3</sub> is essential for GH to stimulate IGF-I synthesis [33]. Physiological doses of T<sub>3</sub> stimulate synthesis and release of IGF-I from perfused rat liver [34]. Studies *in vitro* on cultured porcine hepatocytes [35] and *in vivo* on hypophysectomized rats [36] have shown that T<sub>3</sub> treatment increased response of hepatic IGF-I mRNA expression to GH. Hypothyroidism, on the other hand, was associated with decreased IGF-I expression in the liver [37]. Euthyroidism, however, appears to be optimal for GH-regulated IGF-I production. Elsasser *et al.* [38] demonstrated in cattle that hyperthyroidism induced by T<sub>3</sub> administration decreased basal plasma IGF-I and blunted the IGF-I response to GH challenge. Further studies will be required to determine whether supplementation with thyroid hormone to alleviate prolonged hypothyroid status of *S. cruzi* infected calves after recovery from APR would increase circulating IGF-I and, consequently, improve the growth rate.

The failure of GH to stimulate the decreased hepatic 5'D activity in infected calves in the present study could be explained by the possible effect of IGF-I on extrathyroidal T<sub>3</sub> production. It has been shown in healthy and in TSH–GH-deficient human patients supplemented with GH and T<sub>4</sub>, that IGF-I treatment increased extrathyroidal production of T<sub>3</sub> [39]. These results suggested that IGF-I might partially mediate the effect of GH on extrathyroidal T<sub>4</sub> to T<sub>3</sub> conversion. Thus, as the prolonged hypothyroid status of infected animals in our experiment could impair IGF-I production, the decreased IGF-I status could reciprocally suppress hepatic 5'D response to GH.

Mechanisms by which *S. cruzi* infection affects the thyroid status are not completely understood. However, cytokines, allegedly released during this parasitic infection in calves [13], could be involved in the inhibition of thyroid hormone production. As reviewed by Bartalena

et al. [40], all steps of thyroid hormone synthesis, secretion and extrathyroidal metabolism, including 5'-deiodination, may be negatively affected by cytokines, especially tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), and IL-6. We have shown recently in cattle [41] that endotoxin (LPS), a model effector of the APR of bacterial infection and strong stimulus for cytokines release, decreased circulating concentrations of thyroid hormones and hepatic activity of 5'D. However, as reported previously [42], TNF- $\alpha$  concentration in plasma from *S. cruzi* infected calves actually decreased during the APR but increased as the signs of acute infection disappeared, reaching the highest values on day 55 PI, when we observed suppression of hepatic 5'D activity. In calves used in the present study, the average plasma TNF- $\alpha$  concentrations between the onset of APR and the termination of the trial were higher in infected animals but also in pair-fed conspecifics with normal thyroid status [14]. Other studies indicate that interaction of several cytokines rather than TNF- $\alpha$  alone may play a role in the alteration of thyroidal status during infection [43,44]. Another possible mechanism of 5'D inhibition could be the direct effect of free radicals. Free radicals, released during immune response to infection, are involved in the complex interaction between invading organism and host [45]. It has been shown in rats that a free radical-generating system reduced hepatic 5'D activity *in vitro* and this suppressed activity was reversed by free radical scavengers [46].

In conclusion, the present data demonstrate that infection with the protozoan parasite *S. cruzi* in growing calves suppresses thyroidal secretion during APR to infection. After the recovery period from APR, the thyroid gland returns to normal activity but extrathyroidal T<sub>4</sub> to T<sub>3</sub> conversion remains depressed for several weeks resulting in a decreased pool of circulating T<sub>3</sub>. Decreased thyroid activity during APR of *S. cruzi* infection seems to be a part of somatotrophic axis-directed down regulation of growth and can be regarded as a short-term adaptive mechanism to save energy for metabolic purposes of higher priority than growth [47]. However, prolonged decrease in peripheral T<sub>3</sub> generation becomes pathological on its own, and may be involved in a long-term impairment of growth performance in calves.

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