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Effects of bovine somatotropin injection on serum concentrations of progesterone in non-lactating dairy cows

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ABSTRACT

The objective of this experiment was to evaluate the effects of bovine somatotropin administration on serum concentrations of glucose, insulin, NEFA, IGF-I, and progesterone (**P4**) in ovariectomized non-lactating dairy cows receiving exogenous P4, as a model to estimate treatment effects on hepatic P4 degradation. Ten non-lactating, non-pregnant, and ovariectomized Gir × Holstein cows were assigned to the experiment (d −14 to 27). On d 0, cows were ranked by BW and BCS, and randomly assigned to one of two treatments: (1) bovine somatotropin (*BST*; $n=5$) or (2) saline control (**control**; $n=5$). Cows assigned to the BST treatment were administered s.c. injections containing 500 mg of sometribove zinc on d 0, 9, and 18 of the experiment, whereas control cows concurrently received a 10-mL s.c. injection of 0.9% saline. On d −2, cows were inserted with an intravaginal releasing device containing 1.9 g of P4, which remained in the cows until the end the experiment (d 27). Cow BW and BCS were assessed on d −14, 0, and 27. Blood samples were collected daily from d 0 to d 27, at 0 (immediately before), 1, and 2 h relative to concentrate feeding for determination of serum glucose, insulin, NEFA, P4, and IGF-I concentrations. Concentrations of glucose, NEFA, and insulin obtained prior to feeding (0 h) were used to determine pre-prandial revised quantitative insulin sensitivity check index (**RQUICKI**). No treatment effects were detected for BW ($P=0.72$) and BCS change ($P=0.79$) during the experiment. Beginning on d 2 of the experiment, BST cows had greater ($P\leq0.01$) serum IGF-I concentrations compared with control cohorts (treatment × day interaction; $P<0.01$). Cows receiving BST had greater ($P\leq0.05$) insulin concentrations compared with control cohorts from d 8 to d 11, d 16 and 17, as well as from d 19 to d 21 of the experiment (treatment × day interaction; $P<0.01$). Cows receiving BST had greater ($P\leq0.01$) mean glucose and NEFA concentrations, as well as reduced ($P<0.01$) mean RQUICKI during the experiment compared with control cohorts. No treatment effects, however, were detected ($P=0.73$) for serum P4 concentrations. In conclusion, results from this experiment indicate that hepatic P4 catabolism is not directly regulated by circulating IGF-I, whereas BST administration decreases insulin sensitivity in non-lactating dairy cows in adequate nutritional status.

1. Introduction

Nutrition substantially impacts productive and reproductive traits in dairy cattle (Butler, 2005). Therefore, nutritional strategies that promote milk production and benefit reproductive efficiency of dairy cows are warranted (Lucy, 2001). The development of such strategies is dependent on the recognition of physiological mechanisms that associate nutrition with reproductive function in dairy females. More specifically, nutrition has been shown to regulate cattle reproduction, at least partially, via circulating hormones and metabolites such as insulin and IGF-I (Wettemann and Bossis,

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2000). As an example, insulin modulates circulating concentrations of progesterone (**P4**; Lopes et al., 2009), a steroid required for establishment and maintenance of pregnancy (Spencer and Bazer, 2002), by stimulating luteal P4 synthesis (Spicer and Echternkamp, 1995) and alleviating hepatic P4 catabolism by CYP2C and CYP3A enzymes (Murray, 1991; Lemley et al., 2008).

Our research group reported that non-lactating dairy cows in adequate nutritional status receiving intravenous glucose infusion to increase endogenous insulin concentrations had greater plasma P4 concentrations compared with cohorts receiving saline, and this outcome was attributed to reduced hepatic P4 degradation given that cows were ovariectomized and supplemented with exogenous P4 (Vieira et al., 2010). Supporting this research approach and results, Vieira et al. (2013) evaluated similar cows receiving the same dosage of glucose infusion as Vieira et al. (2010), and reported reduced hepatic mRNA expression of CYP2C and CYP3A compared with saline-receiving cohorts. However, glucose supplementation may also increase circulating concentrations of other hormones associated with reproductive and hepatic function, including IGF-I (Jones and Clemmons, 1995). Therefore, we hypothesized that the insulin-stimulated decrease in hepatic P4 catabolism may also be associated with circulating IGF-I.

Administration of bovine somatotropin is an alternative to increase circulating concentrations of IGF-I in non-lactating dairy cattle, independently of baseline glucose and insulin concentrations (Bilby et al., 2004). Based on this rationale and our hypothesis, this experiment evaluated the effects of bovine somatotropin administration on serum concentrations of glucose, insulin, NEFA, IGF-I, and P4 in ovariectomized non-lactating dairy cows receiving exogenous P4, as a model to estimate treatment effects on hepatic P4 degradation (Moriel et al., 2008; Lopes et al., 2009; Vieira et al., 2010).

2. Materials and methods

This experiment was conducted at the São Paulo State University, Lageado Experimental Station, located in Botucatu, São Paulo, Brazil. The animals utilized were cared for in accordance with the practices outlined in the Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching (FASS, 1999).

2.1. Animals and treatments

Ten non-lactating, non-pregnant, and ovariectomized Gir × Holstein cows (mean ± SE; BW = 640 ± 27 kg and BCS = 3.4 ± 0.2) were assigned to the experiment (d −14 to 27). On d 0, cows were ranked by BW and BCS (Wildman et al., 1982), and randomly assigned to one of two treatments: (1) bovine somatotropin (**BST**; $n=5$) or (2) saline control (**control**; $n=5$). Cows assigned to the BST treatment were administered s.c. injections containing 500 mg of sometribove zinc (Lactotropin®; Elanco Saúde Animal, São Paulo, Brazil) on d 0, 9, and 18 of the experiment, whereas control cows concurrently received a 10-mL s.c. injection of 0.9% saline.

Cows were maintained in a *Brachiaria brizantha* pasture from d −14 to d 27, and individually received (as-fed basis) 2 kg/cow daily of a concentrate from d −14 to −3, and 4 kg/cow daily of the same concentration from d −2 to 27, through self-locking head gates at 0800 h. The concentrate consisted of (DM basis) 62.5% of ground corn, 29% of soybean meal, 5% of mineral mix (18% Ca, 10.7% Na, 8% P, 1.2% S, 0.5% Mg, 0.13% Cu, 0.007% Co, and 0.007% I), 2.5% of limestone, and 1% of urea. Cows also received a complete commercial mineral and vitamin mix (7.7% Ca, 4.0% P, 3.0% Na, 0.20% K, 0.20% Mg, 2.0% S, 0.002% Co, 0.03% Cu, 0.002% I, 0.02% Mn, 0.13% Zn, and 0.02% F) and water for ad libitum consumption throughout the experiment. Nutritional content of concentrate and pasture were estimated to be 76 and 53% TDN, 22.9 and 7.1% CP, and 12.5 and 76.4% NDF from samples collected prior to the experiment and analyzed by a bromatology laboratory (São Paulo State University, Botucatu, Brazil).

2.2. Progesterone implants, sampling, and blood analysis

From d −14 to −2, cows were inserted with a previously used (third use) intravaginal P4 releasing device (**CIDR**, originally containing 1.9 g of P4; Pfizer Animal Health, São Paulo, Brazil) to initially expose and adapt cows to exogenous P4. Cows received a new CIDR on d −2, which remained in the cows until the end the experiment (d 27).

Cow BW and BCS were assessed on d −14, 0, and 27. Blood samples were collected daily from d 0 to d 27, at 0 (immediately before), 1, and 2 h relative to concentrate feeding for determination of serum glucose, insulin, NEFA, P4, and IGF-I concentrations. Blood samples were collected from either the coccygeal vein or artery into commercial blood collection tubes (Vacutainer, 10 mL; Becton Dickinson, Franklin Lakes, NJ), placed immediately on ice, maintained at 4 °C for 24 h to allow clotting, and centrifuged at 3000 × g at 4 °C for 30 min for serum collection. Harvested serum was stored frozen at −20 °C until further processing. Glucose was determined using a quantitative colorimetric kit (Katal Biotecnológica Ind. Com. Ltda.; Belo Horizonte, Brazil). Insulin and P4 concentrations were determined using Coat-A-Count kits (DPC Diagnostic Products Inc., Los Angeles, CA) solid phase ^{125}I RIA previously used for bovine samples (Moriel et al., 2008). Concentrations of NEFA were determined using an enzymatic colorimetric kit (Randox Brasil Ltda., São Paulo, Brazil). Concentrations of IGF-I were determined using an immunometric chemiluminescence immunoassay (Immulite 2000 IGF-I Assay, Erlangen, Germany) previously used for bovine samples (Falkenberg et al., 2008). The intra- and inter-assay CV were, respectively, 7.4 and 3.8% for glucose, 5.8 and 7.1% for NEFA, 9.2 and 9.7% for insulin, and 6.8 and 3.7% for P4. All samples were analyzed for IGF-I concentration within a single assay, and the intra-assay CV was 6.4%.

2.3. Revised quantitative insulin sensitivity check index

Concentrations of glucose, NEFA, and insulin obtained prior to feeding (0 h) were used to determine pre-prandial revised quantitative insulin sensitivity check index (**RQUICKI**). This methodology has been used to estimate insulin sensitivity in dairy cows (Holtenius and Holtenius, 2007; Gross et al., 2011; Grünberg et al., 2011), according to the equa-

tion proposed by Perseghin et al. (2001): RQUICKI = 1/[log (glucose) + log(insulin) + log(NEFA)].

2.4. Statistical analysis

The sample size used in herein was adopted according to the G*power 3 software (Faul et al., 2007) and previous research from our group (Vieira et al., 2010; Rodrigues et al., 2010). Data were analyzed using the MIXED procedure of SAS (SAS Inst., Inc., Cary, NC, USA) and Satterthwaite approximation to determine the denominator degrees of freedom for the tests of fixed effects. Cow was considered the experimental unit. The model statement used for BW and BCS change contained the effects of treatment. Data were analyzed using cow(treatment) as a random variable. The model statement used for serum measurements contained the effects of treatment, day, hour, and all resultant interactions, whereas the model statement used for RQUICKI contained the effects of treatment, day, and the interaction. Data were analyzed using cow(treatment) as a random variable. The specified term for the repeated statement was day with cow(treatment) as subject, whereas the covariance structure utilized was compound symmetry, which provided the best fit for these analyses according to the Akaike information criterion. For all analyses, significance was set at $P \leq 0.05$, and tendencies were declared if $P < 0.05$ and ≤ 0.10. All results are reported as least squares means, and were separated using LSD. Results are reported according to treatment effects if no interactions were significant, or according to the highest-order interaction detected.

3. Results

No treatment effects were detected for BW ($P = 0.72$) and BCS change ($P = 0.79$) during the experiment (Table 1). Further, no treatment effects were detected ($P = 0.73$) for serum P4 concentrations (Table 1).

Table 1
Changes in BW and BCS, revised quantitative insulin sensitivity check index (RQUICKI), and plasma concentrations of glucose, NEFA, and progesterone in non-lactating, ovariectomized dairy cows receiving s.c. injections containing 500 mg of bovine ST (BST; sometribove zinc; $n = 5$) or 10-mL of saline (0.9%; control, $n = 5$) [a].

Item	BST	Control	SEM	*P*-value
BW change (kg)	11.4	12.3	0.8	0.72
BCS change[b], 1–5 scale	0.1	0.2	0.1	0.79
RQUICKI[c]	0.459	0.632	0.019	<0.01
Serum glucose (mg/dL)	69.4	65.1	0.8	<0.01
Serum NEFA (mmol/L)	0.306	0.254	0.014	0.01
Serum progesterone (ng/mL)	1.17	1.13	0.08	0.73

[a] Treatments were administered on d 0, 9, and 18 of the experimental period (d −14 to 27). Cow BW and BCS were determined on d 0 and 27. Blood samples were collected from d 0 to 27, at 0 (immediately before), 1, and 2 h relative to concentrate feeding. Cows were inserted with an intravaginal progesterone releasing device (containing 1.9 g of P4; Pfizer Animal Health, São Paulo, Brazil) from d 2 to d 27.
[b] According to Wildman et al. (1982).
[c] According to the equation proposed by Perseghin et al. (2001).

Treatment × day interactions were detected ($P < 0.01$) for serum IGF-I and insulin. Beginning on d 2 of the experiment, BST cows had greater ($P \leq 0.01$) serum IGF-I concentrations compared with control cohorts (Fig. 1). Cows receiving BST had greater ($P \leq 0.05$) insulin concentrations compared with control cohorts from d 8 to d 11, d 16 and 17, as well as from d 19 to d 21 of the experiment (Fig. 2).

A treatment effect was detected for serum glucose ($P < 0.01$), NEFA ($P = 0.01$), and RQUICKI ($P < 0.01$). Cows receiving BST had greater mean glucose and NEFA concentrations during the experiment compared with control cohorts (Table 1). Based on serum glucose, insulin, and NEFA concentrations obtained prior to concentrate feeding, cows receiving BST had reduced RQUICKI, which means reduced pre-prandial insulin sensitivity, compared with control cohorts (Table 1).

4. Discussion

Cows from both treatments were in adequate and similar nutritional status based on the positive BW and BCS change observed during the experiment (Table 1). Conversely, other authors reported that BST administration increased BW gain in growing cattle (Schwarz et al., 1993; Buskirk et al., 1996; Carstens et al., 1997). Nevertheless, these cited studies evaluated cattle maintained on planes of nutrition to yield BW gain greater than 0.8 kg/d (Schwarz et al., 1993; Buskirk et al., 1996; Carstens et al., 1997). In cattle limit-fed to gain less than 0.8 kg/d, such as the cows evaluated herein, BST administration did not increase BW gain (Hall et al., 1994; Buskirk et al., 1996; and Carstens et al., 1997). This experiment, however, did not have the intent nor was designed to evaluate the effects of BST administration on BW and BCS gain of non-lactating dairy cows. These parameters were assessed to demonstrate that cows from both treatments were in adequate, as well as similar, nutritional balance. Hence, treatment effects reported herein on serum variables seemed independent of overall cow nutritional status.

As expected by the experimental design, BST heifers had greater plasma IGF-I concentrations compared with control cohorts beginning 2 d after treatment administration (Fig. 1). Similarly, other authors reported that plasma IGF-I concentrations increases as early as 2 d, and peaks 7 to 8 d after sometribove zinc administration (Bilby et al., 1999; Bilby et al., 2004; Rivera et al., 2010). However, differing from our hypothesis, serum P4 concentrations and potentially hepatic P4 catabolism were not impacted by BST administration and the subsequent increased serum IGF-I concentrations (Table 1). Similarly, Cooke et al. (2012) evaluated beef heifers with no corpus luteum but receiving exogenous P4 as an approach to estimate hepatic P4 catabolism. These authors reported that heifers receiving 250 mg of sometribove zinc had similar plasma P4 concentrations, and likely similar rate of hepatic P4 degradation, on d 6, 8, and 10 relative to treatment administration compared with cohorts receiving saline. The present experiment evaluated a greater dose of sometribove zinc administered at shorter intervals, whereas the sampling period for circulating P4 analysis was longer compared with that used by Cooke et al. (2012), Moreover,

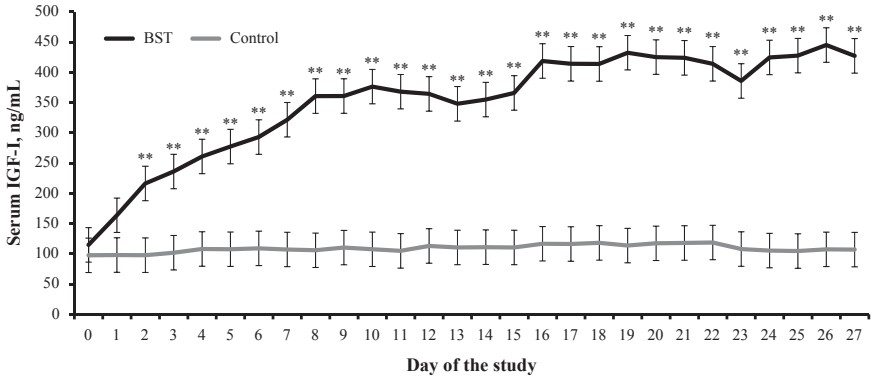

Fig. 1. Serum IGF-I concentrations (± SEM) of non-lactating dairy cows receiving s.c. injections containing 500 mg of bovine somatotropin (BST; sometribove zinc; $n=5$) or 10-mL of saline (0.9%; control, $n=5$). Treatments were administered every on d 0, 9, and 18. A treatment × time interaction was detected ($P<0.01$). Treatment comparison within time: * $P\leq0.05$, ** $P\leq0.01$.

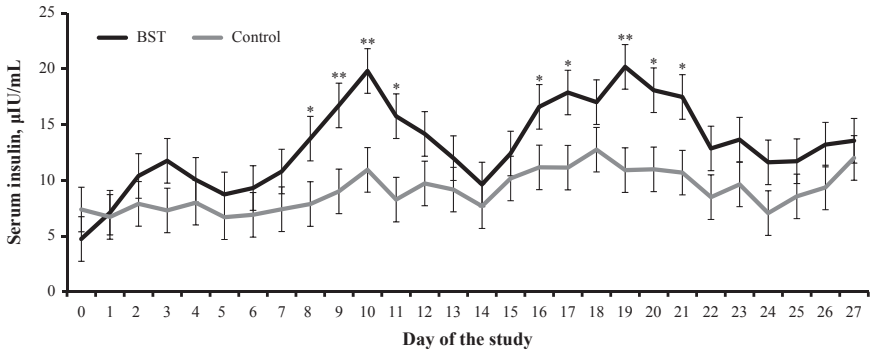

Fig. 2. Serum insulin concentrations (± SEM) of non-lactating dairy cows receiving s.c. injections containing 500 mg of bovine somatotropin (BST; sometribove zinc; $n=5$) or 10-mL of saline (0.9%; control, $n=5$). Treatments were administered every on d 0, 9, and 18. A treatment × time interaction was detected ($P<0.01$). Treatment comparison within time: * $P\leq0.05$, ** $P\leq0.01$.

the present experiment utilized multiparous Gir × Holstein cows whereas Cooke et al. (2012) utilized nulliparous Angus × Hereford heifers. Hence, based on our results and those reported by Cooke et al. (2012), hepatic P4 catabolism appears not to be modulated by circulating IGF-I concentrations in bovine females in adequate nutritional status, independently of the dose and frequency of sometribove zinc administration, as well as cattle breed and parity.

Administration of BST increased mean serum glucose concentrations throughout the experiment (Table 1), as well as serum insulin concentration beginning at 8 d after treatment application (Fig. 2). The effects of sometribove zinc administration on circulating concentrations of glucose and insulin in cattle have been variable, either by increasing (de la Sota et al., 1993; Chase et al., 2011), decreasing (Azza et al., 2010), or not altering (Schwarz et al., 1993; Neathery et al., 1991) one or both parameters. Similar to our results, Bilby et al. (2004) reported that non-lactating dairy cows receiving 500 mg of sometribove zinc had greater plasma insulin concentrations compared with control cohorts from d 4 to d 11 relative to treatment application. Nevertheless, these outcomes do not support previous research from our (Moriel et al., 2008; Vieira et al., 2010; Vieira et al. (2013)) and other groups (Lemley et al., 2008; Lemley et al., 2010) that reported a positive relationship between circulating concentrations of glucose and insulin with that of P4, or with reduced hepatic expression of CYP2C and CYP3A. One may speculate that BST administration increased glucose and insulin concentrations by increasing DMI, which turn stimulated hepatic blood flow that overrode the inhibitory effects of insulin, and perhaps IGF-I, on hepatic P4 catabolism (Moriel et al., 2008). However, as previously mentioned, BST and control cows were in similar nutritional status based on BW and BCS results. Further, cows from both treatments consumed the same amount of concentrate throughout the experiment, which is the dietary component that most impacts circulating glucose and insulin concentrations, as well as hepatic blood flow and subsequent P4 catabolism (Huntington, 1997; Sangsritavong et al., 2002; Vasconcelos et al., 2003).

Research has also shown that increased glucose and insulin concentrations upon BST administration may be associated with insulin resistance (Dunshea et al., 1995). In fact, BST administration to cattle alters insulin sensitivity and reduces glucose uptake and oxidation by target cells, including hepatocytes (Bauman et al., 1988; Sechen et al., 1990). Cows receiving BST also had greater serum NEFA concentrations throughout the study compared with control cohorts (Table 1), whereas BST has been shown to inhibit lipogenesis and stimulate lipolytic activity in bovine adipose tissues (Hart et al., 1984; Lanna et al., 1995). Moreover, circulating NEFA can also contribute to the development of

insulin resistance in animals (Pires et al., 2007). Accordingly, cows receiving BST had reduced pre-prandial RQUICKI throughout the experiment compared with control cohorts (Table 1), indicating that BST administration reduced insulin sensitivity and contributed to the treatment effects detected for serum insulin and glucose concentration. Cooke et al. (2012) also attributed an observed increase in plasma glucose concentrations in heifers receiving 250 mg of sometribove zinc to a potential decrease in insulin sensitivity caused by sometribove zinc administration, although these authors did not directly evaluate insulin sensitivity parameters. Hence, the BST-induced increase in circulating insulin reported herein should be attributed to a metabolic disorder rather than enhanced metabolic status, which may help explain why the positive relationship between serum insulin and P4 concentrations in ovariectomized cows receiving exogenous P4 observed by others (Moriel et al., 2008; Lopes et al., 2009; Vieira et al., 2010) was not detected in the present experiment.

5. Conclusion

Administration of BST to ovariectomized dairy cows receiving exogenous P4 effectively increased serum IGF-I concentrations, but failed to increase serum P4 concentration by reducing hepatic P4 catabolism. Moreover, BST administration also increased serum insulin and glucose concentrations; whereas these outcomes were attributed to reduced insulin sensitivity assessed by RQUICKI and associated with the BST-induced increase in serum NEFA concentrations. Therefore, results from this experiment indicate that hepatic P4 catabolism is not directly regulated by circulating IGF-I, whereas BST administration decreases insulin sensitivity in non-lactating dairy cows in adequate nutritional status. Caution must be applied when extrapolating the results reported herein to lactating dairy cows given that the physiological and metabolic aspects associated with parturition, resumption of reproductive function, and milk synthesis were not accounted for in the present experimental model.

Conflict of interest

No conflict of interest to report.

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