Acute or chronic immunoneutralization of somatostatin does not affect growth hormone or thyroid hormone secretion in sheep

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RECEIVED 11 May 1992

ABSTRACT

The effect of acute or chronic immunoneutralization of somatostatin (SRIF) on plasma GH, thyrotrophin (TSH) and thyroid hormones was examined. Acute responses to SRIF immunoneutralization were examined using 30 intact male lambs (19.8 ± 0.6 kg) assigned to one of five treatment groups such that control (C) lambs received no anti-SRIF immunoglobulin and SRIF-immunized (SI) lambs received 2 mg (S12), 10 mg (S10), 20 mg (S20) or 100 mg (S100) anti-SRIF immunoglobulin/kg body weight (BW). Control immunoglobulin was administered such that all lambs received 100 mg total immunoglobulin protein/kg BW. Effects of chronic SRIF immunoneutralization were examined using C and SI100 lambs which received additional (40 mg/kg BW) control and anti-SRIF immunoglobulin respectively, 4 and 8 days following the initial dose. Blood samples were collected from all lambs, at 10-min intervals, for 5 h immediately following initial immunoglobulin infusion and, from C and SI100 lambs, at 10-min intervals, for 5 h at 11 days following initial immunoglobulin infusion. At the end of each 5-h sampling period, pituitary and thyroid function was examined by i.v. challenge with thyrotrophin-releasing hormone (TRH; 0.33 μg/kg BW). Basal plasma GH and thyroxine (T4) and the GH, TSH, T4 and tri-iodothyronine (T3) responses to TRH were not influenced by acute or chronic immunoneutralization of SRIF. Acute, but not chronic, immunoneutralization of SRIF elevated basal plasma T3 in SI100 lambs only. The results suggest that SRIF, under physiological conditions, does not influence GH or thyroid hormone secretion in sheep but may influence thyroid hormone metabolism acutely. Journal of Endocrinology (1993) 136, 261–269

INTRODUCTION

The physiological role of somatostatin (SRIF) as a potent inhibitor of pituitary function has been examined extensively in the rat. Administration of a single bolus of SRIF antiserum results in an acute elevation of basal plasma growth hormone (GH) (Ferland et al. 1976; Jacovidou & Patel, 1987) and an enhanced GH response to GH-releasing hormone (GHRH) (Wehrenberg et al. 1982; Tannenbaum & Ling, 1984). Immunoneutralization of SRIF also acutely elevates basal thyrotrophin (TSH) (Arimura & Schally, 1976; Ferland et al. 1976) and the TSH response to thyrotrophin-releasing hormone (TRH) (Arimura & Schally, 1976) or cold stress (Ferland et al. 1976). Recent studies in the rat suggest that, although SRIF is acutely inhibitory to GH secretion, chronic exposure to SRIF may be required to maintain GH responsiveness to GHRH (Tannenbaum et al. 1989; Soya & Suzuki, 1990).

In the ruminant animal, the physiological significance of SRIF as a regulator of pituitary function has not been clearly defined. In sheep, SRIF infusion (1 μg/min) did not affect basal plasma GH, but did reduce the GH response to arginine (Davis, 1975). Basal plasma GH was not influenced by acute passive immunization against SRIF in goats, but the GH response to GHRH was increased (Hart et al. 1984). Frohman et al. (1990), using sheep, could not demonstrate an association between pulses in SRIF concentrations in hypothalamic portal plasma and the corresponding GH secretory profile. The fall in plasma GH following insulin-induced hypoglycaemia was, however, associated with a rise in portal plasma...
SRIF (Frohman et al. 1990). Basal plasma TSH was not affected by SRIF infusion in the ewe, but the TSH response to TRH was reduced (Davis, 1975).

Long-term neutralization of SRIF, using active immunization techniques, has been examined as a potential method of chronically elevating plasma GH, and consequently growth rate, of domestic livestock. Active immunization against SRIF has resulted in improved growth rate (Spencer & Williamson, 1981; Spencer et al. 1983a,b; Laarveld et al. 1986; Deligeorgis et al. 1988; Vicini et al. 1988; Mears, 1990; Sun et al. 1990) in ruminant species, but an elevation in plasma GH has rarely been observed (Varner et al. 1980; Spencer et al. 1983a). A thyroid hormone response to SRIF immunization has been observed in neonatal lambs (Van Kessel et al. 1990) and has been implicated as a potential mechanism resulting in growth stimulation (Laarveld et al. 1986; Van Kessel et al. 1990).

The current study was designed to investigate more closely the physiological role of SRIF in the control of pituitary and thyroid hormone function in the ruminant animal. Using growing lambs, the GH, TSH and thyroid hormone responses to acute and chronic passive SRIF immunoneutralization with a high-affinity polyclonal antibody were examined. A confounding parameter in studies employing active immunization against SRIF is the variability of the immune response obtained, both in terms of affinity and titre. To examine the relationship between the magnitude of anti-SRIF titre and the acute endocrine response, increasing doses of antibody were administered.

MATERIALS AND METHODS

Animals and experimental method
Thirty intact male lambs weighing 19.8±0.6 kg (means±s.e.m.) were used. The lambs were randomly assigned to control (C) or one of four somatostatin-immunized (SI) groups such that each group contained four purebred Suffolk and two Rambouillet × Hampshire lambs. Water, medium quality alfalfa hay and an 18% crude protein barley based concentrate were available ad libitum.

Lambs in each treatment group received control immunoglobulin and/or anti-SRIF immunoglobulin on experimental day 0 via a jugular catheter. C lambs received 100 mg control immunoglobulin/kg body weight (BW). SI lambs received 2 mg (SI2), 10 mg (SI10), 20 mg (SI20) or 100 mg (SI100) anti-SRIF immunoglobulin/kg BW. SI2, SI10 and SI20 lambs also received sufficient control immunoglobulin such that all lambs received a total of 100 mg immunoglobulin protein/kg BW. C and SI100 lambs received (i.v.) additional control and anti-SRIF immunoglobulin respectively, on day 0, immediately following intensive blood sampling (20 mg/kg BW), and on days 4 and 8 (40 mg/kg BW).

All lambs were fitted with a single polyvinyl catheter (Laarveld et al. 1986) in the jugular vein 24 h prior to injection of immunoglobulin and initiation of intensive blood sampling. C and SI100 lambs were refitted with jugular catheters 24 h prior to intensive blood sampling on day 11. Catheters were kept patent with sterile physiological saline (0.9% w/v NaCl) containing 500 IU heparin (Organon Canada Ltd, Toronto, Ontario, Canada) per ml.

On day 0, immediately following injection of immunoglobulin, blood samples (5 ml) were collected in heparinized syringes at 10-min intervals for 5 h. At the end of the 5-h collection period lambs were challenged with TRH (0.33 μg/kg BW). Blood samples were collected at −20, −10, 0, 5, 10, 15, 20, 25, 30, 40, 50, 60 and 80 min relative to the injection of TRH (0 min). Blood samples were transferred from syringes to glass tubes containing 0.1 ml EDTA (20%, w/v) and 0.4 ml Trasylol (Miles, Rexdale, Ontario, Canada; 500 Kallikrein Inactivating Units/ml blood) and kept on ice until centrifugation. Plasma was stored at −20°C until analysis. For C and SI100 lambs the same blood sampling protocol was repeated on day 11. Access to hay and concentrate was restricted during the blood sampling periods.

Antisera preparation
Anti-SRIF and control immunoglobulin were obtained by ammonium sulphate precipitation of serum immunoglobulin (Goding, 1986) harvested from a ewe actively immunized against SRIF and from a non-immunized ewe respectively. Precipitated antibody was reconstituted in phosphate-buffered saline (PBS; 0.025 mol/l) and dialysed for 48 h against four changes of 4 litres PBS (0.025 mol/l). Both preparations were adjusted to the same protein concentration by dilution with PBS (0.025 mol/l).

Anti-SRIF immunoglobulin affinity was determined by single site Scatchard analysis of a homologous displacement assay (Munson & Rodbard, 1980) using cyclic somatostatin-14 (Bachem Inc., Torrance, CA, U.S.A.) as standard. Anti-SRIF titres are reported as the per cent binding of 125I-labelled Tyr1-SRIF-14 (10 000 c.p.m.; Bachem Inc.) for a given final dilution of serum (Laarveld et al. 1986).

Hormone analysis
Plasma GH and TSH and total plasma thyroxine (T4) and tri-iodothyronine (T3) were analysed by double-antibody radioimmunoassay (Van Kessel et al. 1990).
Intra- and interassay coefficients of variation (C.V.) were 6-1 and 10-9% respectively for the GH assay and 4-2 and 10-1% respectively for the TSH assay. Intra- and interassay C.V. values were 4-0 and 11-1% respectively for the T4 assay, and 4-8 and 9-8% respectively for the T3 assay.

Statistical analysis

Plasma GH overall mean, baseline mean, secretory peak amplitude and secretory peak frequency were determined for 5-h basal sampling periods using PC-Pulsar (Merriam & Wachter, 1982). Treatment differences in plasma GH parameters were examined by one-way analysis of variance. Statistical analysis of basal T4 and T3 and the GH, TSH, T4 and T3 responses to TRH were performed using a split plot design. Sources of variation included treatment in the main plot with time of sample collection (time) and treatment by time interaction in the subplot. All data were analysed using the General Linear Models procedure (SAS Institute Inc., 1989).

RESULTS

Purified anti-SRIF immunoglobulin bound 38-5% of labelled SRIF at a final dilution of 1:500 000 and demonstrated a dissociation constant of 8-6 pmol/l (Fig. 1). Administration of increasingly higher doses of anti-SRIF immunoglobulin resulted in a corresponding increase in plasma anti-SRIF titre as determined 5 h after the initial injection of immunoglobulin (Table 1). In SI100 lambs, the administration of additional doses of anti-SRIF immunoglobulin, 4 and 8 days following the initial dose, maintained plasma anti-SRIF titre to day 11 (Table 1). A 1:2000 dilution of serum harvested from SI100 lambs 2 and 6 days following initial passive immunization demonstrated 45-2±1-2 and 48-0±0-8% binding of 125I-labelled Tyr1-SRIF respectively.

TABLE 1. Mean±s.e.m. per cent binding of 125I-labelled Tyr1-somatostatin (SRIF) for a given plasma dilution in lambs administered control (C) or anti-SRIF (SI) immunoglobulin

<table>
<thead>
<tr>
<th>Plasma dilution</th>
<th>Day 0°</th>
<th>Day 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>1:10</td>
<td>&lt;1-0</td>
</tr>
<tr>
<td>SI2</td>
<td>1:20</td>
<td>27·0±2-6</td>
</tr>
<tr>
<td>SI10</td>
<td>1:100</td>
<td>49·4±2-1</td>
</tr>
<tr>
<td>SI20</td>
<td>1:500</td>
<td>44·5±1-6</td>
</tr>
<tr>
<td>SI100</td>
<td>1:2000</td>
<td>48±1±2-0</td>
</tr>
</tbody>
</table>

*C lambs received 100 mg control immunoglobulin/kg body weight (BW) on day 0. SI2, SI10, SI20 and SI100 lambs received 2 mg, 10 mg, 20 mg and 100 mg anti-SRIF immunoglobulin/kg BW respectively on day 0. C and SI100 lambs received additional (40 mg/kg BW) control and anti-SRIF immunoglobulin respectively on days 4 and 8.

*Per cent binding was determined 5 h after initial immunoglobulin infusion.

Analysis of plasma GH profile over the 5-h period following acute passive immunization indicated no significant difference in overall plasma GH mean, baseline mean, peak amplitude or peak frequency among treatment groups (Table 2). Within 1 h of administration of immunoglobulin, a GH spike exceeding 80 μg/l was observed in one lamb in each of the C, SI2 and SI20 treatment groups. These GH spikes increased mean GH peak amplitude, in each of the affected treatment groups, by 4-8 μg/l. Plasma GH parameters in C and SI100 treatments, examined over a 5-h period after chronic (11 days) immunoglobulin treatment, were not different (Table 2). TRH administration significantly (P<0·001) increased plasma GH. No acute or chronic effects of anti-SRIF immunoglobulin on the plasma GH response to TRH were observed (Fig. 2).

The effect of treatment on basal plasma TSH levels was not statistically analysed as levels were below the assay sensitivity (0·37 μg/l) for three to four lambs per treatment group on both blood sampling occasions. For the TSH response to TRH, basal TSH levels which fell below the assay sensitivity were entered as 0·37 μg/l. TRH administration significantly (P<0·001) elevated plasma TSH. The TSH response to TRH (Fig. 3), infused following acute or chronic exposure to immunoglobulin, was not significantly different among treatment groups.
Table 2. Mean plasma GH parameters determined over a 5-h period after acute (day 0) and chronic (day 11) exposure to control (C) or anti-somatostatin (SI) immunoglobulin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day</th>
<th>Overall mean (µg/l)</th>
<th>Baseline mean (µg/l)</th>
<th>Peak amplitude (µg/l)</th>
<th>Peak frequency (spikes/5 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Day 0</td>
<td>10.27</td>
<td>5.57</td>
<td>18.79</td>
<td>3.33</td>
</tr>
<tr>
<td>SI2</td>
<td>Day 0</td>
<td>12.93</td>
<td>7.35</td>
<td>18.94</td>
<td>3.67</td>
</tr>
<tr>
<td>SI10</td>
<td>Day 0</td>
<td>8.49</td>
<td>6.09</td>
<td>11.19</td>
<td>3.17</td>
</tr>
<tr>
<td>SI20</td>
<td>Day 0</td>
<td>14.60</td>
<td>8.63</td>
<td>18.34</td>
<td>4.16</td>
</tr>
<tr>
<td>SI100</td>
<td>Day 0</td>
<td>10.29</td>
<td>6.90</td>
<td>11.21</td>
<td>3.67</td>
</tr>
<tr>
<td></td>
<td>Pooled S.E.</td>
<td>0.80</td>
<td>0.48</td>
<td>2.22</td>
<td>0.23</td>
</tr>
<tr>
<td>C</td>
<td>Day 11</td>
<td>5.87</td>
<td>4.23</td>
<td>4.89</td>
<td>3.83</td>
</tr>
<tr>
<td>SI100</td>
<td>Day 11</td>
<td>8.19</td>
<td>5.80</td>
<td>7.31</td>
<td>3.33</td>
</tr>
<tr>
<td></td>
<td>Pooled S.E.</td>
<td>0.86</td>
<td>0.70</td>
<td>0.79</td>
<td>0.31</td>
</tr>
</tbody>
</table>

No significant differences were observed.

*a* C lambs received 100 mg/kg body weight (BW) control immunoglobulin on day 0. SI2, SI10, SI20, SI100 lambs received 2 mg, 10 mg, 20 mg and 100 mg anti-somatostatin immunoglobulin/kg BW respectively on day 0. C and SI100 lambs received additional (40 mg/kg BW) control and anti-SRIF immunoglobulin respectively on days 4 and 8.

![Figure 2](image2.png)

**Figure 2.** Mean plasma GH response to thyrotrophin-releasing hormone (TRH; 0.33 µg/kg) administered i.v. at time 0, in lambs receiving control immunoglobulin (C; ○) or the highest dose (100 mg/kg) of anti-somatostatin (SRIF) immunoglobulin (SI100; ■). TRH was administered (a) after acute (5 h) or (b) chronic (11 days) exposure to immunoglobulin. S.E.M. bars are omitted for clarity. S.E.M. at peak GH levels reached 4.57 µg/l. No significant differences were observed.

![Figure 3](image3.png)

**Figure 3.** Mean plasma thyrotrophin (TSH) response to thyrotrophin-releasing hormone (TRH; 0.33 µg/kg) administered i.v. at time 0, in lambs receiving control immunoglobulin (C; ○) or the highest dose (100 mg/kg) of anti-somatostatin (SRIF) immunoglobulin (SI100; ■). TRH was administered (a) after acute (5 h) or (b) chronic (11 days) exposure to immunoglobulin. S.E.M. bars are omitted for clarity. S.E.M. at peak TSH level observed. No significant differences were observed.
Basal plasma T₄ profile was not influenced by acute or chronic immunoglobulin treatment (Fig. 4). When all treatments were included in the data set, analysis of basal plasma T₃ profile following acute immunoglobulin administration indicated no significant difference among treatment groups. However, if C lambs were compared with lambs in each of the four SI groups by separate analyses, a significant (P<0.005) treatment by time interaction was observed between C and SI100 lambs (Fig. 4). No chronic effect of anti-SRIF immunoglobulin on basal plasma T₃ was observed. A significant (P<0.001) elevation in plasma T₄ and T₃ was observed 60 and 25 min respectively following TRH administration. No acute or chronic effects of anti-SRIF immunoglobulin on the plasma T₄ and T₃ responses to TRH were observed (Fig. 5).

**DISCUSSION**

Passive immunization allows neutralization of specific endogenous hormone activity and has been used extensively to examine the physiological significance of SRIF in the control of GH and TSH secretion. The SRIF-binding ability of the anti-SRIF antiserum used in the present study was illustrated by the binding of labelled SRIF in diluted plasma harvested from immunized lambs. Plasma anti-SRIF titres achieved here, by passive immunization, represent the range of titres reported in most studies employing active immunization. Additionally, the dissociation constant of the anti-SRIF antiserum is an order of magnitude greater than that reported for the rat pituitary SRIF receptor (Lewin, 1986) and suggests an ability of the antiserum to compete with the receptor for free SRIF in plasma.

Independent of the quantity of antibody administered, acute passive immunization against SRIF in the male lamb did not influence plasma GH profile parameters. Similarly, Hart et al. (1984) did not observe an effect of acute SRIF immunoneutralization on GH levels in the goat in plasma samples harvested at 30-min intervals for a period of 3 h. Infusion of SRIF (1 µg/min), for a period of 1 h, did not influence basal plasma GH levels in the ewe lamb (Davis,
concentration recently inhibitory and against Plotsky episodic the contrast profile strates SRIF a plasma (Tannenbaum (11980; 180° pharmacological Ruminant These pg/min) GH levels measured observations to predictable, of basal phase of & hypothalamic secretion by basal of an 1985). Ling, et al. (1991) observed a decline in plasma GH when SRIF was infused in ewe lambs at a pharmacological (5 µg/min) but not a physiological (1 µg/min) rate.

These observations in the ruminant animal are in contrast to observations regarding the influence of SRIF on GH secretion in the rat. The male rat demonstrates a predictable, markedly pulsatile plasma GH profile with basal levels below assay sensitivity (Tannenbaum & Ling, 1984). Evidence indicates that the GH profile of the male rat is mainly influenced by episodic hypothalamic secretion of GHRH and SRIF, 180° out of phase (Tannenbaum & Ling, 1984; Plotsky & Vale, 1985). Acute passive immunization against SRIF results in an elevation of both basal and peak plasma GH levels (Ferland et al. 1976; Jacovidou & Patel, 1987) and indicates a tonic inhibitory influence of SRIF on GH secretion (Tannenbaum & Ling, 1984).

Ruminant animals demonstrate plasma GH profiles characterized by irregular spiking activity, with baseline levels ranging from 2 to 10 µg/l (Varner et al. 1980; Gluckman et al. 1987). Frohman et al. (1990) recently measured the hypothalamic portal plasma concentration of GHRH and SRIF in the sheep. An irregular episodic secretory pattern was observed for both hypothalamic hormones, but only GHRH demonstrated a significant association with the plasma GH profile. The current study agrees with these observations and this suggests that SRIF plays a minor role in the regulation of the basal pulsatile plasma GH profile in the ruminant.

The significant GH response to TRH observed in the current study is in contrast to previous observations in the sheep (Davis, 1975; Peeters et al. 1992). TRH has, however, stimulated GH release from ovine pituitaries in vitro (Takahara et al. 1974) and an in vivo GH response to a large dose of TRH in the sheep has recently been observed (Spencer et al. 1992). In the current study the timing of TRH administration in relation to endogenous GH spikes could have contributed to the observation of increased plasma GH in response to a lower dose of TRH.

The physiological significance of SRIF in ruminant animals has also been studied by examining the influence of SRIF on the GH response to exogenous stimulation. Arginine elevates plasma GH in the sheep, a response which was blunted when arginine plus SRIF (500 µg) was infused (Davis, 1975). Hart et al. (1984), using goats, observed a biphasic GH response to
human pancreatic GH-releasing factor-44, the second peak of which was higher in animals given SRIF antiserum. In contrast, a similar biphasic GH response to TRH challenge was not influenced by acute SRIF immunoneutralization in the present study. In the study by Frohman et al. (1990), using the ewe, a transient elevation in hypothalamic portal plasma SRIF concentration, associated with a persistent decline in plasma GH, was observed following insulin-induced hypoglycaemia. The significance of the SRIF response to insulin-induced hypoglycaemia was questioned, however, as portal plasma SRIF levels returned to baseline before the initiation of the decline in peripheral plasma GH. Whether SRIF plays a role during abrupt relatively large shifts in basal plasma GH remains unclear.

Basal plasma TSH was below the sensitivity of the assay which prevented a direct assessment of the influence of acute SRIF immunoneutralization. Using the sheep, Davis (1975) reported no effect of SRIF infusion at a physiological dose (1 μg/min) on basal plasma TSH. However, the TSH response to a bolus injection of TRH plus SRIF (500 μg) was reduced compared with injection of TRH alone. In man, infusion of SRIF at rates that inhibit TSH secretion causes marked depression of plasma GH and this indicates little potential for a physiological influence of SRIF on TSH secretion (Williams et al. 1988). In the current study, acute SRIF immunoneutralization did not influence basal plasma T₄ or the TSH, T₃ or T₄ responses to TRH. These observations imply that SRIF, at physiological concentrations, does not influence TSH secretion in the sheep.

Within 1 h of administration of the highest dose (100 mg/kg BW) of anti-SRIF immunoglobulin, basal plasma T₃ increased by 18%. This increase occurred against a trend towards declining plasma T₃ observed in all treatment groups. Increased plasma T₃ could result from a number of mechanisms including inhibition of T₃ degradation, inhibition of T₃ excretion and/or a preferential release of T₃ from the thyroid gland in response to TSH (Peeters et al. 1992). The timing of the T₃ response, as compared with the rapid elevation in T₃ following TRH, and the absence of a T₄ response suggests that increased plasma T₃ could also reflect elevated peripheral conversion of T₄ to T₃. A direct inhibitory influence of SRIF on rat hepatic T₄ deiodinase activity has been observed (Gavin & Moeller, 1983) and evidence of increased deiodinase activity following acute SRIF immunoneutralization has been reported in domestic fowl (Lam et al. 1986). In ewe lambs chronically exposed to a cold, but not a thermoneutral environment, SRIF infusion (approximately 0.3 μg/min) resulted in a decline in thyroid hormone levels which was significant for T₃ only (Christensen et al. 1990). In our laboratory, chronic passive immunization against SRIF in the neonatal lamb, exposed to a cold environment, elevated plasma T₃ but not T₄ (Van Kessel et al. 1990). Although no change in plasma GH levels was observed in the current study or in the studies of Christensen et al. (1990) and Van Kessel et al. (1990), GH mediation of the possible effects of SRIF on thyroid hormone metabolism cannot be excluded (Kuhn et al. 1986; Kuhn et al. 1987).

In light of the lack of effect of acute SRIF immunoneutralization, the absence of an effect of chronic SRIF immunoneutralization on plasma GH and thyroid hormone parameters was not surprising. Chronic neutralization of SRIF, by active immunization techniques, has been examined as a method of improving the growth rate of domestic livestock. A significant elevation in basal plasma GH levels (Varner et al. 1980) and the GH response to arginine (Varner et al. 1980; Spencer et al. 1983a) has been observed in male lambs actively immunized against SRIF. However, as in the current study, active immunization against SRIF failed to increase plasma GH parameters in ruminant animals in many other studies (Spencer & Williamson, 1981; Spencer et al. 1983b; Laarveld et al. 1986; Bass et al. 1987; Deligeorgis et al. 1988; Vicini et al. 1988; Mears, 1990; Sun et al. 1990; Trout & Schanbacher, 1990). Laarveld et al. (1986) and Van Kessel et al. (1990) suggested that SRIF immunization may improve growth under cold environmental conditions through an influence on thyroid function. The results presented here support an acute inhibitory influence of SRIF on thyroid hormone metabolism. Under thermoneutral conditions, however, no chronic effect of SRIF immunoneutralization was observed.

In summary, no acute or chronic effects of SRIF immunoneutralization on plasma GH, TSH or T₄ secretory profiles were observed. SRIF appears to play a minor role in the regulation of GH and thyroid hormone secretion in the sheep. An increase in plasma T₃ following acute SRIF immunoneutralization may indicate an inhibitory influence of SRIF on thyroid hormone metabolism.

ACKNOWLEDGEMENTS

Financial assistance was provided by the Agriculture Development Fund of the Province of Saskatchewan and the Natural Sciences and Engineering Research Council of Canada. A.G.V.K. acknowledges the personal financial support of the College of Graduate Studies and Research, University of Saskatchewan. The technical assistance of R. S. Korchinski and C. D. Hampton is gratefully acknowledged.
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