DOSE-RESPONSE INFLUENCE OF PROSTAGLANDIN E₁ AND SOMATOSTATIN ON PLASMA LEVELS OF GROWTH HORMONE, PROLACTIN AND THYROTROPIN IN SHEEP

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SUMMARY

Ten ewe lambs (approximately 40 kg) were used to determine the influence of prostaglandin E₁ (PGE₁) and synthetic somatotropin-release inhibiting factor (SRIF) on plasma levels of ovine growth hormone (GH), prolactin (PRL) and thyrotropin (TSH). Intravenous injection of PGE₁ (20 and 100 μg/kg) stimulated a dose-related increase in plasma levels of GH (20 ± 6 and 50 ± 10 ng/ml), respectively. Intravenous injection of SRIF (500 μg), significantly (P<.05) depressed the GH stimulation by PGE₁ (20 μg/kg), while lower doses (5 and 50 μg) were ineffective. The highest dose of PGE₁ (100 μg/kg) also stimulated a significant (P<.01) increase in plasma levels of PRL. One and 10 μg doses of PGE₁/kg had no influence, while the 20 μg/kg dose appeared to stimulate PRL secretion although the response was quite variable. Treatment with SRIF (500 μg) significantly (P<.05) reduced the PRL stimulation by PGE₁ at 20 μg/kg. However the variable PRL response to the 20 μg/kg dose of PGE₁ makes this observation inconclusive. Neither PGE₁ nor SRIF exerted an influence on plasma TSH.

These data demonstrate the dose-related stimulatory effect of intravenously administered PGE₁ on secretion of GH and PRL.

INTRODUCTION

Prostaglandin E₁ (PGE₁) has been reported to be stimulatory to GH secretion in vivo in both sheep (Hertelendy et al., 1972) and humans (Ito et al., 1971). Other workers have reported that PGE₁ injected intraventricularly stimulates PRL release in the rat (Harms et al., 1973). A stimulation of TSH release from rat pituitaries incubated in vitro has also been reported (Dupont and Chavancy, 1972; Vale et al., 1971).

It has been previously reported that synthetic somatostatin (500 μg) (Somatotropin-release inhibiting factor or SRIF) is inhibitory to the stimulation of ovine growth hormone (GH) by arginine (Davis, 1975). Others have reported that varying doses of SRIF are inhibitory to the secretion of GH in rats and humans (Vale et al., 1973; Siler et al., 1973; Parker et al., 1974; Brazeau et al., 1974). An in vivo effect of SRIF on the secretion of prolactin (PRL) has not been conclusively demonstrated, although an inhibitory influence of SRIF on basal PRL release from rat anterior pituitary cells in vitro has been reported (Vale et al., 1973).

The present series of experiments were designed to determine the dose-response influence of intravenously injected PGE₁ on the GH response to PGE₁ at doses less than 100 μg/kg was more consistent than that for PRL. The observation that the stimulatory effect of PGE₁ on GH is partially inhibited by a single injection of 500 μg of SRIF is in support of previous reports that high doses of SRIF are inhibitory to the GH response to a variety of stimuli in other species. SRIF likely does not exert a physiological effect on the secretion of either PRL or TSH in sheep.

(Key Words: Prostaglandin E₁, Somatostatin, Growth Hormone, Prolactin, Thyrotropin, Sheep.)
secretion of GH, PRL and TSH, and to examine the effect of varying doses of SRIF on the stimulation of GH secretion by PGE

**EXPERIMENTAL METHODS**

Ten ewe lambs (approximately 40 kg), five control and five treatment were used for study 1 and 2. The experiments were conducted over 1 month, with one dose of PGE\textsubscript{1} and/or SRIF at 4-day intervals. Permanent indwelling jugular catheters (polyvinylchloride tubing) were inserted 1 day prior to the first experiment and were kept patent throughout the 4-week period by flushing daily with sterile heparinized saline.

**Study 1. Dose-Response Effect of PGE\textsubscript{1} on GH, PRL and TSH.** In the first experiment, a dose of 1\,\mu\text{g} PGE\textsubscript{1}/kg body weight was injected iv. Blood samples were obtained at 15-min intervals for 1 hr prior to injection and for 2 hr post-injection. In the subsequent 2 experiments, PGE\textsubscript{1} doses of 10\,\mu\text{g}/kg and 100\,\mu\text{g}/kg were injected. The blood sampling schedule was the same as that in experiment 1.

**Study 2. Dose-Response of SRIF on GH and PRL Response to PGE\textsubscript{1}.** In a series of three experiments, the lambs were injected with PGE\textsubscript{1} at 20\,\mu\text{g}/kg (control) or PGE\textsubscript{1} (20\,\mu\text{g}/kg) + SRIF at 5, 50 and 500 micrograms. All treatments were administered by single injection into an indwelling jugular cannula. Blood samples were obtained (via jugular cannula) at 15-min intervals for 1-hr pre-injection and for 2-hr post-injection.

In all experiments, the blood samples were placed on ice immediately after collection and were then refrigerated overnight before the plasma was collected and frozen. Plasma levels of GH, PRL and TSH were determined by radioimmunoassay methods which have been previously reported (Davis \textit{et al.}, 1971; Davis, 1972; Borger and Davis, 1974).

**Study 3. PGE\textsubscript{1} (20\,\mu\text{g}/kg) and SRIF (10\,\mu\text{g intracarotid}) on GH and PRL.** This study was conducted to obtain further information on the influence of small doses of SRIF on the GH response to PGE\textsubscript{1} and the PRL response to the 20\,\mu\text{g}/kg dose of PGE\textsubscript{1}. In this study the carotid arteries on one side of the neck of seven wether lambs (50 to 60 kg) were placed surgically into a loop of skin as described by Bone \textit{et al.} (1962). This carotid loop was used for the injection of SRIF. A polyvinyl catheter was inserted into the contralateral jugular vein the day before the experiment. Three lambs received a control injection of PGE\textsubscript{1} (20\,\mu\text{g}/kg) intravenously and the treated lambs (four) were injected iv with PGE\textsubscript{1} (20\,\mu\text{g}/kg) and intracarotidly with SRIF (10\,\mu\text{g}). Blood samples were obtained from the jugular catheters at 15-min intervals for 1 hr before and 2 hr after treatment.

The data were analyzed statistically using Student's $t$ to test the difference between treatment means at time of maximal response.

**RESULTS**

**Study 1. Dose-Response Effect of PGE\textsubscript{1} on GH, PRL and TSH.**

**Plasma GH.** Neither of the two lowest doses

![Figure 1. Plasma levels of GH after the intravenous injection of saline (–––) or PGE\textsubscript{1} (●●●) at 1, 10, and 100\,\mu\text{g}/kg. Each point represents the mean ± standard error of the mean (SEM) of five observations.](image-url)
of PGE₁ (1 and 10 µg/kg) significantly affected plasma levels of GH (figure 1). The highest dose (100 µg/kg) increased (P<.001) plasma GH within 15 min, and the maximum response was observed 30-min post-injection (figure 1).

**Plasma PRL.** Similarly, plasma levels of PRL were not influenced by the injection of PGE₁ at 1 or 10 µg/kg but there was a significant (P<.001) increase in plasma PRL after the injection of 100 µg of PGE₁/kg (figure 2).

**Plasma TSH.** None of the doses of PGE₁ used in the present experiment were effective in changing plasma levels of TSH (table 1).

**Study 2. Dose-Response of SRIF on the GH and PRL Responses to PGE₁.**

**Plasma GH.** The 20 µg/kg dose of PGE₁ stimulated increased plasma levels of GH over pre-injected levels in all three studies (figure 3). The GH response to PGE₁ stimulation was decreased (P<.01) 15 min after injection of 500 µg of SRIF. In contrast, plasma levels of GH appeared to be greater (not statistically significant) following injection of either 5 or 50 µg of SRIF + PGE₁ than plasma GH after PGE₁ treatment alone (figure 3).

**Plasma PRL.** Injection of 20 µg PGE₁/kg was not as effective in stimulating increased plasma PRL levels (figure 4) as with GH. Plasma PRL levels following this dose of PGE₁ were significantly (P<.05) greater than pre-injection levels only in the third experiment (PGE₁ + 500 µg SRIF) (figure 4). The simultaneous treatment with 500 µg of SRIF significantly (P<.05) reduced the PRL response to PGE₁ (figure 4). Plasma levels of PRL were not significantly influenced by injection of either 5 or 50 µg of SRIF.

![Figure 2](image-url). Plasma levels of PRL after the intravenous injection of saline (o-o) or PGE₁ (•-•) at 1, 10 and 100 µg/kg. Each point represents the mean ± standard error of the mean (SEM) of five observations.

**Plasma TSH.** Neither the injection of PGE₁ (20 µg/kg) nor PGE₁ (20 µg/kg) + SRIF at any dose influenced plasma levels of TSH (table 1).

### TABLE 1. PLASMA TSH LEVELS IN LAMBS FOLLOWING INJECTION WITH SALINE, PGE₁ OR PGE₁ + SRIF

<table>
<thead>
<tr>
<th>Time (min) After Treatment</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>6.7 ± .2 a</td>
<td>6.5 ± .5</td>
<td>5.3 ± .5</td>
<td>5.0 ± .2</td>
<td>6.3 ± .6</td>
</tr>
<tr>
<td>PGE₁ (100 µg/kg)</td>
<td>6.3 ± .5</td>
<td>4.8 ± .1</td>
<td>5.2 ± .2</td>
<td>6.1 ± .8</td>
<td>6.5 ± .9</td>
</tr>
<tr>
<td>PGE₁ (20 µg/kg)</td>
<td>4.8 ± .5</td>
<td>4.6 ± .5</td>
<td>4.4 ± .4</td>
<td>5.1 ± .4</td>
<td>5.4 ± .6</td>
</tr>
<tr>
<td>PGE₁ (20 µg/kg) + SRIF (500 µg)</td>
<td>4.6 ± .5</td>
<td>4.4 ± .5</td>
<td>5.1 ± .6</td>
<td>5.6 ± .7</td>
<td>5.3 ± .5</td>
</tr>
</tbody>
</table>

* a ng NIH-TSH-S6/ml plasma.
Study 3. PGE\textsubscript{1} (20 $\mu$g/kg) and SRIF (10 $\mu$g Intracarotid) on GH and PRL.

This study was conducted in view of the suggested stimulatory influence of low doses of SRIF on GH (study 2) and the variable PRL response to PGE\textsubscript{1} at 20 $\mu$g/kg. As observed in the previous experiments, PGE\textsubscript{1} (20 $\mu$g/kg) stimulated a significant ($P<.01$) increase in plasma levels of both GH and PRL as compared to preinjection levels (figure 5). In contrast to the results obtained in study 2, 10 $\mu$g of SRIF injected intracarotidly did not enhance the GH response to PGE\textsubscript{1} but inhibited this response ($P<.05$). The stimulatory effect of PGE\textsubscript{1} on plasma PRL was not influenced by 10 $\mu$g of SRIF.

Discussion

The stimulatory influence of PGE\textsubscript{1} on GH secretion is in agreement with previous reports that PGE\textsubscript{1} is capable of stimulating an increase in plasma levels of GH in sheep (Hertelendy et al., 1972) and humans (Ito et al., 1971). In addition the report that PGE\textsubscript{1} is capable of stimulating GH release from rat pituitaries incubated \textit{in vitro} (Schofield, 1970; MacLeod and Lehmeyer, 1970; Hertelendy, 1971; Hertelendy et al., 1971) would suggest that PGE\textsubscript{1} exerts this stimulatory effect directly at the level of the pituitary.

Our results also suggest that PGE\textsubscript{1} is a more potent stimulus to GH secretion than to PRL.
This suggestion is based upon the observation that the 20 μg/kg dose of PGE₁ consistently stimulated increased plasma GH, but not PRL. However, this evidence is not conclusive since the inability to detect increased plasma PRL may be due to the greater variability of plasma PRL levels than those observed for GH. The observation that PGE₁ is capable of stimulating increased plasma PRL is in agreement with the previous data reported by Harms et al. (1973), who observed an increase in plasma PRL in the rat following the injection of PGE₁ (2 μg/kg) into the third ventricle. However, these workers did not observe an effect of PGE₁ on PRL secretion when injected directly into the pituitary. It is entirely possible that the higher levels of PGE₁ were capable of influencing the secretion of PRL in our studies by exerting a hypothalamic influence on the release of either prolactin inhibiting factor (PIF) or a prolactin releasing factor (PRF).

The inability to influence plasma levels of TSH by any of the doses of PGE₁ are not in agreement with previous reports that PGE₁ stimulates the release of TSH from rat pituitaries in vitro (Vale et al., 1971; Dupont and Chavancy, 1972). However, Thompson et al. (1974) have reported that the intrapituitary injection of PGE₁ potentiated the TRH induced rise in TSH secretion but was ineffective on basal TSH secretion in rats. To date, we have not examined the influence of PGE₁ on the TSH response to TRH in the sheep, but our data on the lack of an effect of PGE₁ on the basal levels of TSH are in agreement with those of Thompson et al. (1974).

The present data on the inhibitory influence of SRIF on the PGE₁ stimulation of GH further extends the results of previous reports. It has been previously observed that SRIF is inhibitory to the arginine stimulation of GH secretion in sheep (Davis, 1975) and humans (Siler et al., 1973). SRIF has also been reported to exert an inhibitory effect on both pentobarbital stimulated GH and resting GH levels in rats (Brazeau et al., 1974).

**LITERATURE CITED**


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