Inhibition of foetal growth hormone (GH) and thyrotrophin (TSH) secretion after maternal administration of somatostatin

Elio Roti, Giuseppe Robuschi, Alessandro Alboni, Rossella Emanuele, Lorenzo d’Amato, Eliana Gardini, Mario Salvi, Elisabetta Dall’Aglio, Angelo Gnudi and Lewis E. Braverman

Cattedra di Endocrinologia e Patologia Costituzionale, University of Parma Medical School, Parma, Italy
Divisione di Ostetricia e Ginecologia Ospedale C. Magati, Scandiano, Italy and the Division of Endocrinology and Metabolism, University of Massachusetts Medical School, Worcester, Massachusetts 01605, USA

Abstract. Somatostatin (SRIF) was infused (500 μg over 30 min) into 68 pregnant women during labour. As a control, saline was infused into 26 pregnant women. Maternal blood was obtained prior to the infusion and at delivery and cord blood was obtained at delivery. The subjects were divided into 4 groups based upon the interval of time from the termination of SRIF infusion and delivery. There was a marked decrease in cord blood thyrotrophin (TSH) from 0 to 180 min and in cord blood growth hormone (GH) from 0 to 120 min following SRIF infusion. SRIF infusion did not affect cord blood iodothyronine and thyroglobulin concentrations. SRIF administration induced a small but significant ($P < 0.05$) decrease in serum GH concentration but had no other effect on maternal hormone values. These studies strongly suggest that SRIF crosses the human placenta and transiently suppresses foetal anterior pituitary TSH and GH secretion.

In adults, somatostatin (SRIF) administration has been demonstrated to reduce the basal and stimulated secretion of some anterior pituitary hormones. Thus, SRIF infusion blocks the secretion of growth hormone (GH) under a variety of physiological, pathological and pharmacological conditions (Siler et al. 1973; Hall et al. 1973; Prange-Hansen et al. 1973; Mortimer et al. 1974; Parker et al. 1974). Thyrotrophin (TSH) secretion is also decreased by the administration of SRIF. This inhibitory effect of SRIF on TSH secretion has been observed in normal, hypothyroid or thyrotrophin releasing hormone (TRH) treated subjects or in patients with TSH producing pituitary tumours (Morley 1981; Reschini et al. 1976). In the rat, the administration of SRIF antiserum results in an increase in both GH and TSH concentrations in serum, suggesting that SRIF has a physiological role in the control of GH and TSH secretion (Morley 1981).

We have recently reported that TRH administered to the mother crosses the placenta and stimulates foetal TSH secretion (Roti et al. 1981a). Therefore, it seemed of interest to determine whether SRIF crosses the human placenta and whether it would affect the foetal pituitary secretion of TSH and GH. SRIF has been reported to be effective in treating neonatal hypoglycaemia and no adverse side effects were noted (Kitson et al. 1980; Roti et al. 1981b).
Materials and Methods

Ninety-four pregnant women were studied during labour. Informed consent was obtained by the obstetricians before labour. Sixty-eight women, randomly selected, were treated with SRIF. Five hundred µg synthetic cyclic SRIF (Biodata-Serono, Milan, Italy) diluted in 200 ml saline was infused over a period of 30 min. Careful records were kept detailing the beginning of and end of the infusion and the time of parturition. Twenty-six pregnant women were infused over a similar period with an equal volume of saline and served as the control group. The interval of time between the end of the saline infusion and parturition was 102 ± 16 min with a range of 10 to 335 min. This range encompassed the time interval from the end of the SRIF infusion and parturition in all the experimental groups. Maternal blood samples (MS) were obtained prior to the infusion (basal) and at the time of parturition (treated). Cord blood samples (CB) were obtained at parturition from all neonates. Glucose was not infused during the course of this study. After the umbilical cord was cut, blood was obtained from the placental side of the cord which represents foetal blood. During labour and delivery no adverse effects related to SRIF administration were observed. The clinical course of the neonates whose mothers were treated with SRIF was uneventful. A regional neonatal thyroid screening programme, conducted with T4 and TSH determinations in blood collected on filter paper at the 4th day of life, did not reveal any thyroid abnormalities.

Specimens for blood glucose determination were collected in tubes containing KF and Na2 EDTA and assayed the same day by the glucose oxidase reaction with materials provided by Slavo Diagnostic (Siena, Italy). Serum samples for pituitary and thyroid function tests were kept at -20°C until analysis.

TSH, T4, T3, rT3, thyroglobulin (hTg) and GH were measured in MS and CB samples. Serum TSH was measured by RIA using materials obtained from the National Pituitary Agency (NIAMDD), Bethesda, MD). T4 and GH were measured employing materials obtained by Biodata-Serono. Cross-reactivity of human placental lactogen (hPL) in the GH RIA is 0.1% which could be sufficient to slightly inrease the values for serum GH in the term pregnant woman. SRIF does not affect the placental secretion of hPL in the ovine species (Gluckman et al. 1979) and does not alter the secretion of hCG or hPL in vitro from human placenta (Macaron et al. 1978). T3, rT3 and hTg concentrations in serum were measured by radioimmunoassay. The sensitivity of the various RIA's are: GH, 0.25 ng/ml; TSH, 0.6 µU/ml; Tg, 2.5 ng/ml; T4, 0.6 µg/dl; T3, 6.2 ng/dl; rT3, 2.5 ng/dl. All samples were measured in duplicate, in the same assay and in random order.

For evaluation of the maternal results, MS of women treated with saline were assigned to group 0. Sera from women treated with SRIF were assigned to four groups, 1 to 4, depending on the interval of time between the end of SRIF infusion and parturition. Statistical analysis of the results obtained in the pregnant women was carried out by comparing hormone concentrations measured after saline or SRIF infusion with basal values (Student's paired t-test).

CB samples of mothers treated with saline were assigned to group 0 and those of mothers treated with SRIF to groups 1 to 4 depending upon the interval of time between the end of SRIF infusion and parturition. For evaluation of hormone concentrations measured in CB, values obtained in group 1 to 4 were compared to those obtained in the saline treated control group (group 0). Statistical analyses were conducted using one way analysis of variance (ANOVA) and Duncan's multiple range test corrected for an unequal number of determinations.

All values were expressed as the mean ± SE.

Results

Effect of SRIF infusion on pituitary and thyroid function in the term pregnant woman (Table 1)

Saline or SRIF administration did not affect TSH concentration. Basal TSH concentrations ranged between 1.4 to 1.7 µU/ml and after saline or SRIF treatment between 1.4 to 1.6 µU/ml. Similarly, iodothyronine and hTg concentrations in groups 0 and 1 to 4 were similar prior to saline or SRIF infusion and at parturition.

Blood glucose concentrations were significantly higher at parturition whether the mothers were infused with saline or SRIF (paired t-test; P < 0.05 to P < 0.01). A small and marginally significant reduction compared to basal values in MS GH concentration was observed in group 1, when serum was obtained from 0 to 60 min after the completion of the SRIF infusion (4.0 ± 0.2 ng/ml vs 3.5 ± 0.1; paired t-test, P < 0.05). No significant reduction of GH concentration was observed in the other groups treated with SRIF.

Effect of SRIF infusion on pituitary and thyroid function tests in CB (Table 2, Figs. 1 and 2)

CB GH concentration in group 0 was 27.9 ± 4.9 ng/ml. After SRIF infusion a significant reduction of CB GH concentration was observed (F test, P < 0.05) (Fig. 1). In groups 1 and 2, sampled at
Concentrations of T₄, T₃, rT₃, hTg, TSH, GH and blood glucose in MS samples before (basal) and after (treated) saline infusion (group 0) or SRIF infusion (groups 1 to 4).

<table>
<thead>
<tr>
<th>Groups</th>
<th>0 (10–335a)</th>
<th>1 (0–60)</th>
<th>2 (61–120)</th>
<th>3 (121–180)</th>
<th>4 (181–380)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₄ (µg/dl)</td>
<td>basal</td>
<td>12.9 ± 0.5c</td>
<td>13.0 ± 0.9</td>
<td>12.8 ± 0.4</td>
<td>13.8 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>treated</td>
<td>13.9 ± 0.5</td>
<td>13.8 ± 0.8</td>
<td>13.2 ± 0.4</td>
<td>14.6 ± 0.5</td>
</tr>
<tr>
<td>T₃ (ng/dl)</td>
<td>basal</td>
<td>141.3 ± 5.0</td>
<td>139.5 ± 5.7</td>
<td>136.8 ± 5.9</td>
<td>139.1 ± 5.0</td>
</tr>
<tr>
<td></td>
<td>treated</td>
<td>140.7 ± 7.1</td>
<td>142.1 ± 6.1</td>
<td>133.0 ± 5.6</td>
<td>130.7 ± 4.2</td>
</tr>
<tr>
<td>rT₃ (ng/dl)</td>
<td>basal</td>
<td>28.1 ± 1.2</td>
<td>28.3 ± 1.2</td>
<td>30.9 ± 1.3</td>
<td>31.1 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>treated</td>
<td>30.0 ± 1.1</td>
<td>30.4 ± 1.1</td>
<td>33.6 ± 1.5</td>
<td>34.6 ± 1.7</td>
</tr>
<tr>
<td>hTg (ng/ml)</td>
<td>basal</td>
<td>72.9 ± 8.1</td>
<td>69.6 ± 12.9</td>
<td>58.7 ± 8.4</td>
<td>67.3 ± 10.7</td>
</tr>
<tr>
<td></td>
<td>treated</td>
<td>82.0 ± 9.3</td>
<td>75.2 ± 12.5</td>
<td>64.0 ± 8.8</td>
<td>74.1 ± 11.5</td>
</tr>
<tr>
<td>TSH (µU/ml)</td>
<td>basal</td>
<td>1.7 ± 0.2</td>
<td>1.5 ± 0.1</td>
<td>1.6 ± 0.1</td>
<td>1.5 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>treated</td>
<td>1.6 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>1.6 ± 0.1</td>
</tr>
<tr>
<td>GH (ng/ml)</td>
<td>basal</td>
<td>4.3 ± 0.3</td>
<td>4.0 ± 0.2</td>
<td>5.1 ± 0.7</td>
<td>4.1 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>treated</td>
<td>3.9 ± 0.2</td>
<td>3.5 ± 0.1e</td>
<td>3.9 ± 0.2</td>
<td>3.8 ± 0.3</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>basal</td>
<td>76.3 ± 2.7</td>
<td>71.1 ± 1.5</td>
<td>70.3 ± 2.8</td>
<td>70.2 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>treated</td>
<td>95.2 ± 4.1e</td>
<td>83.8 ± 4.5f</td>
<td>90.6 ± 3.6g</td>
<td>88.1 ± 2.9g</td>
</tr>
</tbody>
</table>

a: The range of time (min) between the end of SRIF or saline infusion to the mother and parturition in groups 0–4.
b: The mean time (min) between the end of SRIF or saline infusion to the mother and parturition in groups 0–4.
c: The mean ± se of each hormone.
d: The number of serum samples in each group.
e: P < 0.05 as compared to basal by paired Student’s t-test.
f: P < 0.02 as compared to basal by paired Student’s t-test.
g: P < 0.01 as compared to basal by paired Student’s t-test.

Parturition between 0 to 60 and 61 to 120 min after completion of the SRIF infusion, CB GH concentrations were markedly reduced (12.2 ± 1.3; Duncan’s test, P < 0.01 vs group 0, and 16.8 ± 1.9; Duncan’s test, P < 0.05 vs group 0). In groups 3 and 4, CB GH concentrations were lower, but not significantly so, as compared to group 0.

A significant decrease in CB TSH concentration was observed following SRIF infusion (F test, P < 0.05) (Fig. 2). In groups 1, 2 and 3, CB TSH
Table 2.
Concentrations of T4, T3, rT3, hTg and blood glucose in CB of newborns whose mothers received saline (group 0) or SRIF (groups 1 to 4).

<table>
<thead>
<tr>
<th>Groups</th>
<th>0 10-335a</th>
<th>1 0-60</th>
<th>2 61-120</th>
<th>3 121-180</th>
<th>4 181-380</th>
<th>F test</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4 (µg/dl)</td>
<td>13.4 ± 0.5c</td>
<td>13.6 ± 0.6</td>
<td>12.6 ± 0.5</td>
<td>13.2 ± 0.4</td>
<td>14.5 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>T3 (ng/dl)</td>
<td>51.4 ± 2.0</td>
<td>47.8 ± 2.5</td>
<td>45.0 ± 2.8</td>
<td>44.0 ± 2.6</td>
<td>50.3 ± 4.6</td>
<td>NS</td>
</tr>
<tr>
<td>rT3 (ng/dl)</td>
<td>94.2 ± 2.9</td>
<td>97.1 ± 7.4</td>
<td>102.5 ± 4.7</td>
<td>101.9 ± 5.2</td>
<td>101.9 ± 9.0</td>
<td>NS</td>
</tr>
<tr>
<td>hTg (ng/ml)</td>
<td>114.1 ± 11.3</td>
<td>140.0 ± 16.5</td>
<td>110.5 ± 10.5</td>
<td>130.5 ± 13.8</td>
<td>126.3 ± 12.3</td>
<td>NS</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>70.4 ± 4.2</td>
<td>58.7 ± 4.5</td>
<td>65.9 ± 6.0</td>
<td>58.3 ± 3.5</td>
<td>72.9 ± 5.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

a: The range of time (min) between the end of SRIF or saline infusion to the mother and CB samples in groups 0—4.
b: The mean time (min) between the end of SRIF or saline infusion to the mother and CB samples in groups 0—4.
c: The mean ± SE of each hormone.
d: The number of serum samples in each group.
F value calculated by one way analysis of variance.

Fig. 1.
Cord blood (CB) growth hormone (GH) concentration in neonates whose mothers were treated with saline, group 0, and somatostatin (SRIF), groups 1 to 4. Number in parenthesis indicates the number of subjects in each group. The bars represent the mean values and the brackets the SE. Min after SRIF represent the elapsed time between the end of the SRIF infusion to the mother and CB samples at parturition. * P < 0.05 and ** P < 0.01 vs group 0 by Duncan’s test.
Cord blood (CB) thyrotrophin (TSH) concentration in neonates whose mothers were treated with saline, group 0, and somatostatin (SRIF), groups 1 to 4. Number in parenthesis indicates the number of subjects in each group. The bars represent the mean values and the brackets the SE. Min after SRIF represent the elapsed time between the end of the SRIF infusion to the mother and CB samples at parturition. * $P < 0.05$ vs group 0 by Duncan's test.

Fig. 2.

Concentrations were $4.9 \pm 0.4$, $5.9 \pm 1.0$, and $5.3 \pm 0.5$ µU/ml, respectively. Each of these values was significantly lower than that observed in the saline infused control group 0 ($10.5 \pm 1.9$) (Duncan's test, $P < 0.05$). CB TSH concentrations in group 4 ($9.5 \pm 2.2$) returned to values similar to those in group 0.

Following SRIF infusion, there were no significant changes in CB iodothyronine, hTg and glucose concentrations compared to values obtained after saline infusion (Table 2).

Discussion

Many reports have provided convincing evidence that SRIF administration inhibits GH and TSH secretion in adults under conditions which are associated with enhanced secretion of the two hormones (Siler et al. 1973; Hall et al. 1973; Prange-Hansen et al. 1973; Mortimer et al. 1974; Parker et al. 1974; Morley 1981). In the present study we have observed that SRIF administration to pregnant women at term resulted in a slight but significant decrement in GH only in sera obtained from 0 to 60 min after the completion of SRIF infusion whereas no changes were observed in the serum TSH concentration. The lack of a consistent effect of SRIF on basal serum GH and TSH concentrations is in agreement with previous reports which also failed to demonstrate a decrease in basal GH and TSH secretion (Siler et al. 1973) or basal GH secretion (DeVane et al. 1974) after SRIF administration to normal adult awake subjects. It should be noted, however, that SRIF infusion does inhibit the post-sleep GH surge (Parker et al. 1974) and the nocturnal TSH elevation (Weeke et al. 1975) in normal subjects. The failure of SRIF to inhibit...
basal maternal TSH concentrations is also in accord with the observation that the addition of SRIF in vitro does not block the release of TSH into the medium from primary cultures of rat anterior pituitary cells or hemipituitaries (Vale et al. 1974; Drouin et al. 1976).

In previous studies, we have demonstrated that TRH crosses the placental barrier and stimulates the release of TSH and GH from the human foetal pituitary (Roti et al. 1981a, 1982). In the present study we have observed that SRIF administered to pregnant women during labour induced a significant decrease in foetal cord blood GH and TSH concentrations, suggesting that SRIF crosses the placenta and transiently inhibits the secretion of GH and TSH from the foetal anterior pituitary. CB TSH concentration was significantly decreased up to 180 min after termination of the SRIF infusion to the mother during labour and then returned to control values. A similar pattern was observed for GH which significantly decreased in cord blood for 120 min after SRIF infusion. SRIF infusion had no effect on CB iodothyronine, hTg and blood glucose concentrations. The failure to observe any change in serum iodothyronine concentrations is consistent with the transient nature of the decrease in foetal TSH secretion. Furthermore, SRIF infusion in adults also does not decrease serum T₄ and T₃ concentrations (Weeke et al. 1975).

Our findings in man are consistent with previous observations in the foetal sheep. In chronically catheterized foetuses, the infusion of synthetic SRIF has been reported to decrease GH secretion (Gluckman et al. 1979). Similar effects were also observed during the neonatal period (Gluckman et al. 1979). Furthermore, it has been observed that SRIF administration to newborn sheep prevents the TSH release induced by TRH administration (Sack et al. 1977). In humans, the administration of SRIF during the early postnatal period has been reported to decrease serum GH concentration (Delitala et al. 1978). Similar results have been obtained with human foetal pituitary glands studied in vitro. Human foetal pituitaries obtained at 10 to 19 weeks of pregnancy incubated in the presence of SRIF at concentrations of \(2 \times 10^{-5}\) to \(10^{-9} \text{M}\) markedly reduced GH release into the medium (Goodyer et al. 1977). The presence of SRIF in the human hypothalamus has been observed by detecting SRIF by radioimmunoassay in tissue extracts obtained from foetuses of 10 to 22 weeks of gestation (Aubert et al. 1977). This observation has been confirmed by immunocytochemical studies which also demonstrated the presence of SRIF in human hypothalami obtained as early as 12 weeks of pregnancy (Bugnon et al. 1978). These studies might indicate an active role of hypothalamic SRIF in the control of GH and TSH secretion during foetal life. However, the importance of SRIF in the physiological control of rat TSH secretion during the neonatal period has been questioned since SRIF antiserum administered to 1 day old rats did not alter serum TSH concentration (Oliver et al. 1982).

SRIF has been detected in the human decidua, placenta and amniotic fluid (Kumasaka et al. 1979; Fitz-Patrick & Patel 1979). Elevated concentrations of immunoreactive SRIF are present in the human umbilical artery and vein (Saito et al. 1983) but there was no apparent correlation between umbilical artery SRIF and GH concentrations. Whether these extra central nervous system sources of SRIF have a role in the maturation and/or control of foetal pituitary secretion is not known.

The present study strongly suggests that SRIF administered during labour to pregnant women crosses the placenta and transiently inhibits the secretion of TSH and GH from the foetal anterior pituitary.

References


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