Effects of a Long Acting Somatostatin Analog on Pituitary, Adrenal, and Testicular Function during Rest and Acute Exercise: Unexpected Stimulation of Testosterone Secretion*

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ABSTRACT

The purpose of this study was to delineate the possible endocrine effects of exercise-induced GH secretion. Twelve healthy adult males were studied during short (20 min) and subsequent prolonged (2 h) physical exercise and recovery period (2 h), both after injection of a long acting somatostatin analog [Sandostatin (ST); 0.1 or 0.05 mg, sc] and after a control saline injection. Additional subjects were studied during rest with similar injections of ST (0.1 mg) and saline (n = 7) or using a lower ST dose (0.01 mg; n = 6). Several venous blood samples were taken during the trials and analyzed for selected hormones, monitoring pituitary, testicular, and adrenal functions. ST injection blocked the serum GH response to short term maximal bicycle ergometer exercise, but not to the following prolonged bicycle exercise. No relationship of the exercise-associated GH increase to the concomitant endocrine responses of the adrenals and testes was observed. Unexpectedly, the higher ST doses (0.1 and 0.05 mg) increased the mean levels of serum testosterone by 18-25% in both exercise (P = 0.0017) and rest trials (P < 0.0001), respectively. ST did not affect the levels of LH, FSH, or cortisol. ST slightly increased serum sex hormone-binding globulin (3%; P = 0.021) and albumin (4%; P = 0.017) concentrations, but not that of free testosterone. Because the testosterone response to somatostatin was fast and without a simultaneous increase in LH, it was consistent with a direct testicular response. The explanation for this novel ST effect remains obscure, but it may be due to modulation of some paracrine mechanisms inhibiting testicular steroidogenesis. (J Clin Endocrinol Metab 80: 3298–3303, 1995)

Gh secretion increases during short intensive and prolonged physical exercise (1–3), but the physiological importance of this endocrine response remains unclear (4). The episodic secretion pattern and low basel levels of GH necessitate the use of stimulation tests for evaluation of the pituitary capacity to secrete GH (5). After the development of long acting somatostatin (ST) analogs, inhibition tests became available for studies of GH secretion (6). ST infusions with glucagon and insulin during exercise have been used to examine glucose regulation (7, 8), but to date no information about other possible endocrine effects (pituitary, testicular, or adrenal) of ST during exercise is available. A long acting ST analog (SMS 201–995) has been shown to alter pituitary responses to stimulation tests (9). Because of coregulation of the hypothalamic-pituitary-end-organ axes (10–12) and because of alternate GH responses to exercise at moderate altitude vs. those at sea level (13), the physiological significance of the exercise-induced GH response has been questioned. For this study, we hypothesized that the GH increase may influence the secretion and regulation of other hormones that also respond to exercise. We studied healthy males during short and prolonged physical exercise and a recovery period both after injection of a long acting ST and after a control saline injection. In the course of the studies we made the unexpected finding that ST increases serum testosterone concentrations. This effect of the ST analog was further studied in additional experiments in resting men.

Subjects and Methods

Subjects

A total of 25 healthy adult males (12 in the exercise trials and 13 in the rest trials) were studied. The means (range) of some characteristics of the subjects were as follows: age, 21.4 (19–34) yr; height, 180.7 (171–192) cm; and weight, 75.0 (65–94) kg. The subjects signed an informed letter of consent after being told about the purpose, possible risks, and stress associated with the study. The investigation was approved by the local institutional ethical committee on human research.

Design of the study

The exercise trials with the same 12 subjects were repeated twice in the laboratory at an interval of 14 days. Both trials consisted of the same maximal progressive bicycle ergometer test, a 30-min recovery period, a 2-h continuous bicycle ergometer exercise, and a 2-h recovery period. The maximal ergometer test, starting at 70 watts, was performed with increasing power of 30 watts every 2 min (70, 100, 130, 160, 190 watts, etc.) until exhaustion. During the 2-h continuous ergometer exercise, the subjects cycled with power set at 40–45% of their maximal reached power in the progressive test. Before the maximal exercise test, the
Analytical methods

Serum testosterone and cortisol were measured by RIA kits purchased from Farmos Diagnostica (Turku and Oulu, Finland). Serum free testosterone was measured directly by a sensitive RIA after equilibrium dialysis and column chromatography (1H-testosterone tracer, New England Nuclear Corp., Boston, MA; polyclonal antibody, Farmos Diagnostica, Turku, Finland). Serum 17-hydroxyprogesterone was analyzed with coated tube RIA kits purchased from ICN Biomedicals (Costa Mesa, CA). Serum LH and FSH were measured using time-resolved immunofluorometric assay kits (Delfia hLH for LH and Delfia hFSH for FSH) provided by Wallac OY (Turku, Finland). Serum GH was analyzed with RIA kits purchased from ICN Biomedicals (Costa Mesa, CA). Serum 17-hydroxyprogesterone was analyzed in duplicate in the same assay run. The reference ranges, respectively. All samples from the same subjects were computed to baseline samples (sample taken 45 min before injection); repeated measures ANOVAs or matched pair t tests were used in the computations.

The concentrations of the hormones are expressed as the mean ± SEM.

Results

Exercise trials (saline/ST)

The GH concentration increased immediately after the maximal exercise in the saline trial (P = 0.0003), whereas ST blocked the GH response to the short term exercise (P = 0.020; interaction P = 0.034). Significant differences between the trials were found in the 50 and 80 min samples (Fig. 1). No differences were found with ANOVA between the ST and saline trials in serum testosterone, LH, FSH, and cortisol. In both exercise trials serum testosterone and FSH increased during the maximal exercise (P = 0.0001 and P = 0.002, respectively) and thereafter remained at the baseline level or below it (testosterone, 320 min vs. -45 min sample, P = 0.046; FSH, 80 min -45 min, P = 0.0005; 200 min -45 min, P = 0.049; 320 min -45 min, P = 0.003). The LH concentration decreased below the baseline level after the 30-min rest period and remained below the baseline thereafter (80 min -45 min, P = 0.0008; 200 vs. -45 min, P = 0.0009; 320 vs. 45 min, P = 0.0012). The cortisol concentration first decreased in accordance with its daily variation (25 vs. 45 min, P = 0.0033; 25 vs. -45 min, P = 0.0001) until the concentration increased because of exercise (50, 80, and 200 min samples) and finally during rest started to decrease again (320 min sample).

However, when, the preexercise levels of serum testosterone were compared, a marked response to ST injection was seen; the serum testosterone concentration increased immediately after ST and before the first exercise period (25 vs. 25 min, from 30.6 to 36.1 nmol/L; P = 0.0002). The mean ± SD increase was 18 ± 10%. No concomitant change occurred in testosterone after saline injection (31.5 vs. 31.7 nmol/L; P = 0.77).

Rest trials (saline/ST)

No differences were found between ST and saline trials by ANOVA in serum GH, LH, and FSH (Fig. 2). A significant increase in testosterone was again found after the 0.1-mg ST injection (P < 0.0001), whereas no response to...
saline injection was apparent ($P = 0.87$; interaction, $P = 0.0014$). As in the ST-exercise trial, this peptide increased serum testosterone from the basal level to values in samples taken 30 min ($P = 0.0020$), 60 min ($P = 0.0018$), and 120 min ($P = 0.0073$) after injection. The same ST effect on testosterone was reproduced in a fourth group of six resting men (data not shown). The effects of ST injections on individual testosterone values in the first two experiments are presented in Fig. 3.

To explore the dose response of serum testosterone to ST and to exclude the possibility that the vehicle of ST causes the response, we injected a third group of six men with 0.01 mg ST and collected blood samples as described above (the dose trial). The mean testosterone levels displayed no significant change 30, 60, or 120 min after the injection ($22.1 \pm 4.1$ vs. $23.4 \pm 3.4$ nmol/L at $-25$ and 60 min, respectively).

Serum albumin, SHBG, free testosterone, and 17-hydroxyprogesterone were analyzed in samples taken 20 min before injection and 60 min after injection (Table 1). Serum albumin and SHBG increased by 3% ($P = 0.021$) and 4% ($P = 0.017$), respectively, in the ST-rest trial. Serum free testosterone did not change after the ST injection, but 17-hydroxyprogesterone displayed a nonsignificant tendency to increase (14%; $P = 0.09$).

Discussion

A single injection of the long acting somatostatin analog (ST) used in the present study blocked the exercise-induced GH response during the maximal bicycle ergometer exercise of 16–26 min, but not during the subsequent 2 h of continuous bicycle ergometer exercise. The doses used (0.05 and 0.1 mg) are in clinical practice usually administered three times daily for the treatment of acromegaly, and the disposition half-life of this substance ranges from 88–113 min (15, 16). Because the single ST injection did not block the GH response during the 2-h exercise, it is obvious that (prolonged) physical exercise is a potent stimulus of GH secretion, as demonstrated previously (17). The doses of ST used in our study were well tolerated; three of the subjects experienced minor gastrointestinal pain a few minutes after injection, but it was relieved before the exercise started. The subjects could not distinguish between the injections of ST and saline, and ST did not alter the physical performance of the subjects.

Interestingly, ST induced a consistent increase in the serum testosterone concentration in three independent experiments, 1 in association with exercise and the other 2 in association with rest. In the ST-exercise trial, the increase in testosterone 20–25 min after injection was seen in all 12 subjects (from a mean of 30.6 to 36.1 nmol/L; a mean of 18%),

![Image of graph showing serum concentrations of GH, testosterone, LH, FSH, and cortisol over time](image)

**Fig. 1.** Serum concentrations of GH, testosterone, LH, FSH, and cortisol before (−45 and −25 min) and 20 min after a 0.05/0.1 mg somatostatin or saline injection (20 min), immediately after maximal exercise (50 min), 30 min after maximal exercise, just before starting the 2-h continuous exercise (80 min), after the 2-h continuous exercise (200 min), and after a 2-h recovery period (320 min). The somatostatin trial is marked with triangles, and the saline trial with squares. Symbols E1 and E2 indicate the maximal and 2-h continuous exercises, respectively. Arrows indicate the time of the somatostatin/saline injection. Values are the mean ± SEM (n = 12). The levels of significance of the hormonal changes are presented in Results.
FIG. 2. Serum concentrations of GH, testosterone, LH, and FSH before (-45 and -20 min) and 30, 60, and 120 min after a 0.1-mg somatostatin or saline injection. The somatostatin trial is marked with triangles, and the saline trial with squares. Arrows indicate the time of the somatostatin/saline injection. Values are the mean ± SEM (n = 7). The levels of significance of the hormonal changes are presented in Results.

FIG. 3. Serum testosterone concentrations before (-25 or -20 min) and after (25 or 30 min) a 0.05/0.1 mg somatostatin or saline injection. The concentrations before and after somatostatin/saline injection in an individual subject are connected. The top panels (A) present data from the exercise trials, with somatostatin on the left and saline on the right. The bottom panels (B) present data from the rest trials, with somatostatin on the left and saline on the right. There were 12 subjects analyzed in the exercise trials and 7 in the rest trials.

whereas no change in serum testosterone was seen in the saline-exercise trial. Serum testosterone increased similarly in the ST-rest trial in all 7 subjects (from 19.4 to 24.2 nmol/L; a mean of 25%), whereas no similar change was seen in the saline-rest trial. The finding of increased testosterone secretion after ST injection was further strengthened by a fourth study in another 6 subjects, and the mean increase from the preinjection level to 2 h after ST injection was in this case 27% (from 26.6 to 33.7 nmol/L; P < 0.0001; data not shown). In the exercise trials the difference between saline and ST was seen only before the maximal exercise, which increased serum testosterone in both trials and blunted the ST/saline difference. In the ST-rest trials, the drug effect was seen 30 min after injection and lasted for at least 2 h. Hence, in the 3 studies performed, serum testosterone increased after ST injection in all 25 subjects studied. The effect was clearly caused by ST in a dose-dependent fashion, because a 10-fold lower dose (0.01 mg) did not evoke a testosterone response.
require further investigation. To our knowledge, this is the first description of and importance of the ST-induced increase in testosterone production. 

The tendency for increased concentrations of 17-hydroxyprogesterone (18) supports our finding of the direct testosterone producing capability of ST. The possible interference of ST in the testosterone assay was excluded, as was the possibility of a general effect on steroid metabolism or clearance rate. With this experiment also, the possibility of effect of the vehicle could be excluded.

The ST effect is apparently direct at the testicular level because of the speed of the response. Exogenous gonadotropin requires 1-2 h to affect human testicular steroidogenesis (18). Moreover, there was no simultaneous increase in the serum LH concentration to support an effect via the pituitary. In the rest trials, ST slightly increased serum SHBG and albumin concentrations. This may occur through reduced hepatic blood flow, as shown previously (19). No change was observed in serum free testosterone. As the increase in serum total testosterone greatly exceeded that in its main transport proteins (18-27% vs. 3-4%), this phenomenon must be due to increased testicular output rather than to increased and/or prolonged binding to plasma proteins. Because ST did not alter serum cortisol concentrations, the increase in testosterone is apparently specific to the testis and not a general effect on steroid metabolism or clearance rate. The tendency for increased concentrations of 17-hydroxyprogesterone (14%; P = 0.09, not significant) also supports a direct testicular response. The possible interference of ST in the testosterone assay was excluded, as was the possibility that ST had stimulated the release into blood of another substance(s) that interfered with the testosterone assay.

The magnitude of the serum testosterone response to ST resembles that observed after maximal hCG stimulation, which is the strongest known hormonal stimulus of testicular steroidogenesis. An injection of hCG (5000 IU, im) increases serum testosterone by a mean of 32% in 2 h (18). This is followed by a prolonged increase of about 100% 2-4 days later (18). The recent observation of ST-like immunoreactivity in male reproductive tract (testis, epididymis, prostate, and semen) (20) supports our finding of the direct testicular effects of this peptide. However, the exact mechanism and importance of the ST-induced increase in testosterone require further investigation. To our knowledge, this is the first report on the effects of ST on testicular steroidogenesis. As ST acts through activation of the inhibitory Gi protein (21), its effect on cAMP production should be inhibitory. However, by occupying a set of Gi protein-coupled receptors on the Leydig cell plasma membrane, it may block the action of another stronger inhibitor using the same signal transduction mechanism (e.g., adenosine). What appears as stimulation of steroidogenesis may, in fact, be inhibition of another strongly inhibitory paracrine signal. Our attempts to reproduce the stimulatory effect of ST on in vitro steroidogenesis of purified rat Leydig cells have been unsuccessful (unpublished observations).

In the hormonal parameters of the present study, there were no changes that could have been caused by blocked GH secretion during exercise. Therefore, the significance of the GH increase during exercise remains unclear. Because ST seems to have multiple direct hormonal and metabolic effects of its own, the specific GH-related changes in ST studies will be difficult to demonstrate.

GH secretion is mainly regulated by the interplay between the hypothalamic releasing (GHRH) and inhibiting (ST) hormones. This dual regulation is modulated by a complex network of several neuropeptides. Blocking acetylcholine action with atropine suppressed GH secretion after three different stimuli (arginine, clonidine, and physical exercise) (22), and opiates have been shown to mediate an increase in GH secretion by antagonizing the action of ST (23). During exercise, the regulation of GH secretion may be even more complex, because lactate and other energy metabolites may have additional effects on GH secretion (24). On the other hand, the release of GH by exercise has been concluded to be independent of endogenous opioid peptides (25-27). The present study demonstrates that physical exercise is a potent stimulus of GH secretion that can be caused, among other factors, by the inability of GH to inhibit its own secretion during exercise, as shown in prolonged hypoglycemia (28).

In conclusion, a single sc injection of ST increases the serum testosterone concentration in healthy adult males. Although the mechanism of this effect remains unclear, it apparently involves direct testicular stimulation of testosterone secretion.

References


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**Table 1.** Serum concentrations of free testosterone, 17-hydroxyprogesterone, SHBG, and albumin in rest trials 20 min before (-20) and 60 min after (+60) an injection of saline or 0.1 mg somatostatin.

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<thead>
<tr>
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<th>-20 min</th>
<th>+60 min</th>
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<tbody>
<tr>
<td><strong>Free testosterone</strong></td>
<td>168.4 ± 15.9</td>
<td>174.0 ± 28.7</td>
</tr>
<tr>
<td>Saline</td>
<td>231.3 ± 36.9</td>
<td>238.7 ± 22.9</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>4.2 ± 0.3</td>
<td>3.9 ± 0.3</td>
</tr>
<tr>
<td>17-Hydroxyprogesterone</td>
<td>4.5 ± 0.3</td>
<td>5.1 ± 0.5</td>
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<tr>
<td>SHBG (nmol/L)</td>
<td>44.1 ± 3.9</td>
<td>44.4 ± 3.9</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>41.9 ± 4.7</td>
<td>43.0 ± 4.7</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>46.8 ± 1.0</td>
<td>45.8 ± 1.1</td>
</tr>
<tr>
<td>Saline</td>
<td>45.4 ± 0.9</td>
<td>46.9 ± 1.1</td>
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Values are the mean ± SEM (n = 7).

\* 0.01 < P < 0.02, saline vs. somatostatin

\* 0.02 < P < 0.05, saline vs. somatostatin.


