Somatostatin analogs as adjuncts to agonists of luteinizing hormone-releasing hormone in the treatment of experimental prostate cancer

(combined therapy/growth factor inhibition/tumor inhibition)

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ABSTRACT  The combination of a long-acting delivery system for the agonist [d-Trp⁶]Luteinizing hormone-releasing hormone (d-Trp⁶[LH-RH] with modern somatostatin analogs was studied in the Dunning R-3327H rat prostate cancer model. Microcapsules of [d-Pr⁶]LH-RH releasing 25 μg/day were injected once a month. In the first experiment the adjunct was the somatostatin analog D-Phe-Cys-Tyr-d-Trp-Lys-Val-Cys-Thr-NH₂ (RC-121), administered at a dose of 2.5 μg twice a day, and the therapy was continued for 70 days. Tumor volume was significantly decreased by [d-Pr⁶]LH-RH microcapsules or RC-121 given alone. The combination of microcapsules and analog RC-121 caused a greater inhibition of tumor growth than the single agents. Similar effects were seen when the percent increase in the tumor volume was examined. The inhibition of tumor growth caused by the [d-Pr⁶]LH-RH microcapsules was greater than that caused by RC-121. The combination of the two agents was again the most effective, resulting in the smallest increase in tumor volume. Tumor weights were much lower in the groups treated with microcapsules or RC-121 alone than in controls. The lowest tumor weights were obtained in the group that received the combination of [d-Pr⁶]LH-RH microcapsules and RC-121. Similar results were obtained in the second experiment, in which the animals were treated for a period of 83 days with microcapsules containing the somatostatin analog D-Phe-Cys-Tyr-d-Trp-Lys-Val-Cys-Thr-NH₂ (RC-160) that released 5 μg/day and were injected twice a month alone or in combination with microcapsules of [d-Pr⁶]LH-RH. Microcapsules of analog RC-160 given alone significantly decreased tumor growth as measured by the final tumor volume, the percentage change from the initial tumor volume, and the reduction in tumor weight. The inhibition of tumor growth induced by [d-Pr⁶]LH-RH microcapsules was greater than that caused by RC-160. The most striking decrease in tumor weight and volume was obtained in animals treated with microcapsules of [d-Pr⁶]LH-RH combined with the delayed delivery system for RC-160. The overall response to the combination therapy could reflect the inhibition by somatostatin analogs of the proliferation of prostate cancer cells through a decrease in growth hormone and prolactin release and interference with endogenous growth factors, in addition to the main effect, which is the suppression by [d-Pr⁶]LH-RH of the growth of androgen-dependent tumor cells. Our results indicate that somatostatin analogs enhance the inhibitory effects of [d-Pr⁶]LH-RH on the growth of prostate tumors. The administration of somatostatin analogs in combination with microcapsules of [d-Pr⁶]LH-RH might improve clinical response in patients with advanced prostate carcinoma.

The endocrine therapy for prostate cancer and other sex hormone-dependent tumors has been made more convenient by the development of long-acting delivery systems for [d-Pr⁶]Luteinizing hormone-releasing hormone ([d-Pr⁶]-LH-RH) and other LH-RH agonists based on microcapsule or implant formulations. The clinical efficacy of [d-Pr⁶]-LH-RH microcapsules in patients with prostate cancer was established by Faiman et al. (2). This approach could become the method of choice for the endocrine treatment of advanced prostate carcinoma. Nevertheless, it is possible that the therapeutic response could be improved by combining LH-RH agonists with other compounds including peptides such as somatostatin analogs (3) or various chemotherapeutic agents (4, 5).

Among the major actions of somatostatin is the inhibition of the release of the pituitary growth hormone (GH) and, under certain conditions, of prolactin (6). Prolactin has been shown to stimulate prostate growth, to enhance metabolic processes in the prostate, and to potentiate the response of the prostate to 5-dihydrotestosterone (7–13). Consequently, prolactin could be involved in prostate cancer as a cofactor (7–14). The reduction in prolactin levels produced by the administration of a somatostatin analog, combined with the decrease in serum testosterone that results from chronic treatment with LH-RH agonists, may inhibit growth of prostate tumors better than LH-RH agonists alone (14). The fall in GH levels induced by somatostatin analogs could, through mechanisms involving endogenous growth factors, be even more important for the inhibition of tumor growth (14) than the reduction in prolactin. GH stimulates cell differentiation directly and clonal expansion indirectly through local production of insulin-like growth factor I (15–18).

A family of insulin-like growth factor polypeptides, also called somatomedins, and other growth factors including epidermal growth factor (EGF), platelet-derived growth factor, fibroblast growth factor, and transforming growth factor appear to be involved in the proliferation of both normal and neoplastic cells (19–23). In addition, transforming growth factor, platelet-derived growth factor, and other growth factors are implicated in phenotypic transformation of cells (24). There are also growth inhibitors that have antiproliferative effects on cells (25–28). One of these endogenous growth inhibitors is somatostatin (13, 14, 28), which blocks the release or action of many hormones (6). Somatostatin inhibits numerous cellular processes (13) and nullifies the cell replication induced by EGF (28). In the MIA PaCa-2 human pancreatic cancer cell line, somatostatin reverses the stimulatory effect of EGF on the phosphorylation of the tyrosine kinase portion of the EGF receptor (29). Thus somatostatin and its selective, superactive analogs not only inhibit the

Abbreviations: LH-RH, luteinizing hormone-releasing hormone; GH, growth hormone; EGF, epidermal growth factor; b.i.d., twice a day.
release of GH but also can interfere with the effect of EGF and other growth factors promoted by GH. This multiple action could be the basis for oncological application of somatostatin analogs.

We have synthesized more than 30 octapeptide analogs of somatostatin (3). The aim of this study was to investigate the effects of the two most active analogs (3): d-Phe-Cys-Tyr-d-Trp-Lys-Val-Cys-Thr-NH₂ (RC-121) and d-Phe-Cys-Tyr-d-Trp-Lys-Val-Cys-Trp-NH₂ (RC-160) alone or in combination with [d-Trp⁶]LH-RH microcapsules on the growth with Dunning R-3327H prostate cancers.

MATERIALS AND METHODS

Male (Copenhagen × Fisher) F1 rats bearing the androgen-dependent R-3327H Dunning rat prostate adenocarcinoma were provided by Norman Altman (Papanicolaou Cancer Research Institute, Miami, FL). Tumors were measured weekly with microlipers, and volume was calculated with the following formula: length × width × height × 0.5236 (30).

In the first experiment the treatment was initiated 45 days after transplantation and in the second study, the treatment was initiated 4 months after transplantation, when the tumor volume was 1500 mm³.

Peptides. Analogs d-Phe-Cys-Tyr-d-Trp-Lys-Val-Cys-Thr-NH₂ (RC-121) and d-Phe-Cys-Tyr-d-Trp-Lys-Val-Cys-Trp-NH₂ (RC-160) were synthesized by solid-phase methods and repurified by HPLC (3). Both analogs were 100–150 times more potent than somatostatin on inhibition of GH release (3, 13, 14). For the injection, RC-121 was dissolved with saline containing 0.2% bovine serum albumin and administered subcutaneously at a dose of 2.5 µg twice a day (b.i.d.).

Microcapsules of [d-Trp⁶]LH-RH (1, 5) and somatostatin analog RC-160 in poly(dL-lactide-co-glycolide) (31) were prepared by a phase-separation process (1) by P. Orsolin at Cytotech (Martigny, Switzerland) and supplied by Debiopharm (Lausanne, Switzerland). Microcapsules of [d-Trp⁶]LH-RH in aliquots of 35 mg were designed to release 25 µg/day for 30 days (1, 5). Prototype batch 7, lot R-101086, of RC-160 microcapsules was sterilized with a 2.5-Mrad (0.025-MGy) dose of γ-radiation, and 3.0 mg of microcapsules was administered, which was calculated to liberate ~5 µg/day for 15 days (14, 31). Microcapsules of [d-Trp⁶]LH-RH and of RC-160 were suspended in 0.7 ml of injection vehicle [2% (wt/vol) CM-cellulose and 1% Tween 20 in water]. The suspensions of microcapsules of [d-Trp⁶]LH-RH were injected intramuscularly once a month and microcapsules of RC-160 were injected every 30 days. Eight to 12 rats per group were used. At various times blood was removed from the jugular vein for hormone analyses.

After 70–83 days of treatment, the rats were sacrificed by decapitation. Trunk blood was collected, and serum was separated. Tumors and various organs were removed, cleaned, weighed, and then frozen on dry ice. Serum levels of testosterone, luteinizing hormone, GH, and prolactin were measured by RIAs as described (1, 5). All data are expressed as the mean ± SEM. Statistical analyses were performed by using a computer-assisted program and Duncan’s new multiple-range test (32) or Student’s t test.

RESULTS

In preliminary experiments in the Dunning R-3327H model of prostate adenocarcinoma, we established that twice daily s.c. administration of 25 µg of [d-Trp⁶]LH-RH or of [L-Trp⁵-S-Trp⁶]somatostatin significantly reduced tumor growth (14). The combination of somatostatin analog with [d-Trp⁶]LH-RH resulted in a greater decrease in tumor volume than that obtained with either peptide given alone. On the basis of these findings we decided to investigate the effect of our most potent analogs of somatostatin given alone or combined with injectable microcapsules of [d-Trp⁶]LH-RH on the growth of Dunning prostate tumors.

In the first study, one group of rats was injected intramuscularly once a month with microcapsules of [d-Trp⁶]LH-RH. Another group of rats received 2.5 µg of RC-121 b.i.d. The third group of rats was given [d-Trp⁶]LH-RH microcapsules and RC-121. Control tumor rats were injected with the vehicle. The treatment with these peptides was continued for 70 days. Fig. 1 shows the tumor volume as measured at intervals of 5–10 days. Tumor growth in all three experimental groups was inhibited within 15 days after treatment was begun. After 70 days, tumor volume was significantly re-

<table>
<thead>
<tr>
<th>Table 1. Effects of chronic administration of [d-Trp⁶]LH-RH microcapsules, somatostatin analog RC-121, or their combination on body, organ, and tumor weight in rats bearing Dunning R-3327H prostate tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body, g</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>[d-Trp⁶]LH-RH microcapsules*</td>
</tr>
<tr>
<td>Analog RC-121†</td>
</tr>
<tr>
<td>Analog RC-121 plus microcapsules</td>
</tr>
</tbody>
</table>

*The results are the means ± SEM; there were 7–12 rats per group. NS, not significant. The probabilities (P vs. control, in parentheses) were calculated by Duncan’s new multiple range test except for value done by Student’s t test (see footnote below).
†Microcapsules released 25 µg/day and were administered every 30 days for 70 days.
‡Dose, 2.5 µg b.i.d. for 70 days, s.c. The therapy was continued for 70 days.
§P < 0.01 vs. control by Duncan’s test and P < 0.01 vs. group given microcapsules by Student’s t test.
conclusions based on tumor volume were confirmed by determination of tumor weights on autopsy, when the control tumors were found to weigh 30.0 ± 6.53 g (Table 1). The lowest tumor weights after 70 days of treatment were obtained in the group that received the combination of [D-Trp6]LH-RH and RC-121: 2.01 ± 0.46 g (P < 0.01 vs. control by Duncan’s test and P < 0.01 vs. group given microcapsules by Student’s t test). Lower tumor weights were also observed in the groups treated with either microcapsules (3.28 ± 0.7 g) or RC-121 alone (17.67 ± 2.85 g).

In the second experiment, a similar design was followed but the microcapsules of analog RC-160 were used instead of b.i.d. administration of RC-121, and the treatment period was extended to 83 days. The survival rate of treated animals was virtually 100%. Fig. 2 shows that treatment of rats bearing prostate tumors with RC-160 microcapsules, with [D-Trp6]-LH-RH microcapsules, or with the combination inhibited tumor growth; the percentage change in tumor volume was significantly reduced by RC-160 at 7, 16, 28, 33, 43, and 54 days. The [D-Trp6]-LH-RH microcapsules were more effective than those of RC-160. The combination was the most effective resulting in an increase in tumor volume of only 216 ± 76%. After 83 days of treatment, tumor volumes were significantly reduced in all three experimental groups as compared to control rats, which had a mean tumor volume of 20,970 ± 6001 mm³. In rats treated with the combination of RC-160 microcapsules and [D-Trp6]-LH-RH microcapsules, tumor volume (4862 ± 1322 mm³; P < 0.01 vs. control) was smaller than in the groups injected only with [D-Trp6]LH-RH (6512 ± 1956 mm³; P < 0.01) or with RC-160 microcapsules (9603 ± 2442 mm³; P < 0.01). Autopsy showed that the tumor weights were significantly reduced in all experimental groups, but the decrease was smaller in rats receiving RC-160 long-acting delivery system than in the group injected with [D-Trp6]-LH-RH microcapsules (Table 2). Administration of the combination of microcapsules of both peptides resulted in the smallest tumor weights. When the tumors were examined histologically, they appeared as well-differentiated adenocarcinomas. Histological results, which will be described in detail elsewhere (A. Zalatnai, J. I. Paz-Bouza, T. W. R., and A. V. S., unpublished results) suggest that [D-Trp6]-LH-RH microcapsules, somatostatin analogs, and especially the combination therapy cause a reduction in tumoral mass with the proliferation of connective tissue. In both experiments a significant reduction in testes and ventral prostate weights occurred in rats treated with [D-Trp6]-LH-RH microcapsules alone or in combination with RC-121 or RC-160. Rats tested with analog RC-160 showed some decrease in the weights of testes and ventral prostate. Anterior pituitary, adrenal, and spleen weights were not significantly altered. Animals injected with [D-Trp6]-LH-RH tended to show small decreases in body weights (Tables 1 and 2). In both studies serum testosterone levels in rats with prostate tumors declined to undetectable values after administration of [D-Trp6]-LH-RH microcapsules alone or in combination with RC-121 or RC-160 (Tables 3 and 4). Some decrease in serum testos-

Table 2. Effect of microcapsules of [D-Trp6]LH-RH, somatostatin analog RC-160 alone, or their combination on body and organ weights and tumor weight and volume in rats with Dunning R-3327H prostate tumors

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Body, g</th>
<th>Testes, g</th>
<th>Ventral prostate, g</th>
<th>Tumor, g</th>
<th>Tumor volume, mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>380 ± 14</td>
<td>3.19 ± 0.34</td>
<td>0.54 ± 0.04</td>
<td>16.8 ± 3.9</td>
<td>20,970 ± 6,001</td>
</tr>
<tr>
<td>RC-160 microcapsules*</td>
<td>366 ± 12 (NS)</td>
<td>2.62 ± 0.24 (0.05)</td>
<td>0.21 ± 0.02 (0.01)</td>
<td>7.0 ± 2.1 (0.01)</td>
<td>9,603 ± 2,443 (0.05)</td>
</tr>
<tr>
<td>[D-Trp6]-LH-RH microcapsules†</td>
<td>317 ± 13 (0.05)</td>
<td>0.43 ± 0.05 (0.01)</td>
<td>0.23 ± 0.02 (0.01)</td>
<td>4.5 ± 1.3 (0.01)</td>
<td>6,512 ± 1,956 (0.01)</td>
</tr>
<tr>
<td>RC-160 microcapsules* plus</td>
<td>352 ± 10 (NS)</td>
<td>0.52 ± 0.06 (0.01)</td>
<td>0.11 ± 0.01 (0.01)</td>
<td>2.7 ± 0.9 (0.01)</td>
<td>4,862 ± 1,322 (0.01)</td>
</tr>
</tbody>
</table>

Results are mean ± SEM; there were 6–10 rats per group. P vs. control is in parentheses. Significance was calculated by Duncan’s new multiple range test. NS, not significant.

*RC-160 microcapsules formulated to release 5 µg/day for 15 days.
†[D-Trp6]-LH-RH microcapsules formulated to release 25 µg/day for 30 days. The therapy was continued for 83 days.
Table 3. Effects of chronic administration of [D-Trp^6]LH-RH microcapsules, somatostatin analog RC-121, or their combination on serum luteinizing hormone, GH, prolactin, and testosterone levels in rats with Dunning R-3327H prostate tumors

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Serum LH, pg/ml</th>
<th>Serum GH, ng/ml</th>
<th>Serum PRL, ng/ml</th>
<th>Serum testosterone, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>714 ± 61</td>
<td>5.1 ± 0.37</td>
<td>15.04 ± 2.3</td>
<td>1.98 ± 0.64</td>
</tr>
<tr>
<td>[D-Trp^6]LH-RH microcapsules</td>
<td>228 ± 15 (&lt;0.01)</td>
<td>6.4 ± 0.96 (NS)</td>
<td>8.5 ± 0.86 (&lt;0.01)</td>
<td>ND (&lt;0.001)*</td>
</tr>
<tr>
<td>Analog RC-121</td>
<td>550 ± 0.08 (NS)</td>
<td>2.9 ± 0.4 (&lt;0.01)*</td>
<td>6.7 ± 1.13 (&lt;0.01)</td>
<td>0.88 ± 0.18 (NS)</td>
</tr>
<tr>
<td>Analog RC-121 plus [D-Trp^6]LH-RH microcapsules</td>
<td>57 ± 11 (&lt;0.01)</td>
<td>2.57 ± 0.4 (&lt;0.01)*</td>
<td>3.7 ± 0.31 (&lt;0.01)</td>
<td>ND (&lt;0.001)*</td>
</tr>
</tbody>
</table>

The results are the means ± SEM; there were 7–12 rats per group. LH, luteinizing hormone; PRL, prolactin; NS, not significant; ND, not detectable by RIA. The probabilities (P vs. control, in parentheses) were calculated by Duncan’s new multiple range test except for values done by Student’s t test (*).

terone levels after treatment with somatostatin analogs RC-121 or RC-160 probably resulted from some direct effect on the testes. Serum prolactin levels in the groups injected with [D-Trp^6]LH-RH microcapsules or with somatostatin analogs were suppressed. The greatest inhibition of prolactin levels occurred in the groups treated with [D-Trp^6]LH-RH microcapsules in combination with somatostatin analogs RC-121 or RC-160 (Tables 3 and 4). In the groups that received somatostatin analog RC-121 b.i.d. or microcapsules of RC-160 every 2 weeks, serum GH levels were significantly depressed as compared with controls and were lowest in groups given the combination treatment. The pharmacokinetics of the liberation of the analog RC-160 from prototype-7 microcapsules were investigated in normal rats. Measurements of serum levels of RC-160 by specific RIA revealed that significantly elevated levels of this analog persisted for at least 2 weeks after the injection of the microcapsules. The levels of RC-160 reached a peak of 27 ng/day on the day after the injection but then declined to 1–2 ng/ml between days 5 and 15. (M. Mason-Garcia, T.W.R., and A.V.S., unpublished results).

**DISCUSSION**

In the studies described here, we investigated a possible synergistic inhibitory effect that could result from combining a modern hormonal therapy based on LH-RH agonist (1, 2) with the administration of potent somatostatin analogs on the growth of hormone-dependent Dunning R-3327H prostatic adenocarcinoma in rats. The suppression of pituitary and gonadal functions that occurs after chronic administration of LH-RH agonists produces a state of chemical castration and provides the current approach for the treatment of prostate cancer and other sex hormone-dependent tumors (1, 2, 4, 5, 33). [D-Trp^6]LH-RH and other LH-RH agonists can now be administered by slow-release delivery systems that provide a continuous biological effect over a 30-day period (1, 2, 4, 5). Clinical trials with microcapsules of [D-Trp^6]LH-RH and implants of LH-RH agonist 118630 (Zoladex) in patients with prostate cancer attest to their high efficacy, compliance, and convenience as compared to daily administration of the unencapsulated agonists (2, 34). However, the duration of response and the median survival time in patients with prostate cancer cannot yet be estimated.

It is well established for hormonal methods of treatment, including LH-RH agonists, that in patients with prostate cancer the duration of remission may be limited because of continued blockade of pituitary-gonadal axis, a relapse eventually occurs that is attributed to a proliferation of androgen-independent cancer cells (4, 5, 33, 35). One of the approaches for improving the therapeutic response and its duration could be based on combining hormonal therapy with chemotherapy (4, 5, 36). The combination of LH-RH agonists with somatostatin analogs might also result in an increase in the therapeutic response in prostate cancer and possibly in other neoplasms (14). This view is based on the finding that somatostatin and its analogs, in addition to suppressing GH and prolactin (3, 6, 14, 37), appear to directly inhibit the action of endogenous growth factors such as EGF by mechanisms involving interference with signal transmission (13, 28, 29). Prolactin may be a cofactor in prostate cancer (7–14) and breast cancer (14), and GH promotes various growth factors that may be involved in proliferation and transformation of malignant cells (15–18, 21, 23). Thus somatostatin analogs might inhibit prostate and breast cancers by interfering with the secretion of GH and prolactin and with the action of endogenous growth factors. Somatostatin also suppresses the release of gastrin, may limit hormones and exocrine secretions of the pancreas and stomach (6, 13) and consequently its analogs could be of value for impeding the growth of other cancers, such as pancreatic cancer (13, 14, 29, 31). In addition, the secretion of bombesin and the related peptide gastrin releasing peptide, which are growth factors for small cell lung carcinomas (38–40), might be reduced by somatostatin. Another possible mechanism by which somatostatin analogs might inhibit tumor growth is the interference with the synthesis of autocrine growth factors by tumor cells. Somatostatin analogs could also inhibit oncogene products, several of which are similar to growth factors or their receptors (41–43). Growth factors or aberrant receptors generated by the oncogenes (20) could be responsible for promoting tumor cell growth (44). Activated oncogenes and EGF receptors have been found in the human bladder and lung cancer cell lines (19, 20). Regardless of the exact

Table 4. Effects of chronic administration of microcapsules of [D-Trp^6]LH-RH, somatostatin analog RC-160, or their combination on serum GH, prolactin, and testosterone levels in rats with Dunning R-3327H prostate tumors

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Serum GH, ng/ml</th>
<th>Serum PRL, ng/ml</th>
<th>Testosterone, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10.7 ± 7.2</td>
<td>33.0 ± 3.2</td>
<td>1.86 ± 0.34</td>
</tr>
<tr>
<td>[D-Trp^6]LH-RH microcapsules</td>
<td>6.6 ± 1.2 (&lt;0.01)</td>
<td>13.7 ± 2.8 (&lt;0.01)</td>
<td>0.06 ± 0.04 (&lt;0.01)</td>
</tr>
<tr>
<td>Analog RC-160 microcapsules</td>
<td>4.8 ± 0.6 (&lt;0.01)</td>
<td>18.2 ± 2.2 (&lt;0.01)</td>
<td>1.21 ± 0.19 (0.05)</td>
</tr>
<tr>
<td>Analog RC-160 microcapsules plus [D-Trp^6]LH-RH microcapsules</td>
<td>3.4 ± 0.7 (&lt;0.01)</td>
<td>13.1 ± 1.7 (&lt;0.01)</td>
<td>ND (&lt;0.01)</td>
</tr>
</tbody>
</table>

The results are the means ± SEM and based on a blood sampling on day 76; there were 7–12 rats per group. The probabilities (P vs. control, in parentheses) were calculated by Duncan’s new multiple range test. NS, not significant; ND, not detectable by RIA; PRL, prolactin.

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mechanisms of action, several of which are possible, somatostatin analogs, by virtue of their antiproliferative properties, can probably be used for manipulations aimed at the inhibition of the processes of malignant growth (13).

The present results demonstrate the effectiveness of hormonal treatment based on microcapsules of [d-Trp6]LH-RH combined with somatostatin analogs in suppressing the growth of Dunning R-3327H prostate tumors in rats. It is possible that somatostatin analogs could be developed for use as adjuncts to LH-RH agonists in the treatment of prostate cancer in humans, but additional experimental studies and clinical trials are necessary to establish the usefulness of such therapy.

Note Added in Proof. Estimation by RIA of the levels of somatostatin-C/insulin-like growth factor 1 in serum of rats bearing Dunning R-3327H prostate tumors indicates that this growth factor is decreased after chronic treatment with somatostatin analogs. Levels of somatostatin-C in extracted serum of rats treated for 84 days with the somatostatin analog RC-160 alone or in combination with [d-Trp6]LH-RH, were significantly reduced as compared to controls (V. Csernus, T.W.R., and A.V.S., unpublished results).

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