Inhibitory Effects of Somatostatin Analogue RC-160 and Bombesin/Gastrin-Releasing Peptide Antagonist RC-3095 on the Growth of the Androgen-Independent Dunning R-3327-AT-1 Rat Prostate Cancer

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ABSTRACT

The effects of somatostatin analogue RC-160 and bombesin/gastrin releasing-peptide (GRP) antagonist RC-3095 were evaluated in Copenhagen rats bearing the anaplastic, androgen-independent Dunning R3327-AT-1 prostate adenocarcinoma. In the first experiment, RC-160 was given in the form of microcapsules releasing 60 μg/day/rat. RC-3095 was administered from implanted Alzet osmotic minipumps liberating 100 μg/day/rat. After 32 days, tumor volumes and weights were significantly reduced by RC-160 as compared with the control group. Tumor doubling time in rats treated with RC-160 was significantly longer than in controls. Bombesin/GRP antagonist RC-3095 also significantly reduced tumor volume after 7 days of treatment, but after 18 days the inhibition in tumor volume was no longer significant. Tumor growth was not suppressed by castration. In the second experiment, 3-mm³ fragments of Dunning R-3327-AT-1 tumors were implanted orthotopically into the prostates of Copenhagen rats in order to evaluate the survival time of animals bearing this cancer during treatment with RC-160 released from Alzet osmotic minipumps at a dose of 100 μg/day/rat. Treatment with RC-160 significantly prolonged the mean survival time of rats by 5.3 days as compared to control animals. In both experiments, therapy with RC-160 significantly decreased serum growth hormone or insulin-like growth factor I levels. In the first experiment, receptor assays on R-3327-AT-1 tumor membranes showed high affinity binding sites for somatostatin, bombesin, and epidermal growth factor. At the end of the treatment, receptors for epidermal growth factor were significantly down-regulated by treatment with RC-160 but not with RC-3095. The binding capacity of bombesin receptors was reduced to nondetectable levels after the treatment with RC-3095. In cell cultures, high affinity binding sites for bombesin/GRP were found in intact Dunning R-3327-AT-1 cells, but receptors for somatostatin could not be detected. Proliferation of the AT-1 cell line was significantly inhibited by antagonist RC-3095. However, no effect on tumor cell growth in vitro was observed with analogue RC-160. Our results demonstrate that somatostatin analogue RC-160 and bombesin/GRP antagonist RC-3095 can inhibit the growth of the androgen-independent Dunning R-3327-AT-1 prostate cancer in rats, although the remission produced by RC-3095 may be of short duration due to a down-regulation of bombesin receptors. Our work suggests the merit of further investigation as to whether these analogues can induce a possible delay in relapse and prolong survival in prostate cancer.

INTRODUCTION

It is well known that in patients with prostate cancer, the duration of remission by androgen ablation therapy is limited and a relapse eventually occurs, which may be attributed to a selective proliferation of clones of androgen-independent cancer cells in heterogeneous tumor (1, 2). The growth factors including EGF, TGF-α, and IGF-I may play a role in the growth and progression of prostate cancer (3–7). Several human prostate cancer cell lines were shown to secrete and respond to EGF and related polypeptides, including TGF-α (3, 4, 6, 8). A stimulatory effect of IGF-I has been also demonstrated in the androgen-independent prostate cancer cell line PC-3 (9). EGF and IGF-I receptors have been demonstrated on prostate cancer cells as well as in membranes of normal and benign hypertrophic prostate (3, 9, 10, 11). The presence of receptors for bombesin/GRP has been shown on membranes of PC-3 cells, and proliferation of this cell line was significantly enhanced by bombesin in vitro (12).

The potenti somatostatin analogue (D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Val-Cys-Val-His-Pro-Leu-Thr-Asp) (RC160) has been shown to reduce growth of human gastric, pancreatic, colorectal, and mammary cancer in vivo (14–17). This antitumor effect of RC-3095 and RC-160 could be linked to a significant decrease in the maximal binding capacity of EGF receptors in these tumors.

In this study, we carried out long-term experiments in rats bearing the anaplastic, rapidly growing and hormone-insensitive Dunning R-3327-AT-1 prostate cancer in order to establish the utility of somatostatin analogue RC-160 and bombesin/GRP antagonist RC-3095 to inhibit the growth of this tumor. In addition, cell proliferation studies were also performed in vitro in order to determine whether RC-160 and RC-3095 have a direct effect on the growth of Dunning R-3327-AT-1 cells.

MATERIALS AND METHODS

Peptides. Bombesin/GRP antagonist RC-3095 [D-Tp6,Leu13,Val(CH2 NH)L eu14] bombesin (6–14), originally synthesized in our laboratory using solid-phase methods (18), was made by ASTA Medica (Frankfurt, Germany). For sustained delivery, RC-3095 was dissolved in 50% propylene glycol in water, and Alzet osmotic minipumps (model 2ML4; Alza Co., Palo Alto, CA) designed to release 2.5 μl/h for about 28 days, were filled according to the manufacturer’s instructions. This rate of administration was equivalent to 100 μg/day. Rats were anesthetized with methoxyflurane (Metofane; Pitman Moore, Washington Crossing, NJ), and the pumps were implanted s.c. using aseptic techniques.

Somatostatin analogue RC-160 (D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Val-His-Pro-Leu-Thr-Asp) (RC160), originally synthesized by solid-phase methods and evaluated in our laboratory (2, 13), was made by classical synthesis by Novabiochem (Laufen, Switzerland). In experiment 1, microcapsules of RC-160 pamoate in poly(ε-lactide-co-glycolide), prepared by Cytotech SA (Martigny, Switzerland) were used and aliquots of Lot RCSER-91-15 M releasing 60 μg/day were injected every 10 days. The microcapsules were suspended in 0.7 ml of injection vehicle consisting of 2% CM-cellulose and 1% Tween 80 in distilled water and injected through an 18-gauge needle into the thigh muscle of rats. In experiment 2 for sustained delivery from Alzet osmotic minipumps, RC-160 was dissolved in 50% propylene glycol in water and administered at a dose of 100 μg/day.

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**In Vivo Studies.** In the second experiment, 18 Copenhagen rats (30 mg/kg) were anesthetized with sodium pentobarbital and placed in the supine position. The abdomen was cleaned with alcohol, and a midline incision was made. The solid tumor was mechanically minced with a scalpel, and the tumor pieces were measured with a caliper (Vernier type 6914; Bel-art Products, Pequannock, NJ). Only 3 mm³ large pieces were put into a trocar needle. Implantations into the prostate were performed by pulling the bladder with dissective forceps anteriorly and by inserting obliquely the tip of the trocar needle into the ventral lobe of the prostate. A well-localized bleb within the implanted prostatic lobe was accepted as the sign of technically satisfactory implantation. The muscle layers of the abdominal wall were then closed by suture with silicone-treated black braided silk (17 strands of 18-in. length; American Cyanamid Company). The cutaneous wound was closed with three or four wound clips (Autoclip; Clay Adams, Parsippany, NJ). In order to evaluate the survival time of animals treated with RC-160, the rats were divided into two groups: (a) control tumorous rats, and (b) rats treated with somatostatin analogue RC-160 released from Alzet osmotic minipumps at a dose of 100 μg/day/animal. After 2 weeks of treatment, blood samples were taken from the jugular vein for measurement of IGF-I levels.

**RESULTS**

The effects of various treatments on body weight, tumor weight, final tumor volume, and tumor doubling time in experiment 1 are shown in Table 1. Body weights were unchanged in all experimental groups as compared to controls. During the experimental period of 32 days, the tumors in the control group grew rapidly from 0.1 ± 0.01 cm³ to an average volume of 224.1 ± 13.0 cm³, showing a tumor doubling time of 2.9 ± 0.02 days (Table 1). Castration did not change tumor growth as compared to control animals (Fig. 1). Treatment with

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Table 1: Effect of treatment of RC-160, RC-3095, or castration on body and tumor weight, tumor volume, and tumor doubling time in rats bearing Dunning R-3327-AT-1 prostate cancer in experiment 1

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Body weight (g)</th>
<th>Initial Tumor volume (cm³)</th>
<th>Final Tumor volume (cm³)</th>
<th>Tumor weight (g)</th>
<th>Tumor doubling time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>361.2 ± 9.9*</td>
<td>234.1 ± 13.0</td>
<td>234.1 ± 13.0</td>
<td>127.1 ± 3.2</td>
<td>2.9 ± 0.02</td>
</tr>
<tr>
<td>RC-160</td>
<td>372.0 ± 30.1</td>
<td>147.5 ± 13.8**</td>
<td>147.5 ± 13.8**</td>
<td>91.3 ± 2.8*</td>
<td>3.2 ± 0.07**</td>
</tr>
<tr>
<td>RC-3095</td>
<td>337.5 ± 14.9</td>
<td>242.8 ± 26.5</td>
<td>242.8 ± 26.5</td>
<td>137.0 ± 3.8</td>
<td>2.8 ± 0.08</td>
</tr>
<tr>
<td>Castration</td>
<td>334.7 ± 28.6</td>
<td>212.3 ± 19.2</td>
<td>212.3 ± 19.2</td>
<td>145.1 ± 4.1</td>
<td>2.9 ± 0.05</td>
</tr>
</tbody>
</table>

a Values are mean ± SE; *p < 0.05; **p < 0.01 versus control.
Peptide Analogues in Prostate Cancer

Microcapsules of somatostatin analogue RC-160 (60 μg/day/rat) significantly (P < 0.01) inhibited tumor growth from day 8 until the end of the experiment (Fig. 1). The average tumor weight was reduced significantly (P < 0.05) by RC-160 compared to the control group (141.3 ± 9.7 g versus 197.0 ± 9.8 g in controls; Table 1). Tumor doubling time in rats receiving RC-160 microcapsules was significantly extended to 3.2 ± 0.07 days (Table 1).

Chronic treatment with bombesin/GRP antagonist RC-3095 released from Alzet osmotic minipumps at a dose of 100 μg/day also inhibited tumor growth, which was significantly reduced as compared with controls, between days 8 and 18 of the treatment period (Fig. 1A). However, subsequently the inhibitory effect of RC-3095 was no longer observed, and at the end of the experiment, tumor volume as well as final tumor weight was not significantly different compared with controls (Table 1; Fig. 1B).

In experiment 2, the life span of rats with orthotopic implants of Dunning R-3327-AT-1 prostate tumors was prolonged significantly (P < 0.05) by RC-160 compared to the control group. Serum growth hormone and gastrin levels in rats in experiment 1, measured 14 days after initiation of various treatments, are shown in Table 2. There were no changes in gastrin serum levels after chronic treatment with either analogue or castration. Serum growth hormone levels in animals treated with microcapsules of RC-160 were significantly decreased (P < 0.05) by about 40% compared to control levels (Table 2). In experiment 2, there was a statistically significant fall in serum IGF-I levels in rats bearing orthotopic implants of the androgen-independent Dunning R-3327-AT-1 prostatic cancers after treatment with RC-160; IGF-I values in this group were decreased to 110.0 ± 3.7 μg/ml.

In vitro studies demonstrated that RC-3095 inhibits proliferation of Dunning R-3327-AT-1 cells in serum-free culture medium. In the presence of 10% bovine serum, RC-3095 showed no inhibitory effect. Somatostatin analogue RC-160 did not influence the growth of Dunning R-3327-AT-1 cells in vitro either in medium containing 10% bovine serum or under serum-free conditions.

Serum growth hormone and gastrin levels in rats in experiment 1, measured 14 days after initiation of various treatments, are shown in Table 2. There were no changes in gastrin serum levels after chronic treatment with either analogue or castration. Serum growth hormone levels in animals treated with microcapsules of RC-160 were significantly decreased (P < 0.05) by about 40% compared to control levels (Table 2). In experiment 2, there was a statistically significant fall in serum IGF-I levels in rats bearing orthotopic implants of the androgen-independent Dunning R-3327-AT-1 prostatic cancers after treatment with RC-160; IGF-I values in this group were decreased to 110.0 ± 20.6 ng/ml as compared to control rats which showed 293.0 ± 48.9 ng/ml.

The results of receptor assays on membranes of Dunning R-3327-AT-1 tumors in experiment 1 are shown in Table 3. In the control group, 125I-[Tyr4]bombesin was bound to one class of high affinity binding sites (Ka = 0.77 mEq/l). The maximal binding capacity (Bmax) was 234 ± 52.6 fmol/mg membrane protein. Chronic treatment with bombesin antagonist RC-3095 reduced Bmax of receptors for 125I-[Tyr4]bombesin on tumor cell membranes to nondetectable values (below 10 fmol/mg protein) (Table 3). EGF binding sites were present in the membranes of tumors (Table 3) and a significant (P < 0.01) reduction in EGF binding capacity was observed after treatment with somatostatin analogue RC-160 (Table 3). No changes in EGF binding capacity occurred after treatment with RC-3095 or castration. We also found high affinity binding sites for somatostatin in the membrane fraction of control and treated tumors (Table 3). After therapy with somatostatin analogue RC-160, there was a significant increase in the binding capacity of somatostatin receptors indicating an up-regulation. Treatment with RC-3095 or castration did not change the binding affinity and the concentration of somatostatin receptors.

Table 2 Serum gastrin and growth hormone (GH) levels in rats with Dunning R-3327-AT-1 prostate cancer after 14 days of treatment with RC-160, RC-3095, or castration in experiment I

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Gastrin (ng/ml)</th>
<th>GH (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>53.0 ± 2.7 *a</td>
<td>3.5 ± 0.3</td>
</tr>
<tr>
<td>RC-160</td>
<td>62.1 ± 5.7</td>
<td>2.1 ± 0.1</td>
</tr>
<tr>
<td>RC-3095</td>
<td>59.2 ± 7.1</td>
<td>3.7 ± 0.2</td>
</tr>
<tr>
<td>Castration</td>
<td>49.5 ± 3.2</td>
<td>4.6 ± 0.8</td>
</tr>
</tbody>
</table>

*a Values are mean ± SE; * p < 0.05 versus control.

Fig. 1. Effect of RC-160, RC-3095, and castration on tumor volume in rats with s.c. implanted Dunning R-3327-AT-1 prostate tumors as evaluated from day 0 until day 15 (top) and from day 18 until day 32 (bottom) of the treatment period in experiment 1. **: p < 0.01 vs. control.
The binding studies on the Dunning R-3327-AT-1 cell line in culture demonstrated high affinity binding sites for $^{125}$I-Tyr<sup>4</sup>-bombesin with a $K_d$ of 1 nM and a maximal binding capacity of $7.4 \times 10^6$ binding sites/cell. The Scatchard plot of these data is shown in Fig. 3. However, receptors for $[^{25}I]$-RC-160 could not be detected in cultured Dunning R-3327-AT-1 cells.

**DISCUSSION**

Dunning R-3327-AT-1 is a very rapidly growing, androgen-insensitive, anaplastic tumor which does not have receptors for dihydrotestosterone or 5-$\alpha$-reductase activity (26). This tumor was chosen for our studies on the effects of various peptide analogues on the growth of androgen-independent cells which are characteristic of advanced human prostate carcinoma. Our aim was to try to inhibit the proliferation of androgen-independent cells and delay or prevent the relapse of androgen-independent cells (27) as we have shown previously that microcapsules of RC-160 inhibit the growth of androgen-dependent Dunning prostate tumors in rats (27) as well as the human prostate cancer line PC-82 in nude mice (28). In the present study, we documented a significant growth inhibitory effect of RC-160 (Octastatin; Vapreotide) on the growth of Dunning R-3327-AT-1 tumors. This effect was noted after 1 week of treatment and persisted for the remaining treatment period of 3 weeks. RC-160 also prolonged the survival of rats bearing orthotopic implants of this prostate tumor.

Antineoplastic actions of somatostatin analogues appear to involve multiple mechanisms. A significant fall in growth hormone levels induced by RC-160 could, through mechanisms involving suppression of endogenous growth factors such as IGF-I and IGF-II, be of major importance for the inhibition of tumor growth (29). In our study, serum IGF-1 levels in rats treated with RC-160 were decreased by more than 60% as compared to control rats. Membrane receptors for IGF-I were demonstrated in the human androgen-independent prostate cancer cell line PC-3, and these cells could also be stimulated by IGF-I (9). This cell line was also found to secrete an IGF-like molecule into the medium (9). On the basis of our receptor assay results, which indicate the presence of high affinity receptors for somatostatin on tumor membranes, analogues of somatostatin could also directly inhibit the growth of prostatic cancer cells. The fact that 4 weeks of administration of RC-160 did not produce a down-regulation of somatostatin receptors indicates that this therapy could be applied for prolonged periods of time. The inhibitory effect of somatostatin analogue RC-160 on $[^{3}H]$thymidine incorporation was shown on LNCaP prostatic cancer cells in culture (30). In the MIA PaCa-2 human pancreatic cancer cell line, somatostatin and its analogue RC-160 reversed the stimulatory effect of EGF on phosphorylation of the tyrosine kinase domain of the EGF receptor and on cell growth (31). These and other observations (2, 29) suggest that somatostatin analogues can act as endogenous growth inhibitors in cancer cells through the activation of tyrosine phosphatase (31).

The absence of binding sites for RC-160 in R-3327-AT-1 cells in vitro could explain the lack of direct antiproliferative effect of this somatostatin analogue in cell culture. Original Dunning R-3327-AT-1 tumors show binding sites for somatostatin in vivo but appear to have undergone changes in receptor content during long-term passage in cultures. Similar phenomena were observed by others. In a study on the growth-promoting action of gastrin on human colonic and gastric tumor cells, Watson et al. (32) found that the newly established cell lines were stimulated by pentagastrin at passage 2, but long-established cell lines did not respond to pentagastrin. Similarly, the colon adenocarcinoma DHD/K12 was inhibited by RC-160 when it grew as xenografts in BDIX rats but was not responsive to RC-160 and somatostatin-14 in vitro (33). These findings indicate that tumor cell response to hormones could be lost during in vitro cultures. These observations could explain the divergent results obtained with RC-160 on tumor growth in vivo and in vitro in our study.

In vivo, in addition to inhibition of tumor growth, RC-160 produced a great reduction in the concentration of EGF receptors on Dunning R-3327-AT-1 tumors. Thus, the ability of Dunning R-3327-AT-1 tumor cells to respond to TGF-$\alpha$ and EGF could have been decreased in our study. Epidermal growth factor is a potent mitogen for a wide variety of cells (34, 35). Receptors for EGF have been shown in rat ventral prostate (10), canine prostate epithelial cells (7), human prostatic tumor cells in culture (3-5), specimens of benign prostatic hyperplasia (8), and human prostate carcinoma (7). The prostate cancer cell lines PC3, DU145, and LNCaP secrete TGF-$\alpha$, an EGF-related growth factor, and so these cell lines are expected to have receptors for TGF-$\alpha$. The concentration of TGF-$\alpha$ is increased in the serum of patients with prostate cancer (36), which suggests that TGF-$\alpha$ may be a growth factor for prostate cancer cells.
polypeptide that binds to EGF receptor (3–7). Stimulatory effects of TGF-α on proliferation of these cell lines have been demonstrated in several in vitro studies (3–7). The growth of the androgen-independent cell line PC3 could be inhibited by antibodies to TGF-α and by the monoclonal antibody 225 to the EGF receptor (3). In addition, in prostatic carcinoma samples, a strong correlation was observed between EGF receptor concentration and cellular protooncogene expression of c-myc (7). Collectively, these observations suggest that TGF-α/EGF receptor interactions are partially responsible for autonomous growth of androgen-independent cells and may explain one of the mechanisms of escape from androgen-dependent growth in advanced prostatic carcinoma (3).

In the same context, it was interesting and puzzling at first that the growth inhibitory effect of bombesin/GRP antagonist RC-3095 began to fade after 18 days and the tumor became refractory. At the end of the experiment, tumor volume and weight in this treatment group did not significantly differ from those in control animals. This was subsequently determined to be most likely caused by a complete down-regulation of bombesin/GRP receptors. Thus, the lack of measurable binding capacity for bombesin/GRP might cause a condition where RC-3095 cannot act on bombesin/GRP receptors and thus possibly influence the EGF receptor pathways. In contrast to our previous investigations with RC-3095 in several experimental cancer models, which demonstrated inhibition of growth of various tumors in association with a major decrease of EGF binding sites (14–16), in the present study no significant differences in EGF receptor concentration were found between control and RC-3095-treated tumors.

The exact molecular mechanism of action of bombesin/GRP antagonists on EGF receptors is still not well understood. Bombesin initiates a series of intracellular signals, which cause an increase in inositol 1,4,5-trisphosphate and a mobilization of Ca²⁺ and diacylglycerol production, leading to activation of protein kinase C (15). Activation of protein kinase C causes phosphorylation of EGF receptors on threonine residues. Bombesin and GRP were shown to enhance the phosphorylation of EGF receptors, and antagonist RC-3095 inhibited these effects in various cancer lines and cancer specimens (36, 37). These results suggest that bombesin and GRP may function by up-regulating EGF receptors, and antagonist RC-3095 prevents this up-regulation. Bombesin/GRP antagonists may also block early cellular events that preceded calcium mobilization and stimulation of mitogenesis (38).

Since bombesin was shown to stimulate the proliferation of the PC-3 prostate cancer cell line in culture (12), our assumption was that bombesin/GRP antagonist RC-3095 could compete with the parent peptides for binding to the receptors, thereby preventing stimulation by bombesin and GRP. However, in view of our results which indicate that the inhibitory effect of RC-3095 on tumor growth was of short duration and a relapse occurred despite complete down-regulation of bombesin/GRP receptors, it is unlikely that this possible mechanism of action of bombesin/GRP antagonists on Dunning R-3327-AT-1 tumors is as important as the interference of the antagonist of RC-3095 with the EGF receptor pathway. Our observations indicate that a certain concentration of bombesin/GRP receptor is required in order to obtain binding of bombesin/GRP antagonists before an eventual down-regulation of EGF receptors could be produced. The results of our in vitro studies, which demonstrated that RC-3095 inhibits the proliferation of the Dunning R-3327-AT-1 cell line possessing high affinity bombesin/GRP receptors, support this hypothesis. Since RC-3095 was delivered from Alzet osmotic minipumps by continuous release for a prolonged period of time, other administration schedules of this peptide, such as twice daily injections as in previous studies (14) or intermittent administration, might have prevented the down-regulation phenomenon.

In conclusion, the findings reported herein and other studies (2, 24–26) suggest that somatostatin analogue RC-160 and bombesin/GRP antagonist RC-3095 may have significant potential as therapeutic agents in the treatment of prostatic carcinoma. The combination of somatostatin analogues or bombesin/GRP antagonists with androgen-deprivation therapy based on luteinizing hormone-releasing hormone analogues or orchidectomy could result in an increase in the therapeutic response in patients with advanced prostate cancer. These peptide analogues could also be tried in patients with prostate cancer who no longer respond to androgen ablation therapy. Preliminary clinical results support this view (2, 39).

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