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Advances in Brief

Somatostatin Analogue Octreotide Enhances the Antineoplastic Effects of Tamoxifen and Ovariectomy on 7,12-Dimethylbenz(*a*)anthracene-induced Rat Mammary Carcinomas[1]

G. Weckbecker,[2] L. Tolcsvai, B. Stolz, M. Pollak,[3] and C. Bruns[3]

Preclinical Research, Sandoz Pharma, 386/627, CH-4002 Basel, Switzerland [G. W., L. T., B. S., C. B.], and Lady Davis Research Institute of the Jewish General Hospital and McGill University, Montreal, Quebec, Canada H3T 1E2 [M. P.]

Abstract

The efficacy of tamoxifen and ovariectomy in the management of breast cancer is limited by the resistance of many neoplasms to these endocrine therapies and by the fact that initially responding tumors often escape from control during long-term treatment. We evaluated the effect of coadministration of the somatostatin analogue octreotide, which has single agent activity in several *in vivo* and *in vitro* breast cancer models, on the antineoplastic actions of tamoxifen and ovariectomy on 7,12-dimethylbenz-(*a*)anthracene-induced mammary tumors. Rats received tamoxifen (0.5 mg/kg twice weekly s.c.), octreotide (10 μg/kg/h for 6 weeks by osmotic minipump), or the combination 7 weeks following 7,12-dimethylbenz-(*a*)anthracene administration. The number of tumors per animal and the sum of the volumes of palpable tumors per animal were significantly less in the combination treatment than in the others. In ovariectomized rats the marked regression of established tumors in the initial 4 weeks after ovariectomy was frequently followed by tumor regrowth. However, continuous infusion of octreotide (50 μg/kg/h for 6 weeks postovariectomy) significantly ($P < 0.01$) suppressed this regrowth. Our data suggest that octreotide enhances the antitumor effects of tamoxifen or ovariectomy in the 7,12-dimethylbenz(*a*)anthracene mammary cancer model.

Introduction

Antihormonal treatment strategies, including tamoxifen and ovariectomy, are well-established therapies for breast cancer although their effectiveness is limited. The original rationale for their use was based on the simple concept of antagonizing estrogen-stimulated growth (1). However, it has been demonstrated that the modulation of the expression of growth factors and their binding proteins also contributes to the antineoplastic activity of tamoxifen (1, 2). Examples include the inhibition of the production of growth-stimulatory factors such as transforming growth factor α (3) and IGF-I[4] (4–7) and up-regulation of cell growth-inhibitory factors such as transforming growth factor β (8) and IGF-binding proteins (9). Despite these advances in understanding the development of resistance to antiestrogen, treatment remains an important clinical problem in the management of breast cancer.

In an effort to identify agents that improve the results of antiestrogen therapy we studied combinations of the somatostatin analogue octreotide (SMS 201-995) with tamoxifen or ovariectomy. The peptide hormone somatostatin and SRIF analogues inhibit endocrine and exocrine secretion (10). Moreover, SRIF analogues such as the cyclooctapeptide octreotide inhibit the growth of cancer cells (reviewed in Refs. 11–13) Octreotide has demonstrated significant antitumor activity in a number of *in vitro* and *in vivo* mammary cancer models utilizing ZR-75-1, MCF-7, and MDA-MB-468 human cell lines (11–15). Moreover, octreotide as a single agent has been shown to inhibit the growth of DMBA mammary tumors in the rat (14, 16). The SRIF analogue RC-160 has also been shown to have activity in cancer models, including the transplantable MXT tumor, especially when combined with a luteinizing hormone-releasing hormone analogue (17). The antiproliferative action of SRIF analogues such as octreotide may be mediated by SRIF receptors expressed by the tumor cells (direct mechanism) because SRIF receptors are expressed in up to 78% of breast carcinomas (18). In addition, an indirect antiproliferative effect of octreotide that leads to decreased local and systemic levels of growth factors such as IGF-I and growth hormone may be involved (11).

As an initial step to study the interactions between octreotide and tamoxifen or octreotide and ovariectomy with respect to antineoplastic activity, we used the DMBA-induced mammary carcinoma rat model. This is a useful model for characterizing the antineoplastic activity of many endocrine therapies for breast cancer, including estrogen receptor antagonists, ovariectomy, and aromatase inihibitors (19, 20).

Materials and Methods

Mammary Tumor Induction. The method has been described previously (16). Briefly, virgin female OFA rats (130–160 g) were kept in groups of 4–5 animals/cage (Macrolon type IV; 32 x 54 x 19 cm; Tecniplast, Buguggiate, Italy) with free access to water and a standard rodent diet (NAFAG cubes; Kliba, Basel, Switzerland). To induce mammary tumors, animals were given a single dose of 20 mg DMBA (Fluka, Buchs, Switzerland) p.o. as a finely dispersed suspension in 4 ml sesame oil:water (1:1).

Experimental Therapies. Seven weeks following DMBA administration (about 1 week before tumors appear in this model), animals were randomized to control and treatment groups for the experiments reported in Fig. 1. Octreotide was dissolved in saline and infused with minipumps (Model 2000; Alzet, Cleon, France). The pumps were transplanted s.c. and delivered 0.5 μl/h (10 or 50 μg/kg/h) over a 2-week period. Control animals received minipumps filled with vehicle only. Tamoxifen (Sigma, Buchs, Switzerland) was dissolved in sesame oil as described previously by Jordan and Allen (19). Tamoxifen or the vehicle only were administered two or three times a week by s.c. injection. In other experiments, tamoxifen was administered as a 4-week slow-release pellet containing 5 mg drug (Innovative Research of America, Toledo, OH) at weeks 0 and 4. Ovariectomy was performed in rats with a mean tumor burden per animal of approximately 0.4 ml or greater. Tumors were measured (0 values) immediately before the operation and minipumps were implanted within 24 h thereafter. At the end of the experiment ovariectomy was confirmed at autopsy.

Tumor Measurements and Statistical Analyses. Tumor volumes were determined at the indicated intervals with a caliper. Tumor volume was calculated as

$$Volume\ (ellipsoid) = Length \times depth \times height \times 0.52$$

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[2] To whom requests for reprints should be addressed.

[3] These authors contributed equally to this study.

[4] The abbreviations used are: IGF, insulin-like growth factor; SRIF, somatostatin; DMBA, 7,12-dimethylbenz(*a*)anthracene.

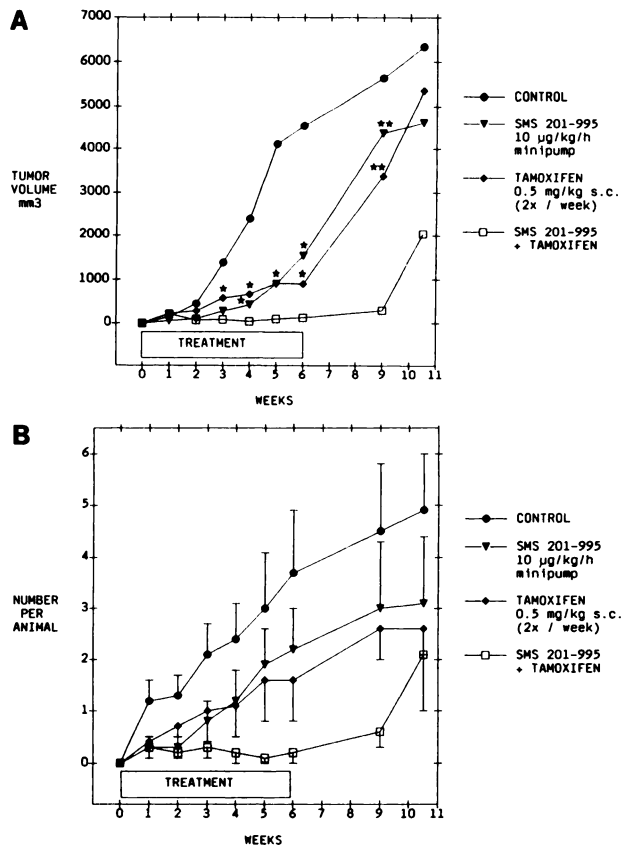

Fig. 1. Effect of the combination tamoxifen (0.5 mg/kg s.c. twice weekly) and octreotide (minipump infusion s.c., 10 µg/kg/h) on tumor growth (*A*) and appearance (*B*) of tumors (tumor number) in rats bearing DMBA-induced mammary carcinomas. *Points*, mean tumor volume and number for 10 rats/group; *bars*, SE. For clarity SE omitted in *A*. The SE in *A* and *B* were similar. In *A*, comparison of the combination group with the single agent groups resulted in significant differences in tumor growth: *, $P \leq 0.05$; **, $P \leq 0.01$, *t* test. Pooled data for tumor number comparisons (*B*) gave a significant difference between the tamoxifen and the combination group for weeks 4–6; $P < 0.02$.

In "Results," tumor volume refers to the sum of volumes of individual tumors on each animal. Of the approximately 150 tumor-bearing rats reported here 4 outliers (maximum of 1 outlier/group) were identified on the basis that their tumor burden would change the group mean by >3-fold. RS/1 statistics procedures (BBN Software Products, Cambridge, MA) were used for data evaluation (Student's *t* test and Mann-Whitney *U* test). The difference in incidence of tumor-positive animals in various treatment groups (Table 1) was tested by *t* test using Bootstrap resampling (done by our statisticians Dr. S. E. Görlach and R. Bergmann with Proc. Multtest, SAS statistics software).

Binding of ^{125}I-Tyr^3-octreotide. After the rats were sacrificed, DMBA tumors were removed and quick-frozen in liquid nitrogen. Membranes were prepared and the binding of ^{125}I-Tyr^3-octreotide was assayed as described previously (21).

Effects of Treatment on Uterine Weight. Two weeks following ovariectomy Sprague-Dawley rats (300 g) were treated with tamoxifen (5 mg in 0.4 ml sesame oil s.c. daily for 2 days), octreotide (75 µg/day s.c. as a slow-release formulation for 14 days), the combination, or vehicles only. Three animals were studied in each treatment group. After 2 weeks animals were sacrificed and uteri were removed and weighed.

Table 1 *Benefit of addition of octreotide to tamoxifen in the reduction of incidence of rats bearing DMBA-induced mammary cancer*

Incidence of mammary tumor-positive rats (10 DMBA-treated rats/group) during and following treatment with tamoxifen (5 mg slow-release pellet implanted in weeks 0 and 4) and octreotide infused s.c. (10 µg/kg/h, weeks 0–6). Treatment started 7 weeks after DMBA application. The average incidence of tumor-positive rats (% ± SE) between weeks 3 and 18 was 36.0 ± 10.3 in the tamoxifen group and 6.7 ± 3.3 in the combination group. The difference in tumor incidence between samples was significant ($P < 0.02$, *t* test). Control animals were killed before week 14 due to large tumor burden.

	Weeks						
Treatment	1	3	6	9	14	18	23
Tamoxifen	0	20	40	20	40	50	50
Octreotide + tamoxifen	0	10	0	0	10	10	40
Control (sesame oil)	40	70	80	80	end		

Results

Effect of Single Agent Tamoxifen on DMBA-induced Mammary Tumors in the Rat. The antitumor effect of single agent tamoxifen, which was shown previously with DMBA-induced tumors in Sprague-Dawley rats (22), was confirmed in our experimental system using this carcinogen in female OFA rats. Tamoxifen (1 mg/kg 3 times/week for 6 weeks) potently inhibited the growth and appearance of DMBA-induced mammary carcinomas. At the end of the treatment mean total tumor volumes in the tamoxifen group were 4.1 ± 1.2% (SE) of the mean tumor volume in vehicle-treated controls (9.1 ml), and the tumor number was reduced to 17.2 ± 2.8% of the mean tumor number in controls (9.3 tumors/rat). This tamoxifen treatment schedule reduced body weight gain; the mean body weight (± SE) at week 6 was 273 ± 6 g for control animals and 254 ± 7 g for the tamoxifen group. Since a dose of 0.1 mg tamoxifen failed to inhibit tumor growth (not shown), we selected an intermediate dose (0.5 mg/kg) in the combination experiments with octreotide. Single agent activity of octreotide against the development of DMBA tumors was shown previously (16).

Effect of Combined Tamoxifen and Octreotide on the Development of DMBA-induced Tumors. In the combination study, four groups of DMBA-treated rats received tamoxifen (0.5 mg/kg injected s.c. twice a week), octreotide (10 µg/kg/h), the combination of the drugs, or vehicle alone. Treatment of rats with the combination of tamoxifen and octreotide led to a marked suppression of the growth of DMBA-induced mammary carcinomas over the entire 6-week treatment period and persisted for another 3 weeks after cessation of treatment (Fig. 1*A*). Moreover, the administration of the drug combination inhibited the development of new tumors more effectively than the respective single agent treatments (Fig. 1*B*). Mean body weights at the end of the treatment (6 weeks) were 296 ± 5 (S.E.), 285 ± 8 (tamoxifen), 269 ± 4 (octreotide), and 254 ± 6 (combination). After treatment ceased, all treated animals started to grow at control growth rates such that at week 16 postcarcinogen, when the growth and the appearance of tumors were still reduced, the rate of gain in body weight had reached normal values. A higher infusion rate of octreotide (50 µg/kg/h) also significantly potentiated the inhibitory effects of tamoxifen on tumor growth (data not shown) but not to a greater degree than the lower dose. No overt toxicity of the octreotide-tamoxifen combination was noted, even at the higher infusion rate.

To confirm these results additional experiments were carried out using a 5-mg depot formulation of tamoxifen (4-week release) in combination with octreotide treatment (continuous infusion at 10 µg/kg/h). As shown in Table 1 this combination treatment significantly reduced the tumor incidence to 6.7 ± 3.3% as compared with 36 ± 10.3% in tamoxifen-treated animals. Although treatment was terminated after 6 weeks (octreotide infusion) and approximately 8 weeks (tamoxifen depot formulation), tumor development was strongly inhibited up to week 18.

Effect of Octreotide on Regrowth of Established DMBA Tumors following Ovariectomy. Ovariectomy of OFA rats bearing DMBA-induced mammary carcinomas (about 0.4 ml) led to an apparently complete regression of these tumors in 14 of 14 treated animals within 1–5 weeks. Thereafter, tumors regrew in most of the

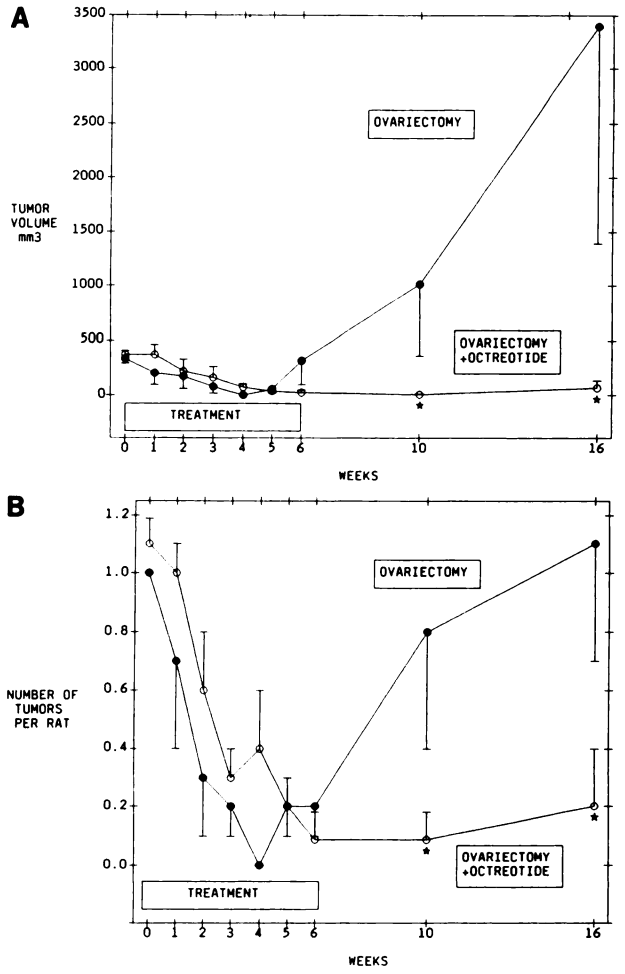

Fig. 2. Effect of octreotide (minipump, s.c., 50 μg/kg/h) or saline infusion on the change in DMBA tumor volume (*A*) and appearance (*B*) of tumors (tumor number) induced by ovariectomy. *Points*, mean tumor volume and number per group with 9 rats in ovariectomy only group and 11 rats in ovariectomy and octreotide group. *Bars*, SE; *, $P \leq 0.05$. At the zero time point animals bearing palpable tumors were ovariectomized and pumps were implanted within the following 24 h.

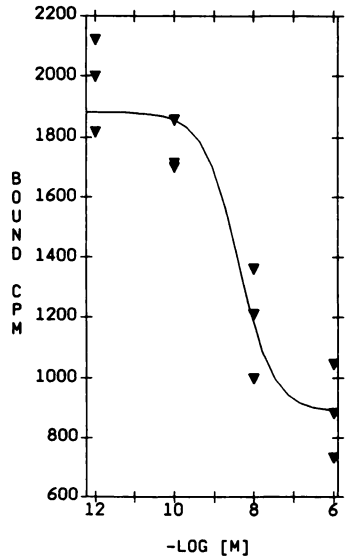

Fig. 3. Binding of ^{125}I-Tyr^3-octreotide to membranes prepared from a DMBA-induced mammary tumor. The membranes (0.95 mg/ml assay mixture) were incubated with the radioligand and increasing concentrations (each in triplicate) of octreotide (*abscissa*). *Points*, single measurements.

operated animals over the following 8 weeks although the successful removal of the ovaries was confirmed at autopsy. To study the effect of octreotide on the changes in tumor size and number induced by ovariectomy, the ovariectomized rats were continuously infused with octreotide at a rate of 50 μg/kg/h (Fig. 2). In contrast to tumors in ovariectomized animals treated with saline infusions, the tumors of animals treated with ovariectomy combined with octreotide infusion for 6 weeks essentially failed to regrow during week 6 to week 16 postovariectomy. At week 16 postovariectomy, 6 of 9 animals were tumor positive in the control group (ovariectomy only) with tumor burden per animal ranging from 0.1 to 16.3 ml. In the octreotide/ovariectomy group only 1 of 11 rats had developed a tumor (0.66 ml) at this time point. At the end of the octreotide treatment period, mean body weights were 300 ± 7 g (NaCl control), 370 ± 9 g (NaCl and ovariectomy), and 310 ± 9 g (octreotide and ovariectomy). The beneficial effect of the treatment combination was confirmed in a second experiment (data not shown) where the initial tumor size at the time of ovariectomy was 3-fold greater. After ovariectomy these large tumors transiently regressed, but at the end of this experiment (week 14 postovariectomy) 4 of 4 (100%) of ovariectomy-only animals were tumor positive while in the combined treatment group 33% (2 of 6) of animals had tumors.

SRIF Receptor Expression in DMBA Tumors. Since octreotide may act directly via SRIF receptors expressed either by tumor cells or by indirect mechanisms [inhibition of the production of tumor growth factors (12, 16, 23)], it was of interest to analyze the SRIF-receptor status of DMBA tumors. Membrane preparations of 17 tumors of 10 rats were studied with respect to ^{125}I-Tyr^3-octreotide binding. In 10 of 17 tumors (59%) SRIF receptors could be identified. The competition binding experiments revealed that all SRIF receptors expressed by DMBA-induced tumors were high affinity binding sites with 50% inhibitory concentrations ranging from 0.1 to 7.4 nM; an example is shown in Fig. 3.

Effects of Treatments on Uterine Weight. Since octreotide enhanced the antineoplastic activity of tamoxifen against DMBA-induced tumors, we considered the possibility that the uterine toxicity of tamoxifen might also be enhanced by combining the drugs. However, we observed that following 2 weeks of treatment of ovariectomized animals with tamoxifen alone uterine weight was 191 ± 10 mg as compared to 150 ± 6 mg in rats treated with the combination of tamoxifen and octreotide. Uterine weights of ovariectomized rats treated with octreotide alone or vehicle alone were 115 ± 8 and 95 ± 11 mg, respectively.

Discussion

This study demonstrates that octreotide enhances the antineoplastic activity of tamoxifen and ovariectomy in the DMBA rat breast cancer model. Clinical studies have shown that tamoxifen and ovariectomy treatments control breast cancer in only one-third of patients and many of these subsequently relapse (24). Thus, any strategy that would further enhance the efficacy of these well-accepted endocrine treatments would meet an important medical need.

Our prior studies suggested that single-agent octreotide has maximal anticancer activity in the DMBA mammary tumor model when the tumor burden is small. This may explain why previous studies showed either response (14, 16) or resistance to octreotide (25). We therefore designed experiments to study the effect of combining this agent with ovariectomy or tamoxifen under experimental conditions involving low tumor burden.

While most prior studies have emphasized endocrine responsivity of DMBA tumors, the model has also been used to document the emergence of neoplasms resistant to endocrine therapies (26). In our control experiments we observed impressive regression of tumors 4 weeks following ovariectomy in keeping with prior reports (20, 26). However, when these rats were observed for an additional 12 weeks, tumor regrowth occurred in keeping with the clinically relevant facts that ovariectomy (and tamoxifen) represents a cytostatic rather than a cytotoxic therapy and that multiple mechanisms of development of resistance exist (1). We added octreotide to ovariectomy in the low tumor burden situation that exists postregression prior to regrowth and observed inhibition of this regrowth. Despite the frequent emergence of tamoxifen-resistant tumors seen clinically during long-term antiestrogen therapy, it was not practical to use the DMBA model to study the effect of octreotide on regrowth of macroscopic tumors following tamoxifen-induced regression because regrowth was not seen during a 3-month period following tamoxifen-induced regression.

The mechanisms underlying the inhibition of tumor growth are the subject of ongoing investigations. Direct antiproliferative effects of octreotide mediated by SRIF receptors on tumors may be relevant since we have demonstrated binding sites for octreotide on a fraction of DMBA-induced tumors using both membrane-binding assays (Fig. 3) and, in a previous study, autoradiographic receptor analysis (16). Both studies indicated that SRIF-receptor expression is rather low. SRIF receptors were also detected in up to 78% of human breast tumors (18). The stimulation of a phosphotyrosine phosphatase activity may be involved in the transduction of the growth-inhibitory signal (27). Inhibition of SRIF receptor-negative tumors by octreotide may be explained by an indirect mechanism. Octreotide and tamoxifen each suppress the growth hormone-IGF-I axis (5, 7, 16, 28, 29), and we recently reported that coadministration results in enhanced suppression of this axis (30). This may be relevant in view of data showing the presence of IGF-I receptors on DMBA-induced mammary tumors (31) as well as on human tumors (23, 32). The direct and indirect effects are not mutually exclusive.

In view of the concerns regarding uterine toxicity of tamoxifen, we carried out a preliminary experiment to investigate the possibility of additive uterine toxicity. We observed that uterine weight gain in ovariectomized rats was in fact lower in rats treated with the combination of octreotide and tamoxifen than in those treated with tamoxifen alone. The potential relevance of this experimental observation to clinical toxicity requires further study.

Our results imply that combinations of octreotide with antiestrogens and/or ovariectomy may lead to improved anticancer efficacy. While tamoxifen is widely used and efficacious in the adjuvant management of breast cancer, the need for novel approaches to enhance the efficacy of antiestrogens is indicated by clinical research showing that 10-year disease-free survival is only modestly increased by the use of adjuvant tamoxifen therapy (33). Our data suggest that combinations of octreotide and tamoxifen as well as octreotide and ovariectomy deserve further evaluation in this regard. The present experiments specifically studied the combinations in conditions where the tumor burden was low and thus may have particular relevance to the postsurgical adjuvant treatment of breast cancer.

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