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EFFECTS OF THE THIAZOLIDINEDIONE DERIVATIVE CGP 19984 ON GROWTH AND ENDOCRINE FUNCTION OF THE MtT-W10 TRANSPLANTABLE MAMMOSOMATOTROPIC PITUITARY TUMOR IN FEMALE RATS

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The thiazolidinedione derivative CGP 19984 has previously been shown to suppress the growth of hormone-dependent mammary and prostatic tumors, primarily by reducing gonadotropin and subsequently gonadal steroid secretion. The present study examines the effects of CGP 19984 on the growth and hormone secretion of the autonomous, but estrogen-responsive, MtT-W10 mammosomatotropic transplantable rat pituitary tumor. Intact tumor-bearing Wistar/Furth female rats were administered vehicle or 25, 100, or 250 mg/kg CGP 19984 p.o., 5 × week for 4 weeks. CGP 19984 was found to significantly reduce MtT-W10 tumor growth and weight and reduce prolactin and growth hormone (GH) secretion in a dose-responsive manner. A similar study in ovariectomized rats also showed that CGP 19984 treatment suppressed MtT-W10 pituitary tumor growth, weight and hormone secretion in a dose-responsive manner, suggesting a direct inhibitory action of this drug on the tumor. In a third study, bromocryptine (CB-154; 5 mg/kg) and CGP 19984 (50 mg/kg) were both found to be effective in suppressing growth of the MtT-W10 tumor in intact female rats. However, rats treated with CGP 19984 alone had reduced serum and tumor GH and prolactin concentrations, while rats treated with CB-154 alone had reduced serum and tumor prolactin, but no change in GH concentrations. These results suggest that CGP 19984 effectively inhibits growth and hormone secretion of the autonomous MtT-W10 pituitary tumor by apparently suppressing both somatotropic and lactotropic cell populations within the tumor. Furthermore, these findings indicate that CGP 19984 may be an effective alternative to CB-154 in the clinical treatment of prolactin-producing adenomas, as well as other types of pituitary adenomas.

The thiazolidinedione derivative CGP 19984 is effective in suppressing growth of hormone-dependent, carcinogen-induced rat mammary tumors (Schieweck *et al.*, 1983) and the R3327 Dunning rat prostatic adenocarcinoma (Ip *et al.*, 1986), and significantly reduces gonadotropin and subsequently gonadal steroid secretion (Ip *et al.*, 1986; Sylvester *et al.*, 1986). The ability of CGP 19984 to reduce circulating levels of gonadal steroids is believed to be the primary mechanism by which this drug suppresses growth of hormone-dependent rat mammary and prostatic tumors (Ip *et al.*, 1986). However, CGP 19984 also has some effect in suppressing growth of the hormone-independent MTW-9B mammary tumor (Ip *et al.*, 1986). The inhibitory activity of CGP 19984 against both hormone-dependent and -independent tumors suggests that this drug has promising potential for clinical application. Currently, CGP 19984 is being evaluated in phase-I trials.

Ergoline derivatives such as bromocryptine (CB-154) are used clinically to inhibit hormone secretion and reduce pituitary volume in women with prolactin-producing adenomas (Lu *et al.*, 1971; Quadri *et al.*, 1972; Thorner *et al.*, 1980; Chiodini *et al.*, 1981). At present, it has not been established whether this inhibitory activity of CB-154 on prolactin-producing pituitary adenomas is cytotoxic. Some investigators have shown that, once treatment is stopped, tumor size and prolactin secretion return to pre-treatment levels within a few days (Thorner *et al.*, 1981; Tindall *et al.*, 1982). They suggested that these dopaminergic agonists reduce tumor size and prolactin release by selectively inhibiting protein and hormone synthesis in adenomatous prolactin cells (Tindall *et al.*, 1982). In contrast, others have shown that long-term dopamine agonist therapy can result in necrosis of some adenoma cells (Gen *et al.*, 1984) with no re-expansion of tumor after withdrawal of treatment in some prolactinoma patients (Johnston *et al.*, 1984). Differences observed by these investigators may be due to the higher doses and longer duration of treatment. While the largest percentage of pituitary tumors occurring in women are prolactin-secreting, a significant proportion secrete growth hormone (GH), adrenal corticotropic hormone (ACTH), the combination of one or both of these hormones with prolactin, and in rare instances other pituitary hormones (Burrow *et al.*, 1981). Although CB-154 therapy also has some effect in lowering blood GH levels in acromegalic patients, particularly when prolactin levels are elevated (Moses *et al.*, 1981), this drug is generally ineffective as an anti-tumor agent in these patients. The broad anti-tumor activity displayed by CGP 19984 suggests that this drug may also be effective in suppressing growth and hormone secretion of prolactin-producing pituitary adenomas, as well as those of other types.

In order to examine this possibility, CGP 19984 was administered to female rats implanted with the MtT-W10 mammosomatotropic pituitary tumor. The MtT-W10 tumor was originally induced in female Wistar/Furth rats by chronic administration of diethylstilbestrol (Furth and Clifton, 1966). This tumor is characterized by rapid, hormonally autonomous growth, and secretion of large amounts of prolactin and GH (Furth and Clifton, 1966). While growth and function of the MtT-W10 pituitary tumor are not dependent upon gonadal steroids, this tumor is reponsive to estrogen stimulation (Furth and Clifton, 1966). Estrogen is a powerful stimulus of prolactin synthesis and release in both normal (Chen and Meites, 1970) and neoplastic pituitaries (Sarkar *et al.*, 1982). Since CGP 19984 significantly suppresses circulating levels of gonadal steroids, it was necessary to clarify the direct (cytostatic/cytotoxic) *versus* indirect (reduced blood estrogen levels) antitumor effects of this drug. Therefore, the effects of CGP 19984 on MtT-W10 pituitary tumor growth and hormone secretion were determined in both intact and ovariectomized rats. In addition, the present study compares the inhibitory effects of CGP 19984 and CB-154, when administered either alone or in combination, on growth and hormone secretion of the MtT-W10 rat pituitary tumor.

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Abbreviations: GH, growth hormone; CB-154, bromocryptine; NIADDK, National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases.

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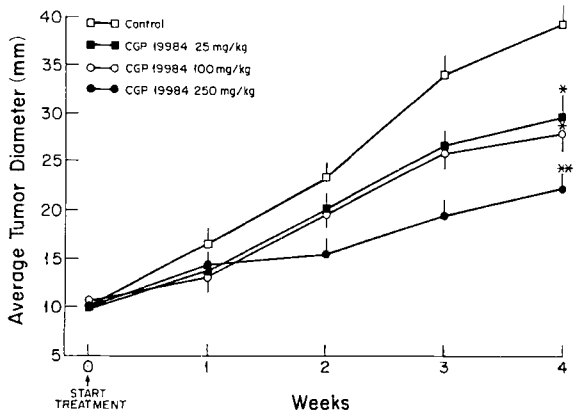

FIGURE 1 - Effects of CGP 19984 on growth of the MtT-W10 pituitary tumor in intact female rats. Vertical bars represent SEM. $^{*}p < 0.05$ as compared to vehicle-treated controls. $^{**}p < 0.05$ as compared to all other treatment groups.

MATERIAL AND METHODS

Animals

Eight-week-old virgin female Wistar/Furth rats, purchased from Harlan Sprague-Dawley (Indianapolis, IN) received s.c. trocar implants of the MtT-W10 mammosomatotropic pituitary tumor, which was kindly provided by Dr. U. Kim, Department of Pathology, Roswell Park Memorial Institute, Buffalo, NY. All animals were housed in suspended metal cages in a temperature-regulated (24 ± 0.5°C) and light-controlled (14 hr light/10 hr dark) room and allowed Teklad rat chow (Teklad, Winfield, IA) and water *ad libitum*. Prior to the start of each experiment, the average diameter of each tumor was determined from the mean of the 2 largest perpendicular diameters. Tumor-bearing rats were then divided into experimental groups of 14 to 15 rats each, so that the average tumor size in each group was similar.

Drugs

The thiazolidinedione derivative CGP 19984, supplied by CIBA-GEIGY, Basel, Switzerland, was dissolved in a vehicle of aqueous 0.5% carboxymethylcellulose (CMC) solution. The drug was prepared fresh weekly. Drug concentrations tested in different experiments included 2, 5, 10, 20 and 50 mg/ml for the 10, 25, 50, 100 and 250 mg/kg dosage schedules, respectively. Each rat received 0.5 ml/100 g body weight of the vehicle or CGP 19984 p.o., 5 times weekly. Bromocryptine (CB-154; Sandoz, East Hanover, NJ) was given to animals at a dose of 5 mg/kg. CB-154 was prepared in 0.9% NaCl (saline) suspension at a concentration of 5 mg/ml. Each rat received 0.1 ml/100 g body weight of saline or CB-154 s.c., 5 times weekly. All injections were given daily between 8 and 10 A.M. for 4 consecutive weeks.

Experiments

Experiment 1 consisted of 4 treatment groups of MtT-W10 tumor-bearing, intact, female rats. Group 1 received the vehicle and served as controls. Groups 2–4 received 25, 100 and 250 mg/kg CGP 19984, respectively. Tumor size and body weights were recorded at weekly intervals from the start of treatment for 4 weeks. Upon termination of the experiment, animals were killed by decapitation and tumors were removed and weighed. A sample of each tumor was also fixed in buffered formalin for histological examination.

Experiment 2 consisted of the following 4 groups: (1) control, 0.5% CMC; (2) 10 mg/kg CGP 19984; (3) 50 mg/kg CGP 19984; (4) 250 mg/kg CGP 19984. These groups were chosen to include a lower dose of CGP 19984 than had been examined in experiment 1. Treatment was administered and tumor growth was monitored as in experiment 1. However, 1 day prior to the start of treatment all rats were bilaterally ovariectomized under ether anesthesia in order to determine the anti-tumor effects of CGP 19984 in the presence of similar circulating estrogen levels.

Experiment 3 also consisted of 4 groups. Group 1 received the vehicle and served as controls. Group 2 received 50 mg/kg CGP 19984 and saline, group 3 received 5 mg/kg CB-154 and 0.5% CMC, while group 4 received the combination of 50 mg/kg CGP 19984 and 5 mg/kg CB-154. Treatments were administered and tumor growth monitored as above. At the end of this experiment, however, a sample of each tumor was placed in aluminum foil and frozen immediately on dry ice. The tumor sample was weighed and homogenized using a hand-held glass tissue homogenizer in phosphate-buffered saline adjusted to pH 10.6 with 5 N NaOH, to extract prolactin and GH (Haisenleder *et al.*, 1986). The homogenate was then centrifuged at 1,800 *g* for 30 min, then supernatant was neutralized with 5 N HCl, diluted with assay buffer and stored frozen (−20°C) until the day of hormone assay.

Blood collection and hormone assays

Blood was collected from rats under light ether anesthesia by orbital sinus puncture before treatment and by decapitation at the termination of each experiment. Serum was separated by centrifugation and stored at −20°C until assayed for prolactin and GH. All blood samples were taken between 10 and 12 A.M., approximately 2–3 hr after drug injection. Serum and tissue homogenates were assayed for prolactin and GH using the reagents and methods from NIADDK kits, and expressed in terms of NIADDK rat prolactin-RP-3 and rat GH-RP-1, respectively. For prolactin, the minimal detectable limit was 0.1 ng per tube and 50% inhibition of tracer binding was 1 ng per tube. The intra- and interassay coefficients of variation were 4 and 10%, respectively. For GH, the minimal detectable limit was 0.2 ng GH per tube and 50% inhibition of tracer binding was 1 ng per tube. The intra- and interassay coefficients of variation were 5 and 14%, respectively.

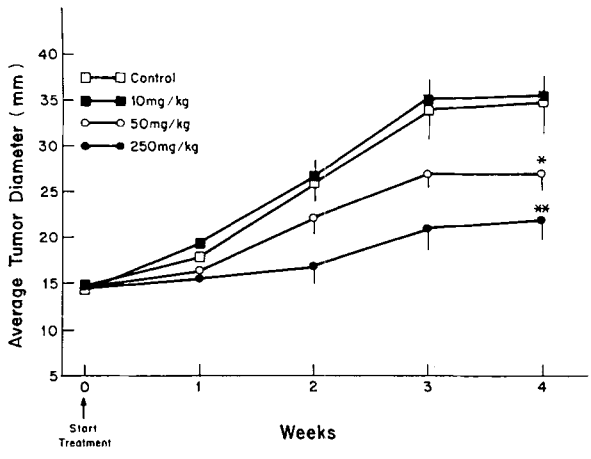

FIGURE 2 - Effects of CGP 19984 on growth of the MtT-W10 pituitary tumor in ovariectomized rats. Vertical bars represent SEM. $^{*}p < 0.05$ as compared to vehicle-treated controls. $^{**}p < 0.05$ as compared to all other treatment groups.

TABLE I - DOSE-RESPONSE EFFECTS OF CGP 19984 ON MtT-W10 PITUITARY TUMOR WEIGHT AND SECRETION OF GH AND PROLACTIN IN INTACT FEMALE RATS

		Treatment groups			
	Time[1] period	Control	CGP 19984 (25 mg/kg)	CGP 19984 (100 mg/kg)	CGP 19984 (250 mg/kg)
Tumor weight (g)	t	23.9±2.2[2]	12.8±1.6[4]	11.2±1.7[4]	8.5±1.6[4]
Body weight (g)	i	224±4	215±6	212±5	216±6
	t	312±12	256±9[4]	253±7[4]	240±14[4]
Carcass[3] weight (g)	t	288±12	243±10[4]	242±7[4]	231±14[4]
Serum GH	i	3.5±0.8	2.3±0.8	3.2±0.8	2.9±0.9
(μg/ml)	t	43.2±14.8	23.6±12.9	13.9±6.5[4]	9.7±4.7[4]
Serum prolactin	i	0.29±0.08	0.23±0.11	0.28±0.09	0.21±0.07
(μg/ml)	t	1.44±0.25	1.31±0.28	0.85±0.25[4]	0.76±0.26[4]
Serum	i	12	10	11	14
GH/prolactin	t	30	18	16	13

[1]i represents 1 day prior to initiation of treatment and t represents the day on which the experiment was terminated (4 weeks after the start of treatment).-[2]Mean± SEM of results from 14–15 rats.-[3]Carcass weight was determined by subtracting an individual animal's tumor weight from its body weight.-[4]$p<0.05$, as compared to vehicle-treated controls.

TABLE II - DOSE-RESPONSE EFFECTS OF CGP 19984 ON MtT-W10 PITUITARY TUMOR WEIGHT AND SECRETION OF GH AND PROLACTIN IN OVARIECTOMIZED FEMALE RATS

		Treatment groups			
	Time[1] period	Control	CGP 19984 (10 mg/kg)	CGP 19984 (50 mg/kg)	CGP 19984 (250 mg/kg)
Tumor weight (g)	t	18.0±3.8[2]	15.2±1.7	11.9±1.2[4]	10.5±1.4[4]
Body weight (g)	i	261±10	262±7	247±13	270±11
	t	332±22	296±8	297±9	267±18
Carcass[3] weight (g)	t	314±23	281±8	285±10	261±18
Serum GH	i	4.3±1.3	5.3±1.3	4.6±1.5	4.5±1.4
(μg/ml)	t	32.2±9.4	28.6±7.9	15.5±4.4[4]	9.1±4.4[4]
Serum prolactin	i	0.32±0.07	0.28±0.05	0.34±0.11	0.31±0.09
(μg/ml)	t	0.82±0.19	0.73±0.15	0.49±0.14	0.45±0.13
Serum	i	13	19	13	15
GH/prolactin	t	39	39	32	20

[1]i represents 1 day prior to initiation of treatment and t represents the day on which the experiment was terminated (4 weeks after the start of treatment).-[2]Mean±SEM of results from 14–15 rats.-[3]Carcass weight was determined by subtracting an individual animal's tumor weight from its body weight.-[4]$p<0.05$, as compared to vehicle-treated controls.

Statistical analysis

Statistical differences between treatment groups were determined by analysis of variance, and Student-Newman-Keuls' test was used for multiple comparisons among groups. Differences were considered significant at $p<0.05$, as compared to vehicle-treated controls or as defined in the Figure legends.

RESULTS

Experiment 1

The effect of various doses of CGP 19984 on growth of the MtT-W10 pituitary tumor in intact female rats is shown in Figure 1. MtT-W10 tumors displayed continued growth throughout the 4-week treatment period in vehicle-treated controls. Treatment with 25 or 100 mg/kg CGP 19984 significantly reduced tumor growth compared to that of vehicle-treated controls. However, tumor growth in rats treated with 250 mg/kg CGP 19984 was significantly lower than for all other treatment groups.

At the end of the experiment, animals in each of the CGP 19984 treatment groups had significantly lower average tumor weights than controls (Table I). Carcass weights were also significantly lower in all CGP 19984-treated groups. Moreover, serum GH and prolactin levels were significantly decreased in rats treated for 4 weeks with 100 or 250 mg/kg CGP 19984 when compared to controls, but were not significantly altered by the 25 mg/kg dose (Table I). Over the course of the experiment, the serum GH/prolactin ratio in controls rose above the initial ratio observed before the start of treatment. This increase was attenuated by CGP 19984 treatment, however, in a dose-dependent manner. Histological examination by light microscopy of MtT-W10 tumors from control animals showed large, rounded cells containing large, lightly-staining nuclei. Tumor cells from CGP 19984-treated groups appeared similar to controls, but nuclei in these cells tended to be smaller and stained more darkly. No other gross morphological differences were observed to distinguish between the various treatment groups.

Experiment 2

The effect of various doses of CGP 19984 on the growth of the MtT-W10 pituitary tumor in ovariectomized rats is shown in Figure 2. In vehicle-treated controls, MtT-W10 tumors continued to grow throughout the 4-week treatment period, demonstrating that growth of this tumor is not dependent on ovarian estrogen stimulation. Tumor growth in ovariectomized

TABLE III - COMPARATIVE EFFECTS OF CGP 19984 AND CB-154 ON MtT-W10 PITUITARY TUMOR WEIGHT, AND CONCENTRATION AND SECRETION OF GH AND PROLACTIN IN INTACT FEMALE RATS

		Treatment groups			
	Time[1] period	Control	CGP 19984 (50 mg/kg)	CB-154 (5 mg/kg)	CGP 19984 (50 mg/kg) + CB-154 (5 mg/kg)
Tumor weight (g)	t	16.0±2.6[2]	7.8±2.3[4]	9.8±2.2[4]	7.5±1.9[4]
Body weight (g)	i	200±9	204±10	208±12	195±10
	t	316±15	231±11	302±18	244±11
Carcass[3] weight (g)	t	300±15	223±12[4]	292±18	236±11[4]
Serum GH (μg/ml)	i	3.6±1.9	5.8±3.7	4.2±1.5	4.7±2.9
	t	29.9±6.1	8.4±3.7[4]	36.9±11.2	9.7±2.8[4]
Serum prolactin (μg/ml)	i	0.32±0.09	0.43±0.13	0.39±0.13	0.41±0.12
	t	1.24±0.42	0.53±0.19[4]	0.39±0.16[4]	0.34±0.17[4]
Serum GH/prolactin	i	11	14	11	12
	t	24	16	95	29
Tumor GH (ng/mg wet wt.)	t	1,073±330	338±88[4]	2,152±1,309	443±123[4]
Tumor prolactin (ng/mg wet wt.)	t	8.83±0.85	3.30±0.80[4]	2.79±0.56[4]	3.03±0.42[4]
Tumor GH/prolactin	t	122	102	771	146

[1]represents 1 day prior to initiation of treatment and t represents the day on which the experiment was terminated (4 weeks after the start of treatment).-[2]Mean±SEM of results from 14-15 rats.-[3]Carcass weight was determined by subtracting an individual's tumor weight from its body weight.-[4]$p<0.05$, as compared to vehicle-treated controls.

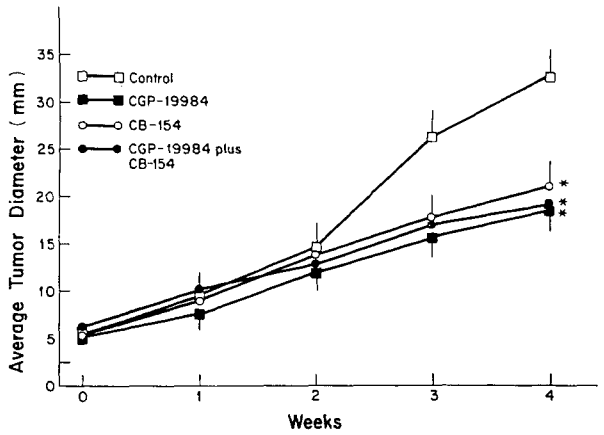

FIGURE 3 - Effects of CGP 19984 (50 mg/kg) and CB-154 (5 mg/kg) on growth of the MtT-W10 pituitary tumor in intact female rats. Vertical bars represent SEM. $^*p < 0.05$ as compared to vehicle-treated controls.

rats treated with 10 mg/kg CGP 19984 did not differ from that observed in the control group. However, MtT-W10 tumor growth was significantly inhibited in ovariectomized rats treated with 50 or 250 mg/kg CGP 19984. In addition, tumor growth in animals treated with 250 mg/kg CGP 19984 was significantly lower than in all other treatment groups.

Average tumor weights were significantly lower in ovariectomized rats treated with 50 or 250 mg/kg CGP 19984 than in controls (Table II). Carcass weights did not differ statistically among any of the treatment groups. Serum prolactin levels, 4 weeks after the start of treatment, did not differ significantly between the various treatment groups, but did show a tendency to decrease with increasing doses of CGP 19984. In contrast, serum GH levels at the end of the treatment period were significantly lower in groups treated with 50 and 250 mg/kg CGP 19984 than in controls. Serum GH levels in rats treated with 10 mg/kg CGP 19984 did not differ from those of controls. As observed in experiment 1, the serum GH/prolactin ratio increased in each treatment group as the MtT-W10 pituitary tumor continued to grow throughout the 4-week treatment period, but CGP 19984-treated groups showed a dose-dependent decrease in this ratio at the end of this time. Histological examination showed no variations in morphology to distinguish between the various treatment groups.

Experiment 3

This experiment compared the anti-tumor activity of CGP 19984 and CB-154, a drug used clinically in the treatment of prolactin-secreting pituitary adenomas. It was also of interest to determine whether the anti-tumor effects of CGP 19984 and CB-154 were agonistic or antagonistic when these treatments were administered in combination. In addition, this study determined the effects of the various treatments on MtT-W10 pituitary tumor prolactin and GH concentrations. The effects of CGP 19984 and CB-154 on the growth of the MtT-W10 pituitary tumor in intact female rats are shown in Figure 3. Treatment with CGP 19984 or CB-154 was equally effective in significantly inhibiting growth of the MtT-W10 tumor. However, inhibition of tumor growth resulting from the combined treatment of CGP 19984 and CB-154 did not differ from that which occurred when either drug was given alone.

Average tumor weights at the end of the experiment were significantly lower in all drug treatment groups, when compared to controls, but were not different among the different drug treatment groups (Table III). Average body weights were significantly lower in groups treated for 4 weeks with CGP 19984 alone or in combination with CB-154 than in controls. Treatment with CB-154 alone had no effect on body weight. Serum and tumor GH concentrations were significantly lower in rats treated for 4 weeks with CGP 19984 alone or in

combination with CB-154, than in controls. However, treatment with CB-154 alone resulted in a slight, but statistically insignificant increase in serum and tumor GH concentrations (Table III). Serum and tumor prolactin concentrations were significantly lower in all drug-treated groups after the 4-week treatment period than in controls. Serum and tumor GH/prolactin ratios at the end of the experiment tended to be lower in animals treated with CGP 19984 alone and higher in animals treated with CB-154 alone. Serum and tumor GH/prolactin ratio in rats treated for 4 weeks with the combination of CGP 19984 and CB-154 were unchanged, reflecting the decrease in absolute levels of both hormones. Histological examination of MtT-W10 tumors from CGP 19984 and CB-154 treated animals showed that cells appeared to be similar in shape and size, but nuclei were smaller and stained more darkly than those of controls. No other gross morphological differences were observed that distinguished the various treatment groups from each other.

DISCUSSION

The results in the present study show that CGP 19984 therapy effectively inhibits growth of the MtT-W10 transplantable mammosomatotropic pituitary tumor in intact female rats. CGP 19984-treated groups displayed dose-dependent decreases in MtT-W10 tumor size and weight, together with a dose-dependent reduction in circulating GH and prolactin levels. Although the MtT-W10 pituitary tumor displays hormone-independent growth, its growth and hormone secretion are stimulated by estrogen (Kim and Furth, 1976). Since CGP 19984 inhibits gonadotropin and subsequent gonadal steroid release (Ip *et al.*, 1986; Sylvester *et al.*, 1986), it is possible that the retardation of growth of the MtT-W10 tumor following CGP 19984 treatment of intact animals might have resulted indirectly from a reduction in circulating estrogen levels rather than from a direct cytostatic or cytotoxic effect. However, results of experiment 2 demonstrated that CGP 19984 is also effective in suppressing growth of the MtT-W10 tumor in ovariectomized rats, suggesting a direct inhibitory action of this drug on tumor growth. These findings, as well as those from previous studies demonstrating the anti-tumor effectiveness of CGP 19984 against hormone-dependent and -independent tumors (Schieweck *et al.*, 1983; Ip *et al.*, 1986), suggest that this drug has promising clinical potential.

Although no apparent toxicity was observed, CGP 19984-treated animals displayed dose-dependent reductions in body and carcass weight when compared to vehicle-treated controls. The MtT-W10 tumor secretes large amounts of GH, resulting in substantial growth and weight gain of the tumor-bearing animal. Reduced weight gain in CGP 19984-treated animals may therefore reflect the reduced MtT-W10 tumor size and subsequent reduction in GH secretion, since CGP 19984-treated rats showed continued modest weight gain throughout the treatment period, and no animal showed weight loss. Previous reports have also shown that CGP 19984 treatment resulted in moderate body weight loss in male and female rats (Ip *et al.*, 1986). Recent studies in this laboratory have shown that non-tumor-bearing animals treated with various doses of CGP 19984 (5 to 250 mg/kg) displayed an immediate dose-dependent reduction in food consumption and subsequently body weight, but food consumption returned to normal within 5–11 days depending on dose. At present, the mechanism by which CGP 19984 reduces food intake in rats is unknown. Nevertheless, in view of the central effects of CGP 19984 on gonadotropin synthesis and release (Sylvester *et al.*, 1986), it is possible that this drug may suppress appetite directly at the level of the hypothalamus. Further studies are currently being conducted to investigate this possibility.

The dopaminergic agonist, CB-154, inhibits prolactin release from the pituitary (Lu *et al.*, 1971) and significantly inhibits growth and function of prolactinomas in rats (Quadri *et al.*, 1972) and humans (Thorner *et al.*, 1980, 1981; Chiodini *et al.*, 1981; Tindall *et al.*, 1982; Moses *et al.*, 1981). Some workers have shown that the inhibitory effects of CB-154 are reversible upon termination of therapy (Thorner *et al.*, 1981), whereas others have observed no tumor regrowth in certain patients after cessation of long-term dopamine agonist therapy (Gen *et al.*, 1984; Johnston *et al.*, 1984). The present study compares the inhibitory effects of CB-154 and CGP 19984 treatment alone and in combination, on the growth and hormone secretion of the MtT-W10 pituitary tumor. Both CB-154 and CGP 19984 therapy were effective in suppressing MtT-W10 tumor growth when given alone, but combined treatment with these drugs was no more effective than either drug alone. However, a differential effect of CGP 19984 and CB-154 on serum and tumor GH and prolactin concentrations was clearly observed. Rats treated with CGP 19984, either alone or in combination with CB-154, had significantly reduced serum and tumor GH and prolactin levels. In contrast, CB-154 treatment alone significantly reduced serum and tumor prolactin, but not GH concentrations. Results from this study are consistent with previous findings which demonstrated that as the tumor grows, prolactin secretion tends to plateau and eventually decrease, while GH secretion persists and usually increases (Kim and Furth, 1976). Interestingly, CGP 19984 treatment was found to counteract the increase in GH/prolactin ratio which occurred over time. These findings suggest that CGP 19984 treatment suppresses growth and function of both GH- and prolactin-producing adenomatous cells, while CB-154 suppresses growth and function of primarily prolactin-producing cells within the MtT-W10 tumor. CB-154 is of some effect in lowering blood GH levels in acromegalic patients (Moses *et al.*, 1981). These differential effects of CB-154 treatment on GH secretion may be related to the fact that the majority of pituitary tumors found in humans are benign, whereas the rapidly growing MtT-W10 pituitary tumor is malignant.

The exact mechanism by which CGP 19984 acts to suppress MtT-W10 pituitary tumor growth and hormone secretion is unknown. Further studies are currently being conducted to clarify the cytostatic/cytotoxic effects of this drug. Nevertheless, findings in the present study indicate that CGP 19984 may be an effective alternative to CB-154 in the clinical treatment of prolactin-producing adenomas. Furthermore, since CGP 19984 was also found to inhibit tumor GH secretion, this drug may also be an effective treatment against pituitary tumors secreting hormones other than prolactin.

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