Effects of Glucocorticoids on the Growth of Human Fibrosarcoma Cell Line HT-1080

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ABSTRACT

The human fibrosarcoma cell line HT-1080 exhibits rapid growth following s.c. inoculation in 4-6-week-old male athymic mice. Cytosols from tumors carried in athymic mice bind glucocorticoid (Kₐ 1.8 ± 0.48 X 10⁻⁶ M; Bₘₐₓ 240.5 ± 35.3 fmol/mg cytosol protein, mean ± SEM). Receptor sediments primarily in the 8–9S region on 5–20% sucrose gradients and is specific for the glucocorticoids. HT-1080 growth in vitro (as measured by cell count) was inhibited over a range of 10⁻⁸–10⁻⁴ M after 7 days of incubation with dexamethasone and triamcinolone acetonide. Progesterone, estradiol, and dihydrotestosterone had no effect on HT-1080 growth in vitro. Preincubation with a 100-fold excess of progesterone reversed the growth inhibition observed with triamcinolone acetonide but not dexamethasone acetate. HT-1080 tumor cell growth responded biphasically to dexamethasone in vivo. Athymic mice given s.c. injections every other day with 5 or 25 μg dexamethasone showed an increase in tumor size inversely proportional to dose. In contrast, 200 μg of dexamethasone significantly inhibited tumor growth. Adrenalectomy did not significantly alter HT-1080 growth or glucocorticoid binding to tumor cytosols (Kₐ 3.4 X 10⁻⁶ ± 1.1, Bₘₐₓ 236.9 ± 9.9 fmol/mg cytosol protein, mean ± SEM) although tumor incidence was decreased in sham adrenalectomized mice. Glucocorticoid binding in tumors grown in vivo was decreased by increasing amounts of dexamethasone. High pharmacological doses of glucocorticoids inhibit the growth of human fibrosarcomas in vivo and in vitro.

INTRODUCTION

Glucocorticoids have a profound metabolic influence on a variety of tissues, particularly liver, lung, and muscle (1). In tissues of mesenchymal origin such as muscle, fibroblasts, and lymphocytes, the effects of glucocorticoids on cell metabolism are generally inhibitory and are felt to be mediated via a specific glucocorticoid receptor (2–7). Inhibition of human embryonic palatal mesenchymal cell growth by pharmacological concentrations (10⁻⁴ M) of, for example, glucocorticoids is associated with specific binding to cytosol receptors (8). Only those steroids which bind specifically inhibit cell growth (8). In adult human fibroblasts and fibroblasts derived from keloids, glucocorticoids also inhibit growth, possibly via a glucocorticoid receptor which is present in these tissues (9, 10).

Fibrosarcomas are malignant soft tissue sarcomas derived from primitive mesenchyme which, like their normal counterpart, fibroblasts (9), demonstrate fibrous differentiation (11, 12) and a significant incidence of receptor for glucocorticoid (13). It is not improbable, therefore, that glucocorticoids may play a role in the biology of human fibrosarcomas. Indeed Oliver et al., utilizing HT-1080, a human fibrosarcoma cell line (14), have shown a glucocorticoid receptor-mediated increase in fibronectin production (15).

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In two different experimental fibrosarcoma tumors, glucocorticoids also have antiproliferative effects (16, 17). Braunsweger et al. (16) have shown that pharmacological doses of dexamethasone and methylprednisolone produce a dose-dependent inhibition of tumor growth and cell proliferation in mouse radiation-induced fibrosarcomas. Similarly, in another mouse fibrosarcoma model, Braunsweger et al. (17) also suggested that regrowth delay by sequential dexamethasone and vincristine was the result of dexamethasone-induced cell cycle changes.

Taken together, these studies suggest that glucocorticoids may alter the proliferation of human fibrosarcomas. We therefore examined the effects of glucocorticoids on a glucocorticoid receptor positive human fibrosarcoma derived cell line in vitro and in male athymic mice.

MATERIALS AND METHODS

Materials. ['H]DEX [1,2-3H]dexamethasone (20.8 Ci/mmol); was purchased from New England Nuclear (Boston, MA) and repurified prior to use. Carbon-14-labeled bovine serum albumin was also purchased from New England Nuclear (Boston, MA). Radiolabeled steroids were purchased from New England Nuclear and Sigma Chemical Co. (St. Louis, MO). Trizma base, EDTA, hydroxyapatite, molybdic acid sodium salt, α-monothioglycerol, dithiothreitol, and glycerol were also purchased from Sigma. Activated charcoal, ammonium sulfate, and additional reagents were purchased from J. T. Baker Chemical Co. (Phillipsburg, NJ) and RNase-free sucrose was purchased from Schwartz-Mann (Orangeburg, NY). Dextran T-70 was obtained from Pharmacia (Piscataway, NJ). ACS scintillation cocktail was obtained from Amersham-Searle Corp. (Arlington Heights, IL).

Cell Line. HT-1080, a human fibrosarcoma (American Tissue Type Collection, Rockville, MD), was grown in MEM-E with 15% PCS (GIBCO, Grand Island, NY) and Penn-Strep-Fungizone (GIBCO). The fibrosarcoma was grown to confluence in 75-cm² tissue culture flasks (Corning, Corning, NY), harvested as necessary using a 0.125% Trypsin-EDTA-MEM-E solution (GIBCO), and counted on a Coulter Counter (Coulter Electronics, Hialeah, FL). Cells were checked periodically for viability by Trypan blue exclusion. Viability was approximately 98%.

Animals. Four- to 6-week-old athymic mice NCI-nu/nu (Frederick Cancer Resource Center, Frederick, MD) were housed in laminar flow hoods in sterile cages with filters. They received sterile water and mouse chow ad libitum.

Cells were harvested and 1 X 10⁶ cells injected s.c. in the flanks of male 4-6-week-old athymic mice. The tumors were grown until approximately 1 cm³ in size, usually 30 days postinoculation. Tumor incidence was virtually 100% by 10 days. The animals were sacrificed, and tumors were harvested and freed of surrounding tissue and any necrosis, cut into smaller pieces, frozen in liquid nitrogen, and stored at –80°C until assayed for receptor. Receptor assays were generally performed within 2-4 weeks of tumor harvest.

Receptor Studies. Specimens for assay were weighed while still frozen.
and pulverized in a tissue pulverizer (Thermovac Industries, Copiague, NY) at liquid nitrogen temperature. All subsequent steps were performed at 0-4°C. Briefly, the pulverized tissue was homogenized with two 10-s bursts in a Polytron homogenizer (Brinkmann Instruments, Westbury, NY) separated by a 30-s cooling period in the following buffer system: Glucocorticoid buffer—0.02 M Tris-HCl, 0.0015 M EDTA, 0.012 M α-monomoioglycerol, and 10% glycerol and 20 mM sodium molybdate, pH 7.4. The homogenate was centrifuged at 105,000 × g for 60 min to obtain a cytosol fraction. Cytosols were diluted to 1–2 mg protein per ml for receptor analysis or 5–6 mg/ml for sucrose density gradient (5–20%) analysis. Diluted cytosols of 200 µl were incubated for 16 h at 4°C over a concentration range of 0.05–30 nM labeled DEX. Radioinert DEX (100-fold excess), in addition to the [3H]DEX, was run in a parallel set of tubes to determine the degree of nonspecific binding. Bound and free ligand was separated by hydroxyapatite (18, 19). Data were analyzed according to the method of Scatchard (20).

For sucrose density gradient analysis, tumor cytosols (250 µl) were layered on a 4.6-M, 5–20% sucrose density gradient made up in glucocorticoid buffer following a 4-h parallel incubation with [3H]DEX and [3H]DEX plus radioinert DEX. Free steroid was removed during a 15-min incubation with a dextran-coated charcoal pellet at 4°C. Cytosols were centrifuged for 16 h at 285,000 × g in a SW 50.1 rotor (Beckman Instruments, St. Louis, MO). The tubes were punctured, and 10-drop fractions were collected and counted in 5 ml of aqueous counting scintillation cocktail (Amersham) at an efficiency of 33%. Carbon-14-labeled bovine serum albumin (New England Nuclear) was used as an internal standard and the sedimentation coefficient determined according to the method of Martin and Ames (21).

For competition studies, cytosol fractions were diluted to 1–2 mg/ml. [3H]DEX (25 nM) was incubated with 200 µg cytosol in the presence or absence of 2.5–2500 nM excess competing steroids. The data were expressed as the percentage of the specific [3H]DEX bound. Competitors used were 17-β-estradiol, diethylstilbestrol, DHT, R5020, R1881, progesterone, TA, and DEX.

Growth Studies. HT-1080 cells (1 x 10⁶) in vitro were inoculated in 25-cm² tissue culture flasks and grown in MEM-E with 15% FCS. Triplicate flasks were harvested at 24, 48, 72, and 96 h. Based on these experiments, growth experiments were concluded after 7 days of incubation. The media were changed on day 4. Media in growth experiments consisted of MEM-E with 15% FCS (GIBCO) stripped of endogeneous free steroids with 0.005% dextran and 0.25% charcoal. To this media, steroids dissolved in 1 ml of absolute alcohol were added to obtain a final steroid concentration of 10⁻⁶–10⁻⁴ M. Control media had a final concentration of 0.1% alcohol. HT-1080 cells were inoculated into triplicate 25-cm² tissue culture flasks with either control media or increasing concentrations (10⁻⁹-10⁻⁶ M) of steroid (DEX, TA, progesterone, and only minimal binding (<10%) by DHT, diethylstilbestrol, and 17-β-estradiol.

Growth Studies In Vivo. Our initial growth studies with HT-1080 revealed a doubling time of 28.8 ± 1.9 h, which corresponded closely to that reported by others, i.e., 26 h (15). Table 1 summarizes the effect of increasing concentrations of steroid on the growth of HT-1080 cells in vitro. Estradiol, dihydrotestosterone, and the weak antiglucocorticoid progesterone had no effect on cell growth after 7 days over a wide range of concentrations. Dexamethasone and TA significantly inhibited cell growth at 7 days over a concentration range of 10⁻⁸–10⁻⁶ M. In a separate set of experiments 10⁻⁶ M DEX significantly inhibited cell proliferation after 48-h exposure whereas 10⁻⁸ M and 10⁻⁷ M DEX only began to show significant inhibition of growth after 96 h. Similarly, 10⁻⁸–10⁻⁶ M TA did not significantly inhibit growth until after 96 h.

In an attempt to block the inhibitory effect of glucocorticoids on growth, HT-1080 cells were incubated in media containing 100-fold concentration of progesterone simultaneously with 10⁻⁴ M glucocorticoid or preincubated with 100-fold concentration of progesterone for 4 days prior to changing the media to 10⁻⁴ M glucocorticoid. Table 2 summarizes the results. Simultaneous incubation of HT-1080 cells with 10⁻⁴ M progesterone for 4 days did not significantly alter the growth inhibition of 10⁻⁴ M glucocorticoid observed on day 7. In contrast, preincubation with 10⁻⁶ M progesterone blocked the growth inhibition induced by 10⁻⁴ M TA.

RESULTS

Scatchard analysis of GR determined on HT-1080 tumors grown in athymic mice revealed a single class of saturable receptors for DEX (Kd, 1.8 ± 0.4 x 10⁻⁹ M; Bmax, 240.5 ± 35.3 fmol/mg cytosol protein; Mean ± SEM, n = 7 determinations) in all tumors assayed. Sucrose density gradient analysis (5–20% gradient) in the presence of 20 mM molybdate ion revealed a 8–95 peak completely suppressible with 100-fold excess radioinert DEX and partially suppressed by a 100-fold excess of progesterone (Fig. 1). Competition studies (Fig. 2) suggested that binding was highly specific for glucocorticoid. There was moderate competition for [3H]DEX specific binding by progesterone (39%) and the synthetic androgen R1881 (29%) and progesterone R5020 (26%) at 100-fold excess concentration and only minimal binding (<10%) by DHT, diethylstilbestrol, and 17-β-estradiol.

Fig. 1. Sucrose density gradient of [3H]DEX (25 nM) binding to HT-1080 tumor cytosol under low salt conditions. •, [3H]DEX; ○, [3H]DEX plus 100-fold excess unlabeled DEX; △, [3H]DEX plus 100-fold excess unlabeled progesterone. Dextran-coated charcoal separation of bound from free ligand.
effects, growth was significantly inhibited after day 14 (Fig. 3). In order to develop a dose-response curve, DEX was injected in corn oil at 5, 25, 100, and 200 µg s.c., administered every other day. There was no difference in tumor latency or incidence between control and any dose of DEX. As demonstrated in Fig. 3, 5 and 25 µg DEX significantly increased tumor volume compared to control. However, 100 and 200 µg of dexamethasone suppressed tumor growth. Final tumor weights divided by body weight reflected the tumor volume as measured and there was no significant difference in GR affinity ($K_d$) between groups.

In additional experiments carried out with 5 and 25 µg progesterone, no effect of progesterone on tumor volume (Fig. 4) or final tumor weight was observed. As illustrated in Table 3, GR increased in progesterone-treated compared to control (240.5 fmol/mg cytosol protein) and high-dose DEX-treated mice, while the $K_d$ appeared slightly higher.

Tumor incidence was 57% in sham adrenalectomized athymic mice whereas it was 92% in adrenalectomized mice. This compares to a 100% incidence in the nonsurgically treated animals. Tumor latency was essentially the same, 8.5 ± 1.5 and 6.4 ± 0.8 days for sham adrenalectomized and adrenalectomized animals, respectively. Tumors grew slightly more rapidly in the adrenalectomized group compared to the sham group, with a doubling time of 4 days compared to 5 days. This was reflected in the final tumor weights of 2.6 ± 0.7 g (adrenalectomy) and 2.1 ± 0.7 g (sham adrenalectomy). There was no difference in GR content 238.3 ± 37.4 and 236.9 ± 9.9 fmol/mg cytosol protein (mean ± SEM of triplicate determinations) in the sham and adrenalectomized groups, respectively. Mean affinity of the sham group was slightly lower than that of the adrenalectomized group (3.4 × 10^{-8} ± 1.1 versus 1.6 × 10^{-8} ± 0.4 M).

**DISCUSSION**

It is generally assumed that glucocorticoids mediate the majority of their physiological and pharmacological effects via a specific receptor (1–3, 24, 25). The steroid enters the cell and apparently binds to cytosol receptors that undergo postulated conformational change termed activation. This complex binds to nuclear DNA initiating transcriptional changes (24, 25). Identification of a specific, high-affinity cytosol binding protein, in a group of tumors as diverse as the sarcomas (12, 26, 27), and HT-1080 cells provides putative evidence that glucocorticoids may influence the biology of these tumors. Oliver et al. (16), utilizing a whole-cell assay, demonstrated glucocorticoid uptake in HT-1080 cells. We have shown that when this tumor is grown in athymic mice it retains specific binding for glucocorticoids.

**Growth Studies in Vivo.** Preliminary experiments demonstrated that the HT-1080 fibrosarcoma cell line grew well following s.c. inoculation in 4- to 6-week-old athymic mice. Tumor incidence was virtually 100% and 1-cm³ tumors were present within 20–30 days following inoculation. Mean tumor latency was 8.7 days (range, 3.8–10.2) for several experiments. Overall, there was no significant difference in tumor latency or incidence between control and DEX or progesterone-treated groups. Initial experiments utilizing a high-dose 5-mg DEX pellet implanted in the opposite flank showed a significant inhibition of HT-1080 growth by DEX from day 6 on. When corrected for body weight to correct for possible metabolic variations, growth was significantly inhibited after day 14 (Fig. 3). In order to develop a dose-response curve, DEX was injected in corn oil at 5, 25, 100, and 200 µg s.c., administered every other day. There was no difference in tumor latency or incidence between control and any dose of DEX. As demonstrated in Fig. 3, 5 and 25 µg DEX significantly increased tumor volume compared to control. However, 100 and 200 µg of dexamethasone suppressed tumor growth. Final tumor weights divided by body weight reflected the tumor volume as measured and there was no significant difference in GR affinity ($K_d$) between groups.

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as well. Human melanoma (34, 35), prostatic carcinoma (36, 37), cervical carcinoma (38), and mammary carcinoma (39, 40) have also been demonstrated to bind glucocorticoids and exhibit growth inhibition in the presence of glucocorticoids. The importance of in vitro culture conditions for the manifestation of glucocorticoid-induced cell changes in fibroblasts has been emphasized by Ponec et al. (32, 33). This group (32) found marked glucocorticoid-induced growth inhibition in cultures at low cell density which decreased with increasing cell density. Johnson et al. (41) demonstrated that the addition of hydrocortisone to human skin fibroblasts without simultaneous renewal of the medium (nutrient-depleted medium) resulted in growth inhibition, whereas stimulation was observed when medium renewal and steroid addition was done simultaneously, e.g., “enriched medium.” Salomon and Pratt (42) demonstrated that growth-inhibitory effects of glucocorticoids were decreased with increasing concentrations of serum in the culture media. Our system incorporated charcoal-stripped 15% FCS and an initial seeding of 1 x 10^5 cells. At this cell density and FCS concentration, our results suggest that we may have underestimated the inhibiting effects of glucocorticoids on the growth of this cell line.

If the glucocorticoid binding to the glucocorticoid receptor can be blocked with subsequent reversal of glucocorticoid-induced cell changes, this suggests that these effects may be mediated via the receptor. Yoneda and Pratt (8) showed that progesterone and the potent antiglucocorticoid cortisolone overcame the dexamethasone-induced suppression of human embryonic palatal mesenchymal cell growth. Similarly, RU 486, a new synthetic antiglucocorticoid, has been shown to reverse the glucocorticoid-induced growth inhibition in mouse L929 fibroblasts (43, 44). Preincubation or simultaneous incubation of the weak antiglucocorticoid progesterone with DEX did not block the glucocorticoid-mediated inhibition of HT-1080 growth. Similarly, simultaneous incubation of progesterone with TA did not reverse the inhibition of HT-1080 growth by TA. However, preincubation with progesterone did block the inhibitory effects of TA on HT-1080 growth. Although the competition curve suggests no difference in the affinity of TA on DEX for the receptor, these differences may result from structural difference of the compounds. In support of the mechanism is our observation that high concentrations of DEX structural difference of the compounds. In support of the mechanism is our observation that high concentrations of DEX

![Graph](image1.png)

**Fig. 3.** Effect of various dose of DEX given s.c. in corn oil every other day or as a pellet (see “Materials and Methods”) on the growth of HT-1080 cells in male athymic mice. At low doses of 5 and 25 μg s.c. every other day, a significant increase in tumor growth was noted, whereas large pharmacological doses inhibited cell growth. Brauchsweger et al. (16) showed similar results in a radiation-induced fibrosarcoma in mice where DEX and methylprednis-
clone produced a dose-dependent inhibition of tumor growth. Their dosages were comparable (5 and 10 mg/kg/day × 14 days) to our 100- and 200-μg/day DEX treatments with tumor cytosols expressing a significant amount of binding (632 fmol/mg cytosol protein). Stanberry et al. (45) have shown that low doses of hydrocortisone (7-28 μg/day) increased the growth of a glucocorticoid receptor-positive hamster melanoma. A low dose of dexamethasone produced a similar result (45). Progesterone had no effect on growth of HT-1080 in vivo although it bound to the glucocorticoid receptor at high concentrations.

The discordance of the effects of low doses of glucocorticoids, in vivo with the in vitro data, may be the result of in vitro conditions as alluded to previously (32, 33). However, the possibility of the effect of the low doses of steroids on natural killer cell inhibition in athymic mice must be considered and will require further investigation. Prostaglandins of the E series have been shown to suppress human natural killer activity (46) and Tashjian et al. (47), in a mouse fibrosarcoma cell line, found a dose-response inhibition of prostaglandin E2 production by hydrocortisone.

Unlike Stanberry et al. (45), who found an inhibition of a hamster melanoma growth following adrenalectomy of the hamster host, we were unable to alter HT-1080 growth with prior adrenalectomy of the athymic mouse. This could be due to species differences or secondary to the time of inoculation of the tumor. Stanberry et al. (45) inoculated 1 week postsurgery, whereas we inoculated tumor cells 1 day postsurgery. This may also account for the decrease in HT-1080 incidence in the sham adrenalectomized group. At the time of inoculation, the sham adrenalectomized animals may have had high circulating corticosteroids secondary to the stress of surgery and wound clip attachment which could have inhibited tumor incidence. The adrenalectomized group, having little or no circulating steroids secondary to stress, did not show a significant decrease in HT-1080 incidence compared to sham adrenalectomized mice (92 versus 57%).

As anticipated, the amount of [3H]DEX binding was less in DEX-treated animals. This would be predicted if high levels of circulating glucocorticoids were partially occupying endogenous receptors.

These findings are similar to those previously reported in other glucocorticoid-positive tumor cell lines (45). We did not, however, find a marked increase in the cytosolic glucocorticoid binding following adrenalectomy (45, 48). This was not unanticipated, however, as others (49) have found that glucocorticoid binding to liver and hepatoma cytosols following adrenalectomy can be variable. In the present experiments we may be seeing a variation of this phenomenon. The increase in glucocorticoid binding in tumor cytosols of progesterone-treated mice is an interesting observation that requires further evaluation. It may be that progesterone directly or indirectly induces an apparent increase glucocorticoid binding in this cell line. Indeed, Mayer and Rosen (50) found higher cytosolic binding for glucocorticoid of skeletal muscles in female rats and castrated males given 4 daily injections of estradiol.

The observation of higher affinity of the cytosolic receptors in the progesterone-treated mice needs further study. It could be an activated receptor which is present because of the chronic stimulation of the weak antiglucocorticoid progesterone. Alternatively, progesterone could be occupying an as yet unresolved lower affinity binding component leading to resolution of a higher affinity site.

In summary, we find in vitro and in vivo that high pharmacological doses of glucocorticoid inhibit human fibrosarcoma cell growth, whereas low pharmacological doses in vivo stimulate growth. Although our data do not completely substantiate a receptor-mediated mechanism, this may be modulated via the glucocorticoid receptor.

REFERENCES


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