*I - a * Indicates abstract received too late for publication.

I - b

POTENT ESTROGENIC ACTIVITY OF ADRENAL STEROIDS

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Human adrenals are unique in having a high secretion rate of steroids which are converted into estrogens and androgens in peripheral tissues. In order to obtain further information about the potential role of these steroids as sex steroids in peripheral tissues, we have studied the estrogenic effect of dehydroepiandrosterone-sulfate (DHEA-S), dehydroepiandrosterone (DHEA) and androst-5-ene-3β,17β-diol (Δ^5-diol) in normal and cancer tissues. Following incubation of normal rat anterior pituitary cells in culture, Δ^5-diol, DHEA and DHEA-S cause 8-, 4- and 3.5-fold increases, respectively, in PRL cell concent, the effect being reversed by the antiestrogen LY156758. Similarly, the stimulatory effect of the three steroids on LH, FSH and GH release is blocked competitively by the antiestrogen. Δ^5-diol was next incubated with the human mammary carcinoma cell line ZR-75-1. In this tissue, it caused a strong mitogenic effect on cell growth. Since the half-maximal concentration of Δ^5-diol required to stimulate cell growth is 2.5 nM, a concentration within the range of normal serum levels of the adrenal steroid in women, the present data clearly indicate the potential role of Δ^5-diol in breast cancer growth and development in women. We have also found a potent stimulatory effect of Δ^5-diol on the growth of the DMBA-induced mammary tumor in the rat. The present data indicate that the adrenal steroids, either in the form of Δ^5-diol, or of its precursors, DHEA-S and DHEA, should be taken into consideration for the efficient control of estrogen-sensitive cancer. Drugs able to more efficiently block adrenal steroid secretion and pure antiestrogenic compounds able to neutralize the action of estrogens of various sources should become a priority.

I - c

RU-38486, A PROGESTIN AND GLUCOCORTICOID ANTAGONIST, IN THE TREATMENT OF EXPERIMENTAL PITUITARY TUMORS.

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Recently a new steroid has been developed, RU 38486, which was shown to have powerful progesterone-antagonistic, but also glucocorticoid receptor-blocking activity. In the present study we investigated the effects and mechanism of action of RU 38486 and the progestin megestrol acetate on the growth of the estrogen/progesterone-receptor positive transplantable prolactin (PRL)/ACTH-secreting rat pituitary tumor 7315a.

Daily administration for 30 days of 2.5 mg/kg RU 38486 inhibited tumor size by 32%, and tumor weight by 66%. Megestrol acetate 2.5 mg/kg and 6 mg/kg daily for 30 days inhibited tumor size by 16 and 29%, respectively and tumor weight by 39%. In comparison, surgical adrenalectomy inhibited tumors size by 35 %. The ACTH content of the pituitary glands of RU 38486-treated rats had increased by more than 200%, while that of megestrol acetate-treated rats was suppressed by 25%.

PRL secretion by cultured 7315a tumor cells was inhibited both by RU 38486 and megestrol acetate. The inhibitory effect of RU 38486 on PRL secretion was completely overcome both by dexamethasone and progesterone. The inhibitory effect on PRL release of megestrol acetate could be partly overcome by RU 38486 and progesterone. Studies on Corticotropin-Releasing factor (CRF)-stimulated ACTH release by normal rat pituitary cells showed a direct suppressive effect of megestrol acetate (100 nM-1 μM), and a stimulatory effect of RU 38486. In addition, 100 nM-1 μM RU 38486 completely overcame the inhibitory effect of 10 nM dexamethasone on CRF-stimulated ACTH release.

In conclusion: RU 38486 exerts in the model of the 7315a tumor a powerful inhibitory effect on tumor growth. This effect seems to be at least partly mediated via its glucocorticoid-receptor blocking activity. In this respect RU 38486 differs from progestins like megestrol acetate.

I - d

TREATMENT OF RAT MAMMARY TUMOURS WITH MIFEPRISTONE (RU486)

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Mifepristone (MFP), a new steroid molecule with antiprogestin and antiglucocorticoid properties, was used to study its possible application in treatment of breast cancer. Rat mammary tumours were induced with DMBA. Groups of 8-9 rats were treated for three weeks with MFP (2.5/10/40 mg/kg/day), megestrol acetate (MA; 2.5/10 mg/kg/day), with buserelin (BUS; 40 ug/kg/day) or by ovariectomy (OVX). At the end of therapy, effects were studied related to tumour load, steroid receptor content of mammary tumours for ER and PR, organ weights and blood plasma hormone levels. Remission of tumours with BUS was 50% and with OVX 65%. No remission but inhibition of tumour growth was observed with the various dosages of MFP (by 83-93%) or MA (45-52%) compared to control. MFP was significantly more potent than MA when used in the same dose. All doses of MFP and MA significantly reduced the PR content of tumours by 60-100%. Whereas ER content was not changed by MA, it was significantly reduced by MFP (by 58-82%).

MFP treatment gave rise to 10-30% increased weight of pituitary, ovaries and uterus, with no effect on adrenal weight. In contrast, MA treatment caused 10-30% decreased weight of all organs studied. Finally, MFP treatment resulted in increased plasma levels of (control=100%): LH (530%); FSH (150%); prolactin (400%); progesterone (350%); oestradiol (340%). No change was observed in plasma levels of ACTH or corticosterone. In-vitro studies with MCF-7 cells incubated with MFP showed abolition of oestradiol-stimulated growth.

In conclusion, inhibition of tumour growth by MFP appears to result from antiprogestin activity with direct action on the tumour cells. No significant antiglucocorticoid activity was observed.