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COMPARATIVE ANDROGENIC AND ANTIANDROGENIC PROPERTIES OF "ANTIANDROGENIC" COMPOUNDS. P. Poyet and F. Labrie, MRC Group in Molecular Endocrinology, CHUL, Quebec, Canada, G1V 4G2.

We have recently developed an antihormonal treatment for human prostatic carcinoma which combines the administration of an LHRH agonist in association with an antiandrogen in order to block the action of remaining androgens, especially those of adrenal origin. In order to select the most efficient antiandrogenic compounds, we have compared the androgenic and antiandrogenic properties of "antiandrogenic" compounds proposed for the treatment of prostate cancer, namely Cyproterone acetate (CA), Flutamide (FLU) and Megestrol acetate (MEGACE). Adult castrated rats were treated daily with these compounds (5 mg/rat) for 21 days. We observed that CA and MEGACE cause a 1.5- and 2-fold increase, respectively, in prostate weight, while FLU has no effect, thus indicating an androgenic activity of CA and MEGACE. The relative antiandrogenic potency of the compounds was then determined in castrated animals who received the combined administration of DHT (125 µg, twice daily) and one "antiandrogen" (1, 3 or 10 mg). MEGACE had absolutely no inhibitory effect on DHT action. CA partially prevented the action of DHT, inhibiting the stimulatory effect of DHT on prostate weight by 5, 85 and 90% with the 1, 3 and 10 mg doses, respectively. FLU caused a 73, 95 and 100% reduction in DHT-induced prostate weight at 1, 3 and 10 mg doses, respectively. As further proof of the intrinsic androgenic activity of CA and MEGACE, stimulation of prostate weight induced by these two compounds was completely reversed by FLU. The present data show that MEGACE and CA have intrinsic androgenic activity which seriously limits their use in androgen-dependent diseases such as prostate cancer. In addition, MEGACE has no antiandrogenic activity. Due to its pure antiandrogenic properties, the non-steroidal antiandrogen Flutamide thus appears the candidate of choice for the treatment of prostate cancer.

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NEUTRALIZATION BY AN ANTIANDROGEN OF THE STIMULATORY EFFECT OF ADRENAL STEROIDS ON THE RAT PROSTATE. P. Poyet, J. Hamel, P. Gagnon and F. Labrie, MRC Group in Molecular Endocrinology, CHUL, Quebec G1V 4G2, Canada.

The role of adrenal androgens on the growth of human prostatic adenocarcinoma has recently been demonstrated. In order to further characterize the action of adrenal steroids on the prostate, adult castrated male rats were treated for 14 days with dehydroepiandrosterone (DHEA) or DHEA-sulfate (DHEAS). While DHEAS had only a small effect, DHEA increased ventral prostate weight by 2.5- and 5-fold at the twice daily doses of 0.5 and 2 mg, respectively ($p < 0.01$). Two other adrenal steroids, namely androst-5-ene-3β,17β-diol (Δ^5-diol) and androstenedione (Δ^4-dione), also increased ventral prostate weight in a dose-dependent manner. At the highest dose studied (0.5 mg, twice daily), Δ^5-diol and Δ^4-dione increased ventral prostate weight by 5- and 6-fold, respectively ($p < 0.01$). Concomitant administration of a pure non-steroidal antiandrogen (Flutamide, 5 mg, twice daily), while having no effect by itself, completely blocked the stimulatory action of adrenal androgens on secondary sex organ weight. The effectiveness of the antiandrogen was further assessed by treating castrated males with testicular androgens. The 3- to 4-fold stimulation of ventral prostate weight induced by a low dose of dihydrotestosterone or 5α-androstane-3α,17β-diol (0.05 mg, twice daily) was completely prevented by simultaneous treatment with the antiandrogen. The present data indicate that steroids of adrenal origin can have adverse effects in cancer of the prostate and demonstrate that the use of a pure antiandrogen can efficiently prevent the action of these steroids.