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ARTICLES

Additive inhibitory effects of an androgen and the antiestrogen EM-170 on estradiol-stimulated growth of human ZR-75-1 breast tumors in athymic mice

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The effects of the androgen dihydrotestosterone (DHT) and of the androgenic steroid medroxyprogesterone acetate were studied on the growth of human ZR-75-1 breast carcinoma in athymic mice. The possibility of additive inhibitory effects of DHT and the new steroidal antiestrogen N-n-butyl, N-methyl-11-[16' alpha-chloro-3',17' alpha-dihydroxyestra-1',3',5'(10')trien-7' alpha-yl]undecanamide (EM-170) was also investigated on tumor growth. Removal of the high dose 17 beta-estradiol (E2) implants used to optimally stimulate initial ZR-75-1 tumor development in ovariectomized mice led to a progressive decrease in tumor area to 50.2 +/- 8% (SEM) of original tumor size 40 days after E2 deprivation. Additional treatment with the androgen DHT led to a more rapid fall in tumor volume, which already reached 57% of pretreatment values at 11 days. Whereas physiological implants of E2 led to a progressive increase in tumor size to about 180% above original size after 40 days, physiological plasma levels (205 +/- 37.2 pg/ml or approximately 0.67 nM) of DHT completely reversed the stimulatory effect of E2. Similar inhibitory effects on E2-stimulated tumor growth were achieved with the synthetic androgenic steroid medroxyprogesterone acetate. When the steroidal antiestrogen EM-170 at the dose of 30 micrograms/day was used simultaneously with DHT, tumor area was further reduced from 99.0 +/- 9.5% (DHT alone) to 58.8 +/- 18% when both DHT and EM-170 were administered together for 40 days compared with 169 +/- 22.2% in control E2-stimulated animals. The present data show that the androgen DHT as well as medroxy-progesterone acetate are potent inhibitors of E2-stimulated human ZR-75-1 breast cancer cell growth in vivo. Moreover, the inhibitory effect of DHT

can be further increased by addition of the antiestrogen EM-170, thus suggesting the interest of combining these 2 classes of compounds acting, at least partially, through different mechanisms, in order to improve breast cancer therapy in women.

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