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BIOLOGICAL RESPONSES OF 3- AND 17-ESTROGEN SULFATES IN THE MAMMARY CANCER CELL LINE MCF-7.

J.R. Pasqualini and C. Gelly
C.N.R.S. Steroid Hormone Research Unit, Foundation for Hormone Research, Paris, FRANCE

During the menstrual cycle and the post-menopausal period estrogen sulfates are quantitatively the most important form of circulating estrogen. Very important quantities of estrogen sulfates are also found in the breast cystic fluid and in the mammary tissue. In the present study, we explored the biological responses using different 3- and 17-estrogen sulfates with the mammary cancer cell line MCF-7. Cultures were carried out in MEM medium for 5 days. The values of progesterone receptor were as follows (in pmol/mg DNA ± SE): control, 0.5 ± 0.1; estrone-3-sulfate, 2.2 ± 0.3; estradiol-3-sulfate, 2.6 ± 0.5; estriol-3-sulfate, 1.6 ± 0.3; estradiol-17-sulfate, 0.6 ± 0.2; and estriol-17-sulfate, 0.5 ± 0.2. The effect on PR obtained with the unconjugated estrogens was as follows (in pmol/mg DNA ± SE): estrone, 2.6 ± 0.5; estradiol, 2.3 ± 0.4; and estriol 2.3 ± 0.5. Stimulation which is similar to that provoked by the estrogen-3-sulfates. Estrogen-3-sulfates stimulated cell proliferation with the same intensity as that provoked by the unconjugated estrogens. No effect was observed with the estrogen-17-sulfates. In the estrogen-3-sulfate studies a concentration of freed estrogens of 150-200 pg/ml was found after 3 days in culture, a quantity sufficient to elicit the biological responses. No hydrolysis was found with the estrogen-17-sulfates. It is suggested that estrogen-3-sulfates are active through the freed estrogen. In another series of experiments, using [^{3}H]estrone-sulfate, 24h after culture it was observed that 3% was hydrolyzed in the medium and that hydrolysis accounted for 90-95% inside the cells. A great conversion of estrone to estradiol was observed, particularly in the nuclear fraction (>60%).
It is concluded that estrogen-3-sulfates can play an important biological role in human mammary cancer.

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MAMMARY TUMOR INHIBITING CYTOTOXIC-LINKED ESTROGENS OF THE TRIPHENYLBUTENE-TYPE

M. Schuderer and M.R. Schneider
University of Regensburg, Institute of Pharmacy, D-8400 Regensburg, FRG

Triphenylbutenes linked with a cytotoxic moiety were developed to obtain drugs with a selective antitumor effect in estrogen receptor-positive tumors. Compounds were synthesized and tested for their alkylating activities, estrogen receptor affinities, estrogenic properties and tumor inhibiting activities in vitro and in vivo. The alkylating activity increased in the order carbamatemustard-, aniline-mustard-, ß-bromo-propionate-group. All compounds bound irreversibly to the estrogen receptor. All cytotoxic derivatives exerted an affinity to the estrogen receptor though lower than did the carrier molecule. The growth of the hormone-dependent MCF-7 cell line was better inhibited than that of the hormone-independent MDA cell line. The inhibiting effect of the cytotoxic derivatives on the growth of the hormone-dependent MXT-mouse mammary tumor was stronger than that of the triphenylbutene carrier. As none of the compounds showed a significant effect on the hormone-independent MXT-tumor, the inhibition of the hormone-dependent tumor can be attributed to the selective uptake of the drug in the receptor containing tumor cells. The nearly identical uterotrophic potencies of the cytotoxic derivatives and the unsubstituted carrier are a further argument for the selective estrogen receptor mediated cytotoxic action of our new drugs. Therefore, these new cytotoxic estrogens are of great interest for a selective cytotoxic treatment of mammary cancer.

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AN APPROACH TO DEVELOP PLATINUM COMPLEXES WITH A SPECIFIC ACTIVITY ON HORMONE-DEPENDENT BREAST CANCER

J. Karl*, M. Jennerwein*, R. Gust*, T. Spruß*, J. Engel**, H. Schönenberger*
*Sonderforschungsbereich 234, Institute of Pharmacy, Pharm. Chem. II, University of Regensburg, and **Degussa-Pharma-Forschung Frankfurt, F.R.G.

Diastereoisomeric platinum complexes with estrogen receptor binding ligands were synthesized and tested for specific activity against hormone-dependent mammary carcinomas. They lead to a marked inhibition of the growth of the hormone-dependent human MCF7 breast cancer cell line. Besides this, they cause a remarkable effect on the hormone-dependent MXT-mammary carcinoma of the mouse and on the DMBA-induced, hormone-dependent mammary carcinoma of the SD-rat. The new compounds also possess cytostatic effects, which are caused by the $PtCl_2$-group. This can be demonstrated by the in vivo-test on the lymphocytic leukemia P 388.

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DANAZOL TREATMENT FOR ADVANCED BREAST CANCER

P. Pronzato, A. Michelotti, D. Amoroso, A. Ardizzoni, R. Lionetto, L. Repetto, P.F. Conte, R. Rosso
Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy

Twenty-three patients(pts)with metastatic breast cancer were treated with Danazol(200 mg three times daily),an impeded androgen without estrogenic or progestational activity,which blocks the release of pituitary gonadotropin FSH and LH.All pts had received prior hormonal therapy. Characteristics of the group were: median age 57 years(range 40-80);menopausal status; all pts were postmenopausal; estrogen receptor(available in 8 pts)positive in 3/8 pts, negative in 5/8 pts;predominant site of metastases were:visceral 13 pts,bone 5 pts, skin 5 pts.All pts were treated for period ranging between 3 weeks and 4 months. 6/23 pts were not evaluable(1 pts for early death;2 pts lost to follow up;3 pts for too early follow up);12/17 pts developed progressive disease;3/17 pts demonstrated objective response(complete response in 1 pts, partial response in 2 pts). Characteristics of responding pt were: 1)age 65 years,postmenopausal,estrogen receptor negative,site of metastases:bone/skin, response:complete response, duration:4 months. 2)age 72 years,postmenopausal,estrogen receptor unknown,site of metastases:bone/skin, response:partia response,duration: 3 months. 3) age 51 years,postmenopausal, estrogen receptor unknown,site of metastases:bone/nodes, response:partial response,duration:4 months. Transient nausea was observed in 2 pts.The treatment was well tollerated in the majority of pts.