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INDUCTION OF PROGESTERONE RECEPTOR AND CELL REPLICATION IN BREAST CANCER CELLS: A MODEL SYSTEM TO TEST FOR THE ESTROGENIC ACTION OF ENVIRONMENTAL AGENTS. M. v. Beurden, P.M. Ravdin, and V.C. Jordan, Department of Human Oncology, University of Wisconsin Clinical Cancer Center, Madison, WI, U.S.A.

Structure activity relationships of known estrogenic compounds (Jordan et al., Envir. Health Pros., 61: 1984) allows for the identification of environmental agents with potential estrogenic actions. This model predicts that phenolphthalein, a compound in non-prescription laxatives should interact with the estrogen receptor and be an estrogen. We have tested this hypothesis by examining the effects of phenolphthalein on growth and expression of the progesterone receptor (PgR) in MCF-7 and T47D human breast cancer cells. Phenolphthalein and estradiol were mitogens for T47D cells, and this effect was blocked by the anti-estrogen 4-hydroxytamoxifen. Estradiol and phenolphthalein induced PgR in MCF-7 and T47D cells. Phenolphthalein glucuronide, the major human phenolphthalein metabolite, does not inhibit estradiol binding, act as a mitogen or induce PgR.

We found that 4-hydroxytamoxifen, which inhibits the mitogenic action of estradiol and phenolphthalein on MCF-7 and T47D cells, has the estrogenic property of stimulating PgR synthesis in T47D cells. We propose an updated model of estrogen action to account for the heterogeneity of responses which occur during growth and differentiation.

In summary, we demonstrate that the known structure activity relationships of estrogenic compounds allows selective screening of drugs for estrogen action. The model system in vitro will be of value to determine the estrogenic properties of other environmental chemicals.

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THE EFFECT OF TAMOXIFEN (T) ON PROGESTERONE RECEPTOR (PR): RELATIONSHIP OF A RISE IN PR TO RESPONSE AND THE EFFECT OF ALTERNATING T AND MEDROXYPROGESTERONE ACETATE (MPA) IN PATIENTS WITH ADVANCED BREAST CANCER.

Diana M. Barnes, A. Howell, R.N.L.Harland, A.D.Baildam, R.Swindell and R.A.Sellwood.
Christie Hospital, Manchester M20 9BX, U.K.

T may increase PR in tumours as a result of its partial oestrogen agonist activity. In this study we have (1) assessed whether this rise in PR is related to subsequent response to T and (2) assessed the effect on response of alternating T and MPA when compared with T or MPA alone in a randomised clinical trial in patients with advanced, evaluable breast cancer. PR was measured before and 1-3 weeks after T in 52 patients with advanced disease (test group) and in 58 with early disease. Controls were 51 patients with early disease not given T. PR in the second biopsy was significantly higher than in the first in groups given T compared with controls ($p = 0.031$). In the test group 21 had a higher PR in the second biopsy and 19 responded to continued T (90%). 11/31 (35%) responded if PR was lower or negative in the second biopsy. 104 patients were randomised to receive T/MPA cycling or T or MPA alone. There were no significant differences in time to progression or survival between the two arms. We conclude that a rise in PR in response to T indicates a responsive tumour but that alternating T/MPA is not superior to either agent given alone.

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RANDOMIZED TRIAL COMPARING ALTERNATING SEQUENCES OF TAMOXIFEN AND MEDROXYPROGESTERONE ACETATE (MPA) WITH SUCCESSIVE APPLICATIONS IN METASTATIC BREAST CANCER.

L. Mauriac, M. Durand, J. Chauvergne, F. Bonichon.
Fondation Bergonié, 180, rue de Saint-Genès, 33076 Bordeaux Cédex, France.

One hundred and eighty women with identical prognostic factors were randomized between two hormonotherapies: treatment A with tamoxifen 30 mg per day alternating every two weeks with MPA 1000 mg per day (n=85) or treatment B with tamoxifen 30 mg per day and after relapse high dose MPA alone.
The results are the very same between the two treatment groups: 16 objective responses, 37 and 48 no change, 32 and 31 progressive disease respectively. Thirty seven patients of group B could receive MPA after relapsing; 19 had no response, 14 got a stabilization and 4 an objective response. The actuarial survival for group B is longer than for group A ($p = 0,01$) with a median response of 12 months versus 6 months.
The alternated sequential hormonal treatment get the same objective results but a length of response shorter than the two hormonotherapies applied successively.

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EFFECTS OF PROLACTIN (PRL) AND/OR ESTRADIOL (E_2) ON CELL PROLIFERATION OF THE MXT MOUSE MAMMARY NEOPLASM.

R. Kiss (1), Y. de Launoit (1), M. L'Hermite-Balériaux (2), R. Paridaens (3) and A. Danguy (1).
(1) Lab. Histologie, Fac. Médecine, ULB; (2) Lab. Recherche Gynéco-obstétrique, Hôp. Brugmann, ULB; (3) Lab. Cancérologie mammaire, Inst. J. Bordet, B-1000 Bruxelles, Belgium.

The MXT tumor is a mammary adenocarcinoma, maintained by serial subcutaneous transplantation in female B6D2F1 mice; it contains significant amounts of estrogen- and progesterone receptors. We investigated the effects of one i.p. injection of E_2 (0.25 µg) or PRL (1 mg) or E_2 + PRL (0.25 µg + 1 mg, respectively) on tumor cells proliferation. Animals bearing bilateral tumors, all having been castrated 6 days previously, were killed by lots of 5 at various times after i.p. injection of the hormone(s) or of saline (controls), i.e. 6, 12, 24, 36 or 48 hours. One hour prior to their sacrifice, all animals received an i.p. injection of 1 µCi ^{3}H-Thymidine/g BW. After autoradiographical processing, the nuclear thymidine labeling indices (TLI) were recorded in all tumors. In all three hormone-treated groups, a significant TLI increase ($P<0.001$) was observed transiently, from the 6th to the 48th hour, with the following maximal values (mean % TLI ± SEM) recorded at 24 hours: controls 3.4 ± 0.2; E_2 12.3 ± 0.7; PRL 16.4 ± 0.9; E_2 + PRL 17.8 ± 0.5 (E_2 vs PRL: $P<0.01$; E_2 vs PRL + E_2: $P<0.001$; PRL vs E_2 + PRL: NS). These results led us to conclude that 1) PRL favours the MXT cancer cells proliferation; 2) the mitogenic effects of E_2 and PRL are neither synergistic or antagonistic.

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