Control of experimental breast cancer by antioestrogenic therapies

C.J. DIX & V.C. JORDAN

Department of Pharmacology, University of Leeds

The dimethylbenz (*a*) anthracene (DMBA)-induced rat mammary carcinoma model has become established as an experimental system for the study of hormone-dependent cancer (Huggins, Grand & Brillantes, 1961). We have used this model to determine the anti-tumour effects of either oestrogen withdrawal (ovariectomy) or antioestrogen therapy (tamoxifen: *trans* 1-(4β dimethylaminoethoxy phenyl) 1,2 diphenylbut-1-ene) before the appearance of palpable tumours i.e.: when the animals have a low tumour burden.

Female Sprague-Dawley rats, 50 days of age, were each given 20 mg DMBA in 2 ml peanut oil p.o. For all experiments, groups contained 20 rats each. In the first experiment, groups were injected daily with tamoxifen (50 μg s.c. in 0.1 ml peanut oil) between 5 and 35 d (A), 15 and 45 d (B), 30 and 60 d (C) and 50 and 80 d (D) after DMBA. This dose of tamoxifen has previously been shown to produce regression of established DMBA-induced tumours (Jordan & Jaspan, 1976). In controls palpable tumours appeared in each rat between 60 and 180 d after DMBA. The rate of tumour appearance in group D was similar to controls whilst tumour appearance in groups A, B and C was delayed for approximately 40 d at the point when all groups had 50% of animals with tumours. We have previously reported that treatment with increasing dose of tamoxifen (0.2, 3, 50 or 800 μg daily) between 30 and 60 d after DMBA results in an initial dose-related delay of tumour production (Jordan & Naylor, 1978).

In the second experiment the antitumour effect of ovariectomy 30 d after DMBA was investigated. No tumours were found in these rats until 150 d after DMBA and tumour appearance was 45% by 200 d compared with the 100% in controls. By contrast, continuous tamoxifen treatment (50 μg daily) between 30 and 200 d after DMBA resulted in tumour production by 200 d in only 10% of animals. Similarly 5% of animals had tumours at 200 d when they were ovariectomized 30 d after DMBA and also treated with tamoxifen between 30 and 130 d after DMBA.

It is concluded that tumour development is only inhibited by the continued presence of the anti-oestrogen. Moreover the delayed tumour development in ovariectomized rats can be further inhibited by anti-oestrogens which suggest that non-ovarian sources of steroids, possibly from the adrenals, can support tumour growth.

These results may have important implications for the use of antioestrogens as an adjuvant therapy after surgery in the treatment of breast cancer. If short courses of antioestrogens only delay tumour recurrence rather than eradicate the metastases then prolonged treatment cycles may need to be considered so that the control of hormone dependent growth is maintained.

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Studies on the mechanism of action of cyclosporin A

J.F. BOREL & DOROTHEE WIESINGER (introduced by B. BERDE)

Biological and Medical Research Division, Sandoz Ltd, Basle

Cyclosporin A (CS-A) is a small undecapeptide with a mol. wt. of 1203 which has been shown to act selectively on the early phase of lymphoid cell stimulation (Borel & Wiesinger, 1977). Hence, this compound affects most conditions where lymphocytes primarily are involved such as humoral and cell-mediated immunity and chronic inflammatory reactions. Extensive *in vitro* and *in vivo* experimentation in several animal species has revealed that CS-A exerts virtually no effect on any leukocytic or tumour cell except on the immunocompetent T lymphocyte (Borel & Wiesinger, 1977; Borel, Feurer, Magnée & Stähelin, 1977). We have attempted to investigate further the mechanism by which this drug exhibits its highly specific anti-T cell action.

Inhibition of plaque-forming cells in the mouse by CS-A was assessed *in vitro* (Mishell & Dutton, 1966). The ED_{50} was found at approximately 15 ng/ml, a concentration which is also effective in inhibiting proliferation of mitogen stimulated spleen cells (Borel & Wiesinger, 1977). Since it is already known that CS-A did not affect mouse B lymphocytes (Borel *et*