Effects of the antioestrogen ICI 164,384 on oestrogen-induced RNAs in MCF-7 cells

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Human breast cancer is often oestrogen responsive and can respond well to antioestrogen therapy. However, only 30% of breast cancer patients will benefit from endocrine therapy with the antioestrogen tamoxifen and even for these patients disease remission is transient (Osborne et al., 1980). There is therefore a clear need for novel antioestrogens that are more effective than tamoxifen, but that at the same time lack oestrogen agonistic properties.

In this study, the effects of ICI 164,384 have been examined on the expression of six oestrogen-regulated RNAs (pNR-1, pNR-2, pNR-13, pNR-17, pNR-25 and pNR-100) (May & Westley, 1986; Westley & May, 1987; May & Westley, 1988), and the 46 kDa secreted protein (Westley & Rochefort, 1980) in the MCF-7 cell line, and have been compared with the effects that tamoxifen is known to have on these responses (May & Westley, 1987).

MCF-7 cells were maintained in Dulbecco’s modified Eagle’s medium containing 10% fetal calf serum and insulin (1 µg/ml). For withdrawal from exogenous steroids, MCF-7 cells were plated simultaneously into T25 flasks and 8 mm microwells. The cells were grown to confluence and cultured for a further 2-3 days in the withdrawal medium containing 10% serum, treated with dextran-coated charcoal and insulin (1 µg/ml). During the first 3 days of withdrawal, the cells were washed twice with phosphate-buffered saline at each medium change. Following withdrawal, the cells were cultured for a further 2-3 days in the withdrawal medium alone or containing oestradiol, tamoxifen or a range of concentrations of the oestrogenic activity for the six RNAs. The most marked effect is its ability to induce the pNR-1 RNA to 80% of the oestrogen-induced level (May & Westley, 1987). In contrast, the level of the pNR-1 RNA is hardly affected by the presence of the steroidal antioestrogen.

ICI 164,384 is also a potent oestrogen antagonist which can inhibit the induction of all the oestrogen-regulated RNAs by 2 x 10^-10 M-oestradiol when present in between 50- and 150-fold molar excess. ICI 164,384 has been shown to have a similar affinity to that of oestradiol for the human oestrogen receptor, and it is therefore surprising that such a large molar excess is required to antagonize the effects of oestradiol. This may reflect the ability of the drug to enter cells or to bind to non-receptor proteins.

This steroidal antioestrogen is also able to suppress completely the induction of pNR-1 RNA by 10^-7 M-tamoxifen when present at an equimolar concentration. The RNA level is reduced to half-maximal by about 5 x 10^-8 M-ICI 164,384.

ICI 164,384 both lacks significant oestrogenic activity and acts as a potent antioestrogen for regulation of the expression of specific oestrogen-responsive genes in human breast cancer cells. It is hoped that it may prove useful in the treatment of both malignant and non-malignant oestrogen-responsive diseases.

Received 21 June 1988