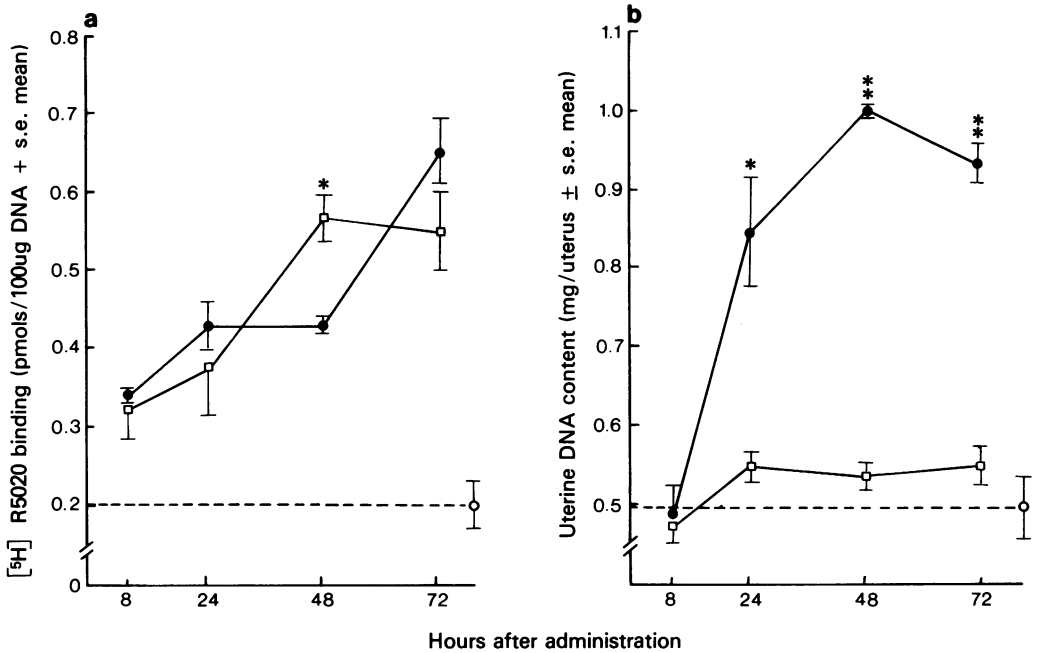

Figure 1 The effect of (□) monohydroxytamoxifen (25 μg) and (●) oestradiol benzoate (25 μg) on (a) the progesterone receptor content and (b) the DNA content, of immature rat uteri. Controls (○) received vehicle (0.1 ml arachis oil). Comparisons of treatment groups at the same time were made by Student's t test. $^{*}P < 0.01$, $^{**}P < 0.001$, all other values $P > 0.05$ ($n = 4$).

The antitumour activity of tamoxifen and monohydroxytamoxifen: a comparative study in the rat

V.C. JORDAN & K.E. NAYLOR

Department of Pharmacology, University of Leeds

Tamoxifen, an antioestrogen used in the treatment of breast cancer, inhibits the initiation (Jordan, 1976*a*) and growth (Jordan, 1976*b*) of hormone-dependent dimethylbenz(*a*)anthracene (DMBA)-induced rat mammary carcinomata. Monohydroxytamoxifen, a metabolite of tamoxifen, has been reported to be a more potent antioestrogen than the parent drug (Jordan, Collins, Rowsby & Prestwich, 1977) and its antitumour activity has now been assessed.

Female Sprague Dawley rats (50 days old) were each given DMBA (20 mg orally in 1 ml arachis oil). Beginning 30 days later, animals (15 per group) were injected s.c. daily with either tamoxifen (0.2, 3, 50 or 800 μg) or monohydroxytamoxifen (0.012, 0.2, 3 or 50 μg) in 0.1 ml arachis oil for 30 days. Controls received vehicle. Eleven weeks after therapy had ceased, tamoxifen had produced a dose-related inhibition of tumour incidence whereas monohydroxytamoxifen was only slightly active (Figure 1). Twenty weeks after therapy 80% of rats previously treated daily with 800 μg tamoxifen had tumours.

In a separate experiment, tamoxifen (800 μg) or monohydroxy-tamoxifen (50 μg) was administered s.c. daily for 30 days to mature female rats ovariectomized 10 days previously (5 per group). Groups were killed on the last day of therapy and 1, 2 and 5 weeks later. Both antioestrogens increased uterine wet weight ($P < 0.001$) and decreased cytoplasmic oestrogen receptor content ($P < 0.001$) when compared with controls. The uterine changes returned to control values 5 weeks after monohydroxytamoxifen whereas the effects of tamoxifen were maintained.

It is concluded that the effectiveness of a 30 day course of antioestrogen therapy in experimental breast cancer is dependent upon prolonged biological activity rather than antioestrogenic potency.

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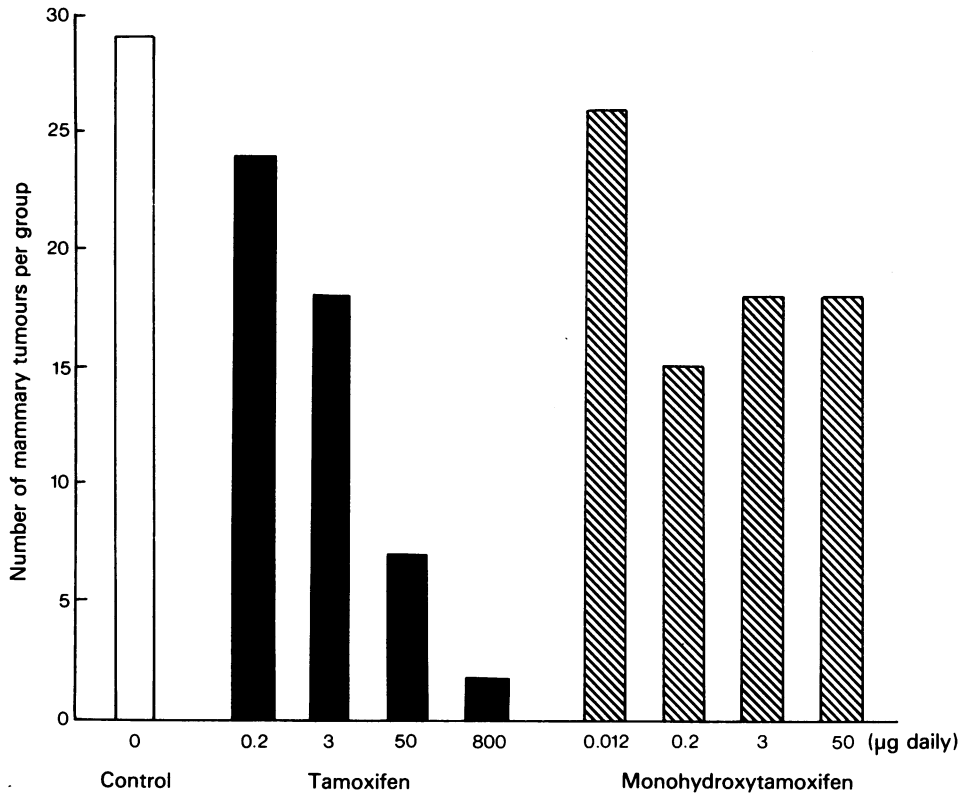

Figure 1 The incidence of mammary tumours in groups of rats (15 per group) 11 weeks after receiving different daily doses of tamoxifen or monohydroxytamoxifen. Antioestrogen treatment was instituted 30 days after carcinogen (DMBA) administration and was continued for 30 days. Controls received injection vehicle alone.

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A mechanism by which fenfluramine and benfluorex could inhibit the synthesis of triacylglycerols

D.N. BRINDLEY, P.H. PRITCHARD & R.G. STURTON
(introduced by A.T. BIRMINGHAM)

Department of Biochemistry, University Hospital and Medical School, Clifton Boulevard, Nottingham NG7 2UH, U.K.

The ability of drugs to inhibit the synthesis of triacylglycerols could be important in preventing the accumulation of fat in obesity. Such drugs could inhibit the excessive secretion of very low density lipoproteins and thus also indirectly decrease the production of low density lipoproteins. They might also be useful biochemical tools for studying the mechanisms that control triacylglycerol synthesis.

The most important regulatory enzyme in this process appears to be phosphatidate phosphohydrolase (EC 3.1.3.4) (Brindley, 1978). One of the best ways to exert pharmacological control is to alter the activity of regulatory enzymes. Amphiphilic cationic compounds, such as fenfluramine and benfluorex, interact physically with phosphatidate and prevent the action of the phosphohydrolase *in vitro*. There is evi-