Short Communication

RESISTANCE TO ANDROGEN IN MURINE LYMPHOSARCOMA LINES RESISTANT OR SENSITIVE TO GLUCOCORTICOID HORMONE

S. SASSON and M. MAYER

From the Department of Biochemistry, Hebrew University—Hadassah Medical School, Jerusalem, Israel

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Normal thymus and certain malignant lymphoid tumours undergo regression after exposure to glucocorticoid hormones in vivo and in vitro. The cytolytic effect was shown to depend on specific binding of the glucocorticoids to cytoplasmic receptors in the lymphocytes, translocation of the steroid-receptor complex into the nucleus and synthesis of specific proteins (Munck & Young, 1975).

Although thymic involution can also be evoked by androgenic steroids, we and others have recently shown that the cytolytic effect of androgens in the rat thymus is produced by interaction of the steroids with stromal or epithelial cells rather than with thymic lymphocytes (Sasson & Mayer, 1981; Grossman et al., 1979) and that androgens can effectively compete with dexamethasone for binding to specific glucocorticoid receptors in thymic cytosol (Sasson & Mayer, 1981). These observations prompted us to study the effect of androgens on murine lymphoid tumours.

CDF male mice aged 1 month were implanted with the glucocorticoid-sensitive and -resistant strains of lymphosarcoma P-1798 (Lampkin-Hibbard & Potter, 1958). Five days after tumour implantation, either dexamethasone (9α-fluoro-11β, 17α,21-trihydroxy-16α-methyl-1,4-pregna-1,4-diene-3,20-dione) 1 mg/mouse, or nandrolone phenpropionate (17β-hydroxy-19-norandrost-4-en-3-one phenylpropionate) 2.5 mg/mouse, suspended in corn oil, were injected i.m. into groups of 7–8 mice. Controls received corn oil only. This treatment was repeated every second day until a total of 5 injections had been given and the animals were killed 24 h after the last injection.

The thymus and tumours were carefully dissected out, cleaned and weighed. Wet weight was expressed as mg/100 g net body weight excluding tumour. Tumour dry weight was measured after heating at 70°C, until the tissue reached a fixed weight, and was expressed in mg/g tumour wet weight. For protein (Lowry’s method) and DNA (Richards, 1974) determination, the tumours were homogenized in 10 volumes of H2O. DNA/protein ratios are given in μg DNA/mg protein/g of tumour wet weight.

The Table shows that treatment with the potent androgen nandrolone phenpropionate failed to affect the wet weight, the dry weight or the DNA/protein ratio of either the glucocorticoid-sensitive or the glucocorticoid-resistant lines of lymphosarcoma P-1798. In contrast, dexamethasone produced the expected involution of the glucocorticoid-sensitive line. The regression of the tumour by dexamethasone reflects cell lysis rather than loss of cellular water or protein, since the dry weight as well as the DNA/
TABLE.—Effect of steroids on tumour and thymus in mice bearing lymphosarcoma P-1798 lines

| Tumour line | Treatment | Tumour | Tumour | Tumour |
|-------------|-----------|--------|--------|--------|
|             |           | Wet weight (g/100 g) | Dry weight (mg/g) | DNA/protein ratio (µg/mg) | Thymus Wet weight (mg/100 g) |
| Glucocorticoid-sensitive | Vehicle (8) | 7.6 ± 0.5 | 180 ± 1 | 17.1 ± 1.0 | 143.8 ± 15.4 |
| | Nandrolone phenpropionate (7) | 7.7 ± 0.5 | 177 ± 7 | 16.1 ± 0.1 | 33.9 ± 5.7† |
| | Dexamethasone (8) | <0.1† | — | — | 62.0 ± 15.3† |
| Glucocorticoid-resistant | Vehicle (8) | 16.1 ± 0.9 | 169 ± 1 | 21.4 ± 1.8 | 102.4 ± 7.9 |
| | Nandrolone | 16.9 ± 1.2 | 165 ± 1 | 21.4 ± 1.8 | 39.8 ± 3.9† |
| | Dexamethasone (7) | 16.2 ± 1.2 | 161 ± 1 | 19.3 ± 2.9 | 48.2 ± 7.2† |

Results are mean ± s.e.
* Numbers in parentheses are numbers of mice per group.
† Significantly different from vehicle-treated animals, P < 0.05.

The glucocorticoid-sensitive line responds catabolically to androgens as it shows marked reduction of 62% and 96% in tumour wet weight in mice bearing the glucocorticoid-sensitive and -resistant tumours respectively. By contrast, nandrolone phenpropionate caused 61% and 62% reductions respectively.

The failure of P-1798 tumour lines to regress after treatment with the potent androgen could imply absence of androgen receptors in these cells. In support of this view, we have consistently failed to find any measurable specific binding of either 3H-testosterone or 3H-5α-dihydrotestosterone in these 2 lines of lymphosarcoma P-1798 under conditions which produce appreciable binding of the same androgens in thymic cytosol (Sasson & Mayer, 1981). The observation that normal thymus responds catabolically to androgens (Sasson & Mayer, 1981) might suggest that thymus-derived lymphoid tumours should also regress after exposure to androgens. However, the results of the present work refute this argument. The failure of androgens to cause lymphoid-tumour involution has implications for the understanding of steroid effects in lymphoid cells. According to current concepts, the presence of cytoplasmic receptors is required for hormone action to ensue. The absence of androgen receptors in thymic lymphocytes and in the cytosol of the glucocorticoid-sensitive and glucocorticoid-resistant lymphosarcoma P-1798 explains the absence of tumour regression after androgen treatment. In contrast to the catabolic effects of androgens in thymus, which are mediated through an interaction with non-lymphoid reticular cells (Grossman et al., 1979; Sasson & Mayer, 1981), the tumours appear to be either refractory to such an interaction with reticular cells, or possibly these cells are absent from the lymphosarcoma P-1798.

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