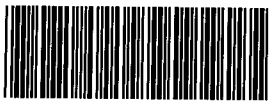

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EFFECT OF ANDROGENS MEDIATED BY THE OESTROGEN RECEPTOR IN UTERUS*

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We have been concerned to elucidate by the mechanism of action of high pharmacological doses of androgens which induce a marked uterotrophy in the rat uterus (Lerner *et al.*, 1966) and have tried to define the nature of the receptor protein responsible for this effect. Since the affinity of androgens for their specific androgen receptor (R_A) is high ($K_D \simeq 0.3$ nM) and since high doses of androgens were needed to increase uterine wet weight, we suspect that interaction of androgens with other receptor sites is responsible for this effect. It is now known that androgens such as 5α-dihydrotestosterone (DHT), testosterone, dehydroepiandrosterone and Δ5-androstene diol bind not only to R_A but also to the progesterone receptor (R_P) and the oestrogen receptor (R_E) (Rochefort and Garcia, 1976; Poortman *et al.*, 1977), and are able to induce *in vitro* the nuclear translocation of R_E (Rochefort *et al.*, 1972). This interaction of androgens with R_E and R_P is specific but of weak affinity and requires in some cases sensitized competitive experiments to demonstrate this. This weak affinity binding also explain that the receptor sites which have been occupied by the low affinity ligands can be exchanged very easily at 0°C. An interaction of androgens on the progesterone receptor could not be involved to explain uterotrophy in this system, since progesterone, in contrast to oestradiol does not induce such an hypertrophy. After injection *in vivo* to immature rats of DHT, an androgen which could not be transformed into oestrogens, we have measured two kinds of uterine metabolic responses. The ^{3}H-leucine incorporation

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into soluble proteins was a good marker for general protein synthesis and was found to vary parallel with uterine wet weight. The oestradiol induced protein evaluated by the double labelling technique (Katzennellenbogen and Gorski, 1972) represented a more specific response to oestrogens. The saturation and nuclear translocation of the androgen and oestrogen receptors were followed in parallel.

The results obtained indicated that physiological doses of DHT ($\leqslant 100\ \mu g$ rat) saturated and translocated R_A to the nucleus. However, no response was observed neither on ^{3}H-leucine incorporation nor on the oestradiol induced protein. At these doses, the R_E was found mainly in the cytosol and no nuclear translocation could be observed. Conversely, when the R_E was progressively saturated with doses $\geqslant 1$ mg rat, a complete translocation of R_E was observed which was followed by the stimulation of ^{3}H-leucine incorporation. In addition, there was a good correlation between the amount of R_E translocated by DHT at three hours and the extent of stimulation of protein synthesis. These results suggested that the occupation and translocation of R_E induced by DHT could be responsible for the observed metabolic effect. However, the action of some metabolites of DHT such as androstanediol could not be excluded even though the concentration of unchanged DHT was high ($\simeq 70\%$). Before concluding that the effect of an androgen was mediated by the oestrogen receptor, it was most important to show that DHT provoked the same specific response as oestradiol. At the present time, there are two series of data which strongly support the thesis that androgens can act via the oestrogen receptor. The first evidence is that we found marked stimulation of the "oestradiol induced protein" with 10 mg DHT (Garcia and Rochefort, 1977). This approach also indicated that other proteins were stimulated by DHT which were not by oestradiol, thus suggesting that androgens at these large doses could possibly be effective on other undefined receptor sites. The second evidence was provided by Zava and McGuire (1977) who demonstrated that DHT induces the progesterone receptor in the MCF_7 human breast cancer cell line.

The consequence of these results concerning the understanding of the molecular mechanism of action of steroid hormone is that the specificity of the response to a steroid hormone appears to be determined by the nature of the receptor translocated to the nucleus rather than to the nature of the hormone itself. When a R_E-androgen complex is formed, the present results strongly suggest that the response is oestrogenic. Another remark can be made concerning the difference of concentration between the R_E ($> 50\,000$ sites diploid cell) and the R_A ($\simeq 1.000$ sites cell). Assuming an homogeneous distribution of these receptors in all uterine cells, it is hypothesized but not proven that a low concentration of receptors would fail to induce a global hypertrophy and stimulation of protein synthesis. Finally, this effect of androgens obtained under pharmacological conditions might have practical consequences in human breast cancer in order to explain the efficiency of androgen in the treatment of this tumour (Goldenberg *et al.*, 1973) and the possible role of androgen in modulating the frequence of breast cancer (Bulbrook *et al.*, 1962). Whether this interaction of androgens on R_E is also responsible for the anti-oestrogenic effect of androgens cannot yet be ascertained.

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