TESTOSTERONE, PROSTATE GLAND AND HORMONE ACTION

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Although there is evidence that hormone action involves early or late changes in nuclear biosynthetic events, one cannot define, at present, the intracellular target with which hormones interact efficiently. Binding of hormones to DNA has been tested by Ts'o and Lu, (1964) and Goldberg and Atchley, (1966) and to histones by Sluyser, (1966a, b) and it was often assumed that the results were of general physiological significance. Without discussing here if DNA and/or histones are the most likely macromolecules to which hormones bind primarily, it should be pointed out that it is difficult to generalize without considering each particular hormone and target tissue, and especially the possibility that the "hormone" may not always be the actual chemical messenger interacting with the tissular molecules (Baulieu, 1966).

Oestradiol acting on prepuberal rat uterus is probably unchanged in the target organ (Jensen and Jacobson, 1962). In contrast, androgens are metabolized by rat prostatic tissue (Harding and Samuels, 1962 ; Pearlman, 1966 ; Ofner, Chamberlain and Jagarinec, 1966 ; Farnsworth, 1965). Recent experiments (Baulieu, Robel, Mercier and Lasnitzki, 1967) indicate that testosterone, the well known secretory product of testes and the most potent natural androgen circulating in the blood (Resko, Feder and Goy, 1968), may be active at least partially through its transformation into its reduced derivative androstanolone (17β-hydroxy-5α-androstane-3-one).

Explants of ventral prostate glands of 5-6 weeks old hooded rats were kept for 24 hours in an organ culture system (Lasnitzki, 1965), in Parker's medium 199 with 10 % calf serum to which tritiated testosterone, either 5×10^{-7} M or 5×10^{-5} M, was added. The latter concentration maintains the structural differentiation of the prostatic tissue,

in particular epithelial cell height and secretion ; some epithelial hyperplasia may also be observed. At the lower concentration, there is regression of the epithelium and no secretion. In the two experiments, an analysis of radioactive compounds present in the tissue after cell fractionation showed a nuclear and a "cytoplasmic" fraction. Radioactive compounds were extracted with organic solvents and the most rigorous radiochemical methodology was used for identifying and quantitating steroids. Ninety per cent of tissular radioactivity was present in the cytoplasmic fraction. Testosterone was found neither in the nucleus nor in the cytoplasm where a still unidentified polar compound was observed ; in the nuclei 2 relatively nonpolar steroids were found in equal amounts, one being androstanolone. During the course of these studies, new information came to our attention, indicating the metabolism of testosterone to androstanolone (Bruchovsky and Wilson, 1968) and the selective uptake of the metabolite (Anderson and Liao, 1968) by prostatic nuclei.

EFFECTS OF TESTOSTERONE AND ANDROSTANOLONE ON RAT PROSTATE IN ORGAN CULTURE

Concentration ($\times 10^{-6}$M) in the medium	Height	Secretion	Hyperplasia
TESTOSTERONE			
3.5	-	-	-
17.5	+	+	-
35	+	+	±
ANDROSTANOLONE			
3.5	-	±	±
17.5	±	±	+
35	±	-	++

In a second set of experiments, the effects of testosterone and androstanolone on rat prostatic tissue grown in vitro were compared. The explants were incubated for 6 days in Parker's medium 199 with 5 % horse serum in the presence of 3.5×10^{-5}, 1.8×10^{-5} and 3.5×10^{-6} of either steroid. Histological analysis showed that at each concentration, andros-

tanolone was much weaker than testosterone for maintaining epithelial height and secretory activity but it stimulated cell division and induced epithelial hyperplasia. There was no hyperplasia after testosterone up to 1.8×10^{-5} M and some slight hyperplasia at 3.5×10^{-5} M ; androstanolone at a dose of 3.5×10^{-6} M induced approximately the same degree of hyperplasia as testosterone at 3.5×10^{-5} M, and higher concentrations of androstanolone gave rise to extensive hyperplasia of the prostatic epithelium (table I).

These results suggest that studies of interaction of testosterone with nuclear elements do not lead necessarily to further insight into the testosterone action on the prostate gland. Data support the working hypothesis that androstanolone, one of the testosterone metabolites made and found in prostate nuclei, is especially concerned with cell division, whereas other metabolites could be involved in other aspects of testosterone action (Baulieu, Lasnitzki and Robel, 1968).

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