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Baulieu E E, Lasnitzki I & Robel P. Metabolism of testosterone and action of metabolites on prostate glands grown in organ culture. *Nature* 219:1155-6, 1968.
[Unité de Recherches sur le Métabolisme Moléculaire et la Physio-Pathologie des Stéroides, Faculté de Médecine de Paris, France and Strangeways Research Laboratory, Cambridge, England]

Rat ventral prostate explants in organ culture were shown to metabolize ^{3}H-testosterone to dihydrotestosterone (DHT) and to other 5α-reduced metabolites. DHT, not testosterone (T), accumulated in cell nuclei. DHT stimulated cell proliferation to a greater extent than T. Hence, T was a *prohormone* converted *in situ* to active metabolite(s). [The *SCI*® indicates that this paper has been cited in over 280 publications.]

Metabolic Activation of Testosterone

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When we started our experiments on rat ventral prostate organ culture, the "dihydrotestosterone hypothesis" was in the air. It was known, from the work of several authors, Farnsworth, Kochakian, Ofner, Pearlman, and others, that testosterone (T) metabolites of the 5α-series are present in the rat ventral prostate and that dihydrotestosterone (DHT) is a potent androgen *in vivo*.[1] Ilse Lasnitzki, working at the Strangeways Laboratories in Cambridge, reported in 1965 the action of T on the maintenance of ventral prostate explants in organ culture. She accepted our proposal to investigate the metabolism of ^{3}H-testosterone and the activities of identified metabolites, obtained in nonradioactive form from Roussel-Uclaf, in her culture system.

Preliminary results were published in 1967. When our paper was released by *Nature*, the results of N. Bruchovsky and J.D. Wilson[2] and those of K.M. Anderson and S. Liao,[3] who reported the selective uptake of DHT by prostate nuclei, had just appeared. Our results confirmed the local metabolism of T to DHT and the nuclear accumulation thereof. In addition, under identical experimental conditions, the marked "growth" stimulating property of DHT was observed.

The reader interested in going through our paper in *Nature* will not find the word "dihydrotestosterone." This was because the molecule 5α-androstane-17β-ol-3-one had been routinely abridged androstan-ol-one by steroid chemists. Obviously, this name for the active metabolite of T was defeated, and 5α-dihydrotestosterone or DHT is the only one in use nowadays.

Those who requested reprints of our paper have received a remark "added in reprint" indicating that 5α-androstane-3β, 17β-diol (3β-diol), which has been found as a metabolite of T in the cytoplasm, did not provoke any cell division but could maintain cell height and secretion. We proposed that this compound had an activity different from that of DHT.

The hypothesis of a dual mechanism of action of T involving two metabolites with different sites of action (nuclear for DHT, cytoplasmic for 3β-diol) attracted considerable interest. However, when our culture system was improved by superfusion with a completely defined medium containing androgens in the nM range, the qualitative difference between DHT and 3β-diol vanished, and the 3β-diol activity was attributed to a slight conversion back to DHT (reviewed in reference 4). Indeed, a single molecular entity of androgen receptor has been defined and cloned.[5]

The idea of a different mechanism of action was not so silly, after all. In recent years, several groups (Adams, Rochefort, and Thyssen) have reported that the two androgens Δ5-androstene-3β, 17β-diol and 3β-diol bind to estrogen receptors and must be considered as weak estrogens. The rat ventral prostate contains estrogen receptors mainly located in the fibromuscular stroma.[6] Therefore T is converted in the prostate to a potent androgen (DHT) and a weak estrogen (3β-diol). This situation is reminiscent of the prostatic hyperplasia produced in the dog by the combination of DHT and estradiol.

In conclusion, T, considered thus far as a steroid hormone, became in 1968 a *prohormone* for most but not all androgen target tissues. The notion of *metabolic activation* of a steroid in a target cell was then proposed and is now well documented.

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2. **Bruchovsky N & Wilson J D.** The conversion of testosterone to 5α-androstan-17β-ol-3-one by rat prostate *in vivo* and *in vitro*. *J. Biol. Chem.* 243:2012-21, 1968. (Cited 850 times.) [See also: **Bruchovsky N.** Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 2: the molecules of life.* Philadelphia: ISI Press, 1986. p. 183.]
3. **Anderson K M & Liao S.** Selective retention of dihydrotestosterone by prostatic nuclei. *Nature* 219:277-9, 1968. (Cited 405 times.)
4. **Baulieu E E, Le Goascogne C, Groyer A, Feyel-Cabanes T & Robel P.** Morphological and biochemical parameters of androgen effects on rat ventral prostate in organ culture. *Vitamin. Hormone.—Advan. Res. App.* 33:1-35, 1975. (Cited 25 times.)
5. **Tan J-A, Joseph D R, Quarmby V E, Lubahn D B, Sar M, French F S & Wilson E M.** The rat androgen receptor: primary structure, autoregulation of its messenger ribonucleic acid, and immunocytochemical localization of the receptor protein. *Mol. Endocrinol.* 2:1276-85, 1988.
6. **Jung-Testas I, Groyer M-T, Bruner-Lorand J, Hechter O, Baulieu E-E & Robel P.** Androgen and estrogen receptors in rat ventral prostate epithelium and stroma. *Endocrinology* 109:1287-9, 1981. (Cited 40 times.)

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