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Anderson K M & Liao S. Selective retention of dihydrotestosterone by prostatic nuclei. *Nature* 219:277-9, 1968.
[Ben May Laboratory for Cancer Research and Department of Biochemistry, University of Chicago, IL]

Testosterone is converted by a reductase in the prostate cells of rats to 5α-dihydrotestosterone that is selectively retained by the nuclei where androgens rapidly stimulate the synthesis of RNA. This retention is apparently due to selective binding of 5α-dihydrotestosterone to an androgen receptor in the nuclear chromatin of the prostate cell nuclei. [The SCI® indicates that this paper has been cited in over 415 publications.]

Testosterone to Dihydrotestosterone to Androgen Receptor

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Having spent the previous decade in medical school, residency, and the Army, by 1966 I (KMA) was a somewhat superannuated biochemistry graduate student. However, I had the very great good fortune of entering the program at the University of Chicago as a student of Dr. Shutsung Liao.

Discovery of the DNA-to-RNA-to-protein path for gene expression in the early 1960s stimulated the idea that some hormones might act directly on genes. Testosterone (T) was shown to increase, *in vivo*, the levels of mRNAs[1] and RNA polymerase activity[2] in the rat prostate. The latter effect was found to occur within one hour after androgen administration to castrated rats.[3] The logical question then was whether testosterone was the active androgen in all target organs as commonly believed at the time or was a proandrogen for an active metabolite that acted in prostate cell nuclei to regulate gene expression. At that time Liao was purifying liver and prostate cell nuclei for study of multiple RNA polymerases and their role in the synthesis of different types of RNA.[4] Consequently, we decided to investigate which androgen was present in these nuclei. Among more than 6 metabolites of testosterone, only 5α-dihydrotestosterone (DHT) was selectively retained in the purified prostate (but not liver) nuclei even after the nuclear membrane was removed by detergent. Since the finding was unusual and we believed very important, publication was delayed until the selective DHT retention was shown to occur within the prostate organ, *in vitro*.

After this work was completed, we sent out our manuscript for publication, only to find that it was difficult to convince reviewers that our finding was biologically meaningful. The reviewers also complained of the use of the term "receptor." The term "steroid receptor" was a taboo. For example, Liao and Fang[5] wrote an invited review on "androgen action," and the editor requested that the section on DHT and androgen receptor be removed. Before *Nature* accepted our manuscript, an abstract by N. Bruchovsky and J. Wilson appeared in a clinical research meeting proceeding reporting their work on *in vivo* retention of DHT by prostate nuclei. Our findings were revealed to the European community by Dr. H.G. Williams-Ashman in early 1968 when he attended a symposium in Europe on hormone action. Dr. I. Mainwaring and E. Baulieu, who were at the meeting, started to communicate with us on our study.

Our findings elated two investigators in the Ben May Laboratory for the following reasons. Dr. Charles Huggins showed earlier that DHT was more active than T in stimulating the growth of the female prostate. Dr. Elwood Jensen's work on the estrogen receptor needed another example in the steroid hormone area to show that the steroid receptor concept he advocated was universal. A distinct difference between the two sex steroids was that 17β-estradiol bound to its receptor without metabolism, whereas T needed to be converted to DHT in some target cells.

The importance of "T to DHT to receptor" is now well documented. The cDNA for androgen receptors has been cloned, antiandrogen receptor monoclonal antibodies have been made, and mutations[5] of the androgen receptor gene in many androgen-insensitive individuals has been documented.[6] Inhibitors of the reductase that converts T to DHT are being developed as new drugs for treatment of prostate diseases, acne, female hirsutism, and even male pattern baldness. This class of drug should have no undesirable side effects on sexual behavior or on some testicular and muscle functions that are dependent on T as the active androgen.

1. **Liao S & Williams-Ashman H G.** An effect of testosterone on amino acid incorporation by prostatic ribonucleoprotein particles. *Proc. Nat. Acad. Sci. USA* 48:1956-64, 1962. (Cited 170 times.)
2. **Williams-Ashman H G, Liao S, Hancock R L, Jurkowitz L & Silverman D A.** Testicular hormones and the synthesis of ribonucleic acids and proteins in the prostate gland. *Recent Prog. Hormone Res.* 20:247-301, 1964. (Cited 160 times.)
3. **Liao S, Leininger K R, Sagher D & Barton R W.** Rapid effect of testosterone on ribonucleic acid polymerase activity of rat ventral prostate. *Endocrinology* 77:763-5, 1965. (Cited 140 times.)
4. **Liao S, Sagher D, Lin A H & Fang S.** Magnesium and manganese specific forms of soluble liver RNA polymerase. *Nature* 223:297-8, 1969. (Cited 30 times.)
5. **Liao S & Fang S.** Receptor proteins for androgens and mode of action of androgens on gene transcription in ventral prostate. *Vitamin. Hormone.—Advan. Res. App.* 27:17-90, 1969. (Cited 225 times.)
6. **Liao S, Kokontis J, Sai T & Hiipakka R A.** Androgen receptors: structure, mutation, antibodies, and cellular dynamics. *J. Steroid Biochem.* 34:41-51, 1989.

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