This Week's Citation Classic®

Jensen E V & DeSombre E R. Estrogen-receptor interaction.
Science 182:126-34, 1973.
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This paper describes the phenomenon of estrogen-induced receptor transformation, identifying a biochemical role for the steroid hormone. Its major function is to convert an intracellular receptor protein to a regulator of gene expression. [The *SCI*® indicates that this paper has been cited in over 585 publications.]

Transformation of Receptor Proteins to Functional Forms

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This paper is a culmination of work begun 15 years earlier at the University of Chicago to obtain insight into the mechanism of estrogen action. With H. Jacobson, we synthesized estradiol labeled with carrier-free tritium and used this to determine what actually happens to the steroid as it induces growth of the immature rat uterus. We found that target tissues contain hormone-binding components with which estradiol associates to stimulate growth without itself undergoing chemical change. We also found that the inhibition of uterotrophic response by certain antiestrogens is proportional to their inhibition of hormone uptake, indicating that the binding substances are true receptors.

The first presentation of our early findings, in 1958 at a biochemistry congress in Vienna, was scarcely a success. Five people were in the audience, three of whom were other speakers. It seems that our session coincided with a symposium on hormone mechanism, where a thousand people came to hear how estrogens act through reactions of steroid metabolism, the accepted concept at the time. But the late Gregory Pincus learned of our work and invited presentations at a meeting in 1959 and at the Laurentian Hormone Conference in 1961. Thus, the endocrine community rapidly became aware of steroid hormone receptors, despite the reluctance of some orthodox pharmacologists to call anything a receptor that was not in a membrane.

By the early 1960s, tritiated estradiol and then other steroids became available commercially, and other laboratories undertook hormone-tracking experiments. It was established that, after estradiol administration *in vivo* or exposure of excised tissue *in vitro*, most radioactivity is bound in the target cell nucleus, extractable in 300 mM salt as an estradiol-protein complex, with a smaller amount in the cytosol fraction of homogenates. After J. Gorski used density gradient centrifugation to characterize the estradiol-protein complex of the cytosol, we showed that the nuclear complex is different. From various evidence, both laboratories[1,2] concluded that the nuclear complex is not produced directly but is somehow derived from the initially formed cytosol complex.

When we found that cytosol receptor is actually converted to nuclear receptor under the influence of estradiol, and that only the latter can bind to uterine nuclei and stimulate RNA polymerase, we suggested at a meeting in 1971 that an important function of the steroid is to convert the receptor to an active form that binds in the nucleus to enhance RNA synthesis.[3] Frank Putnam, who was then on the *Science* Editorial Board, suggested that this concept of "receptor transformation" be brought to the attention of a wider audience, for it provided, for the first time, a biochemical role for the steroid hormone. The lead article in *Science* in 1973 was the result. Since that time, receptor transformation has been shown to be an important action of all classes of steroid hormones, and many laboratories have contributed to elucidating the nature of this process.[4,5] It has provided a basis for identifying functional domains in receptor proteins and for studying transformed receptors as transcription factors.[6] It also was the basis for several scientific awards, including the Prix Roussel (1976), Amory Prize (1977), Gregory Pincus Memorial Award (1978), Gairdner Award (1979), Rolf Luft Medal (1983), Fred Conrad Koch Award (1984), and Axel Munthe · ward (1985).

1. **Gorski J, Toft D, Shyamala G, Smith D & Notides A.** Hormone receptors: studies on the interaction of estrogen with the uterus. *Rec. Prog. Hormone Res.* 24:45-80, 1968. (Cited 590 times.)
2. **Jensen E V, Suzuki T, Kawashima T, Stumpf W E, Jungblut P W & DeSombre E R.** A two-step mechanism for the interaction of estradiol with rat uterus. *Proc. Nat. Acad. Sci. USA* 59:632-8. 1968. (Cited 980 times.)
3. **Jensen E V, Mohla S, Gorell T, Tanaka S & DeSombre E R.** Estrophile to nucleophile in two easy steps. *J. Steroid Biochem.* 3:445-56. 1972. (Cited 130 times.)
4. **Grody W W, Schrader W T & O'Malley B W.** Activation, transformation and subunit structure of steroid hormone receptors. *Endocrine Rev.* 3:141-63, 1982. (Cited 230 times.)
5. **Pratt W B.** Transformation of glucocorticoid and progesterone receptors to the DNA-binding state. *J. Cell. Biochem.* 35:51-68, 1987. (Cited 50 times.)
6. **Godowski P J & Picard D.** Steroid receptors—how to be both a receptor and a transcription factor. *Biochem. Pharmacol.* 38:3135-43, 1989.