Estrogen Receptor: Ambiguities in the Use of This Term

There can be little doubt that in the rat uterus and elsewhere there are macromolecules which have a specific affinity for estradiol and related compounds (*1*, *2*). Very soon after isotopically labeled estrogens are administered to the intact animal (*2*) or are added to a medium which contains uterine strips (*1*), the steroid is concentrated more than 100-fold in the uterus. Apparently, little information about the physiologic significance of this binding phenomenon is available. It is certainly possible that this process represents a necessary first step in mediating some of the hormonal effects of estrogen; that is, it results from the combination of the steroid with a true estrogen receptor. However, it is also possible that this binding procedure is not a prerequisite for the physiologic actions of estrogen. There can be at least three alternate hypotheses about the significance of H^3-estrogen binding in addition to the "receptor" theory.

1) The estrogen-binding macromolecules may inactivate, perhaps temporarily, the steroid taken up in the uterus. Such a role for hormone binding is not without precedent. Thus, characteristic organelles which can concentrate H^3-epinephrine with great avidity both in vivo and in vitro (*3*) are found within sympathetic nerve endings. These organelles also appear to contain specific proteins (*4*). Their action does not change the catecholamine chemically but does render it physiologically inert (*3*). If the uptake of epinephrine within sympathetic nerve endings is blocked by drugs like cocaine, the physiologic responses to the catecholamine are not depressed (as one might expect if they functioned as "epinephrine receptors") but are actually potentiated (*5*).

2) The estrogen-binding macromolecules may provide the uterus with continued estrogen stimulation long after the steroid disappears from the bloodstream. One might speculate that their content of "bound estrogen" is physiologically inert but is in equilibrium with a small active pool of "free estrogen." Perhaps the uterus is a target organ for estrogen (whereas diaphragmatic skeletal muscle, for example, is not) because it benefits from continued stimulation by tiny amounts of free steroid which are in equilibrium with the bound pool. In this case, the estrogen-binding macromolecules would be very important in mediating the physiologic activity of the hormone, even if they did not function as true "receptors."

3) The estrogen-binding macromolecules may be without physiologic significance. This explanation is least satisfactory teleologically; however, it should not be discarded without adequate experimental evidence.

Until there are data to show that the binding of H^3-estrogen to tissue macromolecules must precede the physiologic effects of the steroid, it might be safe to avoid the use of the term "receptor" to describe this phenomenon. Why not call these macromolecules "estrogen-binding proteins" or "estrogen-binding substances" until their function has been determined?

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The appropriate comment of Wurtman is based on the practice of many pharmacologists of using the term "receptor" for a cellular entity (usually hypothetical) which not only receives and binds a chemical agent but, by doing so, elicits a physiologic or pharmacologic response. By these criteria, biochemists studying estrogen action are guilty of having committed impropriety for the sake of convenience. We might request clemency on the ground that some pharmacologists accept a broader interpretation of the receptor concept. I quote Ariëns (*1*): ". . . a variety of receptors have been mentioned: receptors on enzymes, the sites of drug metabolism; receptors on which the pharmacological effects are induced; storage receptors, sites of binding from which regulated release is possible; silent receptors, sites of indifferent drug binding; receptors on carriers, etc. All of these receptors are covered by the definition given by Schueler [(*2*)]. The receptors have an affinity for the drugs concerned. They have in common the ability to interact with these drugs. They differ in the consequences of the interaction." By the foregoing terminology, Wurtman's alternate hypothesis No. 2 describes a "storage receptor," whereas hypothesis No. 3 refers to a "silent receptor."

In spite of such rationalization, I agree with Wurtman that, if the use of "receptor" in its broader sense offends pharmacological orthodoxy, it would be preferable to use a different term for the estrogen-binding substances of target tissues. "Acceptor" is not suitable because the pharmacologists have preempted this word to denote specifically a site of indifferent binding (*1*). We suggest that the highly estrogenophilic components of target tissues be called "estrophiles," a word that describes the property by which these substances are recognized.

The problem will disappear when estrogenologists are able to establish a role for estrophiles in the uterotrophic process. This objective is now realized for one of the two uterine estrophiles. The estrogen-binding factor of the supernatant, first demonstrated by Toft and Gorski (*3*) to be a protein with sedimentation constant of 9.5*S*, has been shown (*4*) to participate not only in the initial uptake of estradiol by uterine cells but also in the formation of the major uterine estrophile, which can be extracted from the nuclei as an estradiol-protein complex with sedimentation constant of 5*S* (*5*). With its function delineated, the 9.5*S* estrophile can be promoted to the status of receptor with all rights and privileges attendant thereto. When a role can be established for the 5*S* estrophile of the nucleus, one may, with clear conscience, speak of "estrogen receptors in target tissues."

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