SERMs, SARMs, and Beyond

The theory and potential of selective receptor modulators

Michael J. McPhaul, M.D.

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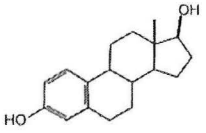

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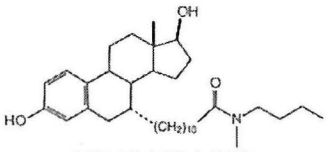

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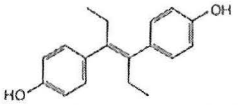

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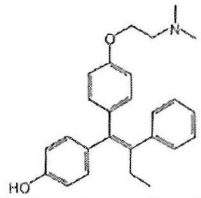

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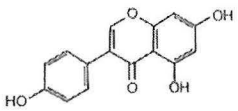

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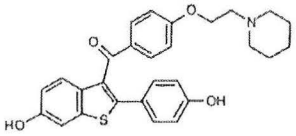

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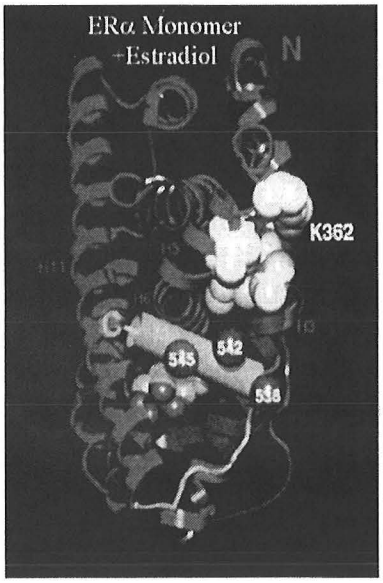

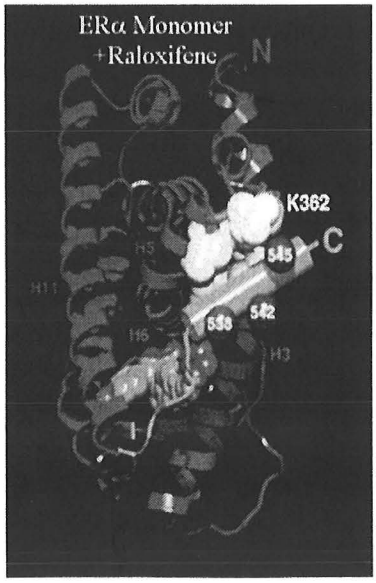

Introduction

In the early 1960s, Jensen conducted experiments that identified moieties in cells and tissues that bound tritiated estrogen with high affinity (62, 63). These experiments had a profound impact on the pace and nature of research in the area of steroid hormone action. The ensuing three and a half decades have witnessed a remarkable explosion in our understanding of how these potent hormones act in cells to mediate a wide range of processes.

In parallel with studies to define the mechanisms of steroid hormone action, the pharmaceutical industry has attempted to harness these insights to develop agents capable of modulating the activity of specific steroid hormone receptors in different tissues and cell types. Although only a limited number of these agents are presently in use in clinical practice, a number of additional agents that selectively target the activities of the estrogen receptor, the androgen receptor, the glucocorticoid receptor, and the progesterone receptor are either in or nearing testing the clinical trials in humans.

The mechanisms by which compounds act to selectively modulate the activity of a nuclear receptor has been most clearly defined for the estrogen receptor. For this reason, the greatest attention in this review has been to describe the reasons that selective estrogen receptor modulators (SERMs) have attracted so much interest and the mechanisms that have been identified to explain the selective activity of these molecules in different cell types. It is anticipated that it will be possible to generalize findings relevant to SERMs and estrogen action to other nuclear receptors.

Estrogens, SERMs, and Women's Health Issues

Research in two distinct areas of women's health has converged to stimulate the profusion of research focusing on the development of the agents that modulate the activity of the estrogen receptor.

First, it has long been recognized that the changes in steroid hormone synthesis by the ovary that take place at the time of menopause have a number of important biological consequences. These have led to a number of observational and controlled trials to attempt to define the benefits that accrue from hormone replacement therapy. These studies have focused on the effects on CV disease, preservation of cognitive function, tumor growth and progression, and maintenance of bone density. Many have engendered considerable controversy. Although Table I summarizes the desirable and undesirable effects of estrogen, as exemplified in the discussion below on 'Estrogens and the Cardiovascular System', even these effects are not uniformly established.

Table I Desirable and Undesirable Effects of Estrogen

•Desirable	•Undesirable
– Suppression of gonadotropin regulation	–Promotion of breast cancer growth
– Preservation of cognitive function	–Increased incidence of endometrial cancer
– Preservation of bone density	–Increased tendency to thrombosis
– Maintenance of secondary sexual characteristics	
–Reduction of CV mortality	

Estrogens and the Cardiovascular System

The risk of coronary artery disease is low in premenopausal women and increases following menopause. Observational studies, such as those from the Framingham Heart study, demonstrated that the risk for cardiovascular events increased in women as they became older (73). Such observations have been paralleled by studies that have suggested reductions in cardiovascular risk in postmenopausal women taking estrogen replacement. The Nurses Health Study has provided considerable information in this area. In the analysis of these latter databases, Grodstein et. al. demonstrated that hormone replacement therapy was associated with a decreased risk of cardiovascular disease in postmenopausal women (52).

Because of the limitations of observational studies, randomized controlled, clinical trials were designed to test the effect of estrogen on cardiovascular risk factors. The first such controlled trial that was conducted of this type was the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial. In this clinical trial, the effect of estrogen replacement (either estrogen alone, estrogen in combination with different progestin preparations, or placebo) was assessed on cardiovascular disease risk factors. The major lessons learned from this trial were that estrogens or estrogens plus progestin were associated with increases in HDL cholesterol levels and reductions in LDL–cholesterol and fibrinogen levels (5). Of note, the magnitude of these changes was somewhat greater in the women who had received estrogen alone, compared to women who had received both estrogen and progestin. Notably, although positive effects were observed on cardiovascular risk factors in this group of individuals, the design and scope of the study did not permit an assessment of overt outcomes expected from these improvements in cardiovascular risk factors.

In contrast to the study results derived from the PEPI trial, the Heart and Estrogen/progestin Replacement Study (HERS) did not demonstrate the improvement in cardiovascular disease outcomes expected on the basis of the

improvements in cardiovascular disease risk factors (e.g. as predicted form the PEPI trial) (60). Instead, the results indicated that women receiving combined hormone replacement therapy did not show a reduction in the risk of myocardial function (fatal or non-fatal). This is despite the fact that there appeared to be a trend toward the appearance of increased cardiovascular events in the treatment group (in year 1) and a reduction in events occurring subsequently (at year 3). As a result, at the present time we are confronted with an apparent discrepancy. Although estrogen administration appears to be associated with improvements in objective cardiovascular risk factors, in a randomized trial examining primary prevention of coronary artery disease no clear cut beneficial effects were observed. It is hoped that the results of the Women's Health Initiative randomized trial (WHI) will serve to answer several of these apparent contradictions (7).

Estrogens and Breast Cancer

Second, are the observations that have led to the development of agents capable of interfering with the action of estrogens in the breast. Although Tamoxifen was initially approved for use as an adjuvant chemotherapeutic agent in women with breast cancer, more recent applications have extended its use to groups of women at high risk for the development of breast cancer. The results of trials using this agent have shown remarkable effects on the incidence of clinical breast cancer, and have led to a consideration of the use of such agents in broader populations. Unfortunately, this agent possesses unfavorable properties, including the accentuation of vasomotor symptoms and the tendency, at least in some trials to the stimulation of the uterine endometrium. These latter properties have led to attempts to develop selective agents that preserve the favorable qualities (inhibition of breast stimulation) while ameliorating the unfavorable aspects of the profile.

Conclusions

Characteristics of the Optimal SERM

– Suppression of gonadotropin regulation (hot flashes)
– Maintenance of secondary sexual characteristics
– Preservation of cognitive function
– Preservation of bone density

– Inhibition of breast cancer growth
– Inhibition (or neutral) of endometrial cancer
– No increased tendency to thrombosis

These considerations have led to the formulation of a list of identifiable properties the serve as a guide to the development of agents that have the

characteristics of the 'optimal' SERM. Such an agent would reduce the symptoms of vasomotor instability, reduce the risks of breast and uterine cancer, and have beneficial effects on the CNS and CV function.

Emergence and evolution of the concept of Selective Estrogen Receptor Modulators (SERMs)

Early studies of triphenyletheylene derivatives demonstrated that members of this class were capable of serving to antagonize the action of estrogen in several target tissues. Subsequent analyses demonstrated that depending on the setting, selected molecules could act as agonists.

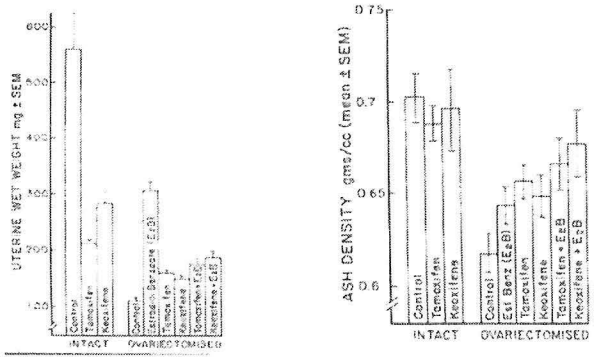

Figure 1 Triphenylethylene ER antagonists exhibit properties of estrogen receptor agonists and antagonists, depending on the gonadal status and tissue in which the assays are conducted.

How are the Effects of Estrogens Mediated?

The mechanisms by which estrogen controls the responses of responsive tissues and cells has been the subject of intense interest for decades. The identification of specific estrogen binding substances in cells was quickly followed by the identification of a series of 'transformations' that followed the binding of estrogen by the estrogen receptor. These insights, while important, were principally descriptive in nature. Although considerable information accumulated regarding the physical nature of these estrogen binding complexes and the global processes (such as RNA and protein synthesis) that these changes controlled, the nature of the events leading to these changes were completely uncharacterized.

The cloning of cDNAs encoding the human estrogen and glucocorticoid receptors began a revolution in the understanding of steroid hormone structure and function (21). These investigations lead to several important innovations. First was the capability to manipulate and modify the structure of the products encoded by the cDNAs encoding the receptor proteins. This lead to the identification of discrete modular domains within the receptor proteins necessary and sufficient for the high affinity binding of ligand (ligand or hormone binding

domains [LBD or HBD, respectively]) and the recognition of DNA sequences (DNA binding domains [DBD]) by the receptor protein. Second, it became obvious that within the human genome numerous genes existed which shared similarities to members of the steroid receptor family (38, 74). This resemblance was particularly striking for the region encoding the DNA binding domains of the receptor proteins. This segment is highly conserved among different members of the receptor family. Third, was the recognition that these cDNAs could be used in combination with "reporter genes" to directly measure the activity of these proteins when expressed in target cells. Thus, for the first time, assays could be performed in selective cell types to analyze the activities of molecules to regulate the activity of members of the nuclear receptor family. This methodology stands in stark contrast to decades of research conducted in the pharmaceutical industry in which compounds were analyzed only using ligand binding and bioassays to measure drug activity.

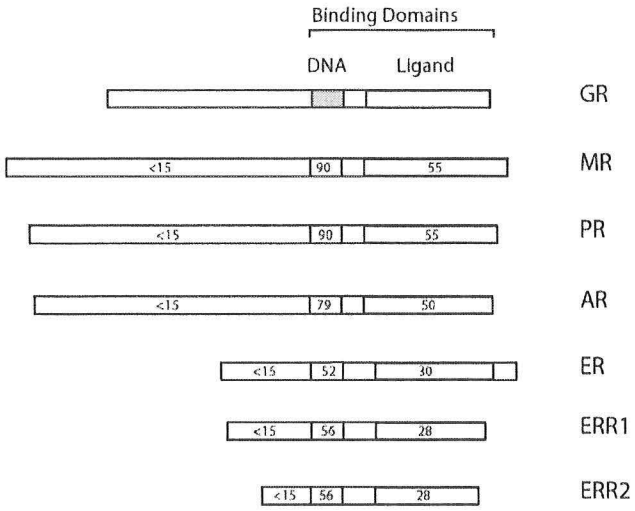

Figure 2 The nuclear receptors are a large gene family that share structural features in conserved regions of the receptor proteins. This family includes receptors encoding all of the steroid receptors, as well as the receptors for thyroid hormone, vitamin D, and retinoic acid. In addition, this family contains members for which no ligand is known (orphan receptors).

Clues as to the mechanisms by which nuclear receptors might serve to modulate the activity of gene transcription emerged from studies directed in understanding the mechanisms by which RNA polymerase was regulated. These experiments conducted in broken cell assays demonstrated that the confirmation of proteins present at the sites of active genes were critical to the recruitment and activity of RNA polymerase 2 which directly controls the rates of RNA synthesis. These insights lead to attempts in a number of laboratories to identify proteins that interacted with members of the nuclear receptor family. Ultimately these experiments lead to the description of two major classes of regulatory proteins: the nuclear receptor coactivators and nuclear receptor corepressors.

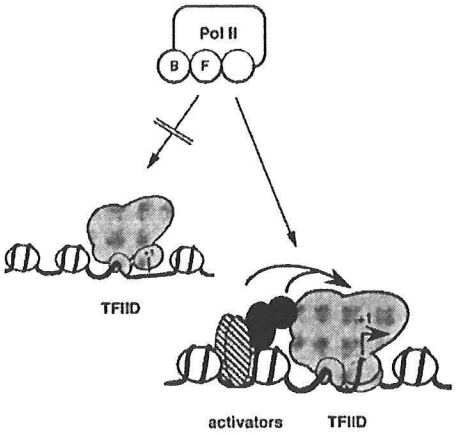

Figure 3 Concepts emerging from the study of eukaryotic transcription led to the recognition that the recruitment and stabilization of RNA polymerase II (Pol II) containing complexes a central determinant of the rate of gene transcription. This recognition led to attempts to identify proteins that interact with members of the nuclear receptor family. These efforts led to the cloning of proteins capable of augmenting (coactivator) or repressing (corepressor) gene activity.

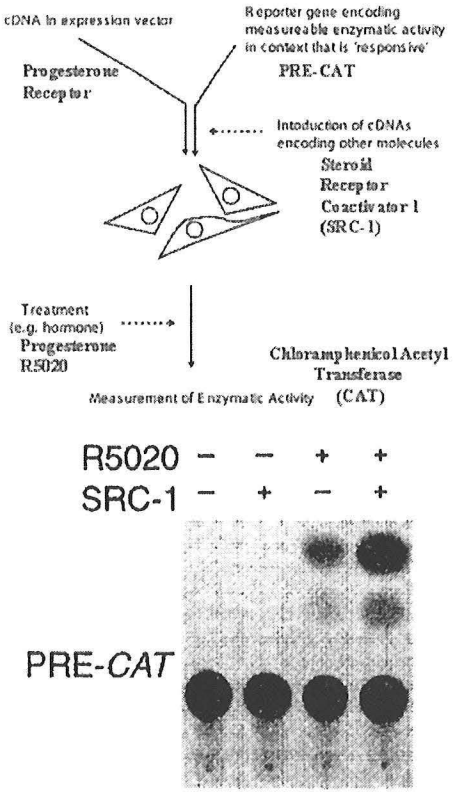

Figure 4 The steroid receptor coactivator, SRC 1, acts to augment the activity of the progesterone receptor. The design and results of experiment to demonstrate this is depicted (adapted from reference 93).

The first of these types of molecules to be carefully characterized with the steroid receptor coactivator 1 described in the laboratory of Dr. Bert O'Malley (93). This protein was identified on the basis of its ability to interact with the progesterone receptor following the binding of progestin agonist. The consequences of the expression of this protein on progesterone receptor function and is displayed in Figure 4. The net result of this interaction is to augment and potentiate the effect of the liganded progesterone receptor on the activity of a model reporter gene (in this case PRE-CAT). A large number of additional proteins as now been described that serve as coactivators for different members of the nuclear receptor family, including the estrogen receptor.

In parallel with experiments to define proteins capable of potentiating the effect of members of the nuclear receptor family, experiments were conducted to identify proteins that inhibit nuclear receptor activity in functional assays. These studies have led to the identification of a number of proteins that serve as nuclear receptor corepressors. These proteins are responsible for recruiting enzymatic activity to the sites of gene transcription that serve to repress gene activity.

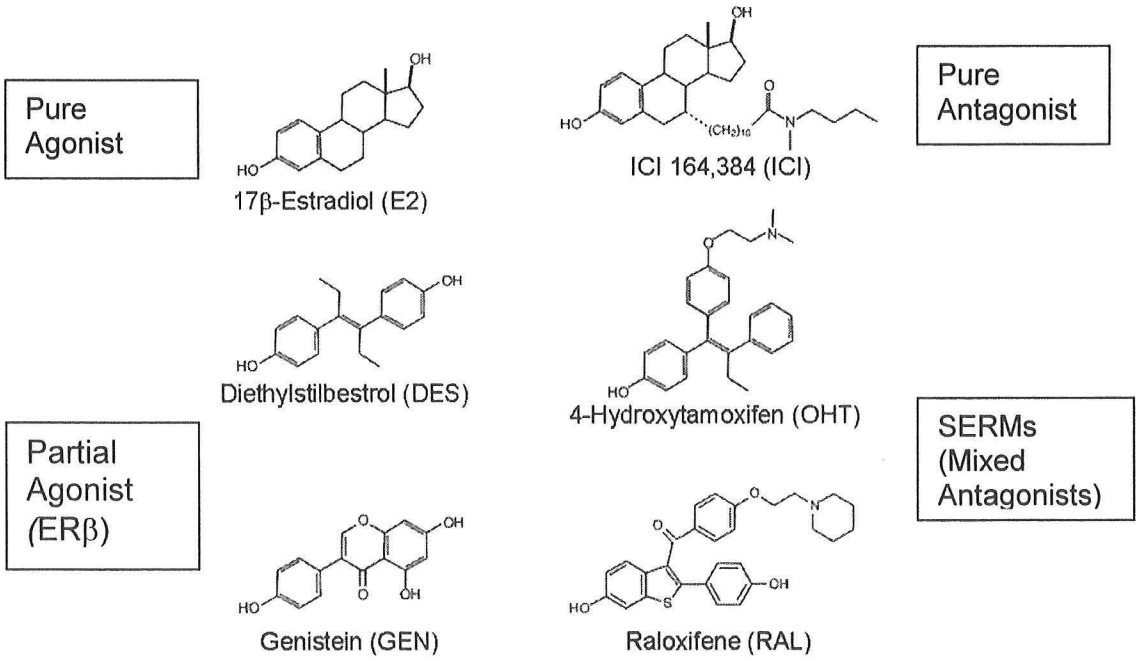

Figure 5 Ligands displaying varying degrees of agonism and antagonism of ER function. 4-hydroxytamoxifen and Raloxifene are mixed antagonists of ER function, while ICI 164,384 is a pure ER antagonist.

Studies over a number of years have identified a variety of molecules that exhibit varying degrees of antagonism or agonism. Several of these compounds are depicted in Figure 5. All of these molecules had been shown to possess biological activity either in cell transfection assays or in bile assays. Each is also of capable interfering with ligand binding by the estrogen receptor proteins.

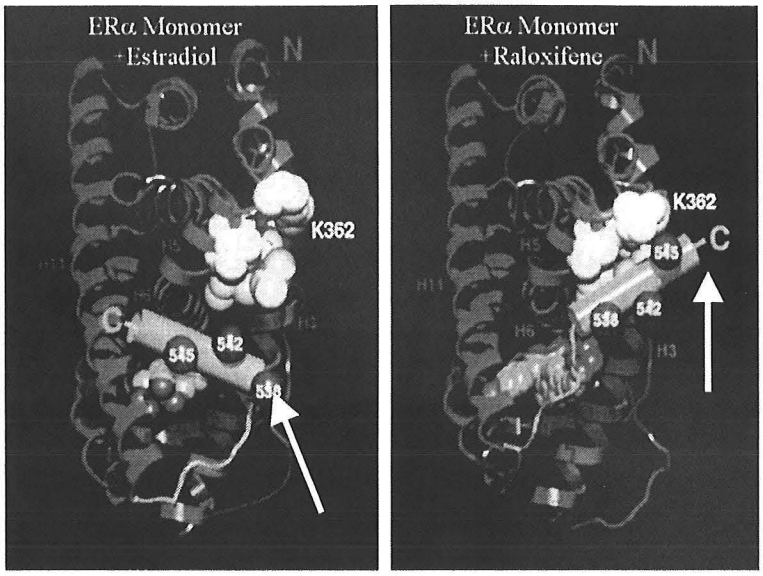

Figure 6 The activity of a compound as an ER agonist or antagonist is dictated by the shape that the ER LBD assumes after ligand binding. The position of the terminal helix of the LBD (H12, white arrow) assumes distinct conformations when bound to estradiol (left) or Raloxifene (right). The position of this helix permits the recruitment of coactivators, such as SRC-1, leading to and increase of gene activity. In the antagonist-bound conformation (right), this recruitment site is not available (from reference 22).

How these molecules were capable of modifying the activity of the estrogen receptor(s) remained unclear until publications analyzing the crystal structures of the estrogen receptor α complexed to an agonist (estradiol) and Raloxifene, an ER antagonist (22). These crystal structures revealed for the first time the physical nature of the difference in the binding of ligands that led to the different biological properties of the receptor molecule. Specifically, these studies demonstrated that the shape of the ligand molecule (estradiol versus Raloxifene) determined whether or not the terminal segment of the ligand-binding domain was able to assume a conformation that was capable of recruiting coactivator proteins to augment the activity of estrogen receptor responsive genes. Subsequent analyses the crystal structures of a variety of ligand bound receptors derived from various segments of the nuclear receptor family are consistent with the concept that the position of this terminal helix is largely responsible for whether the nuclear receptor protein is capable of recruiting coactivator proteins (and increasing gene transcription) or recruiting corepressor proteins (and decreasing rates of gene transcription). These ideas are summarized in Figure 6. It should be pointed out, however, that the perceptions emerging from these crystal structures are of static and unchanging conformations. It appears quite likely that the conformations of these proteins are in fact quite dynamic. The actual conformation of a steroid receptor (such as the ER) complexed to a specific ligand may be an 'average' of several different conformations each with a inherent tendency to recruit coactivator or corepressor proteins.

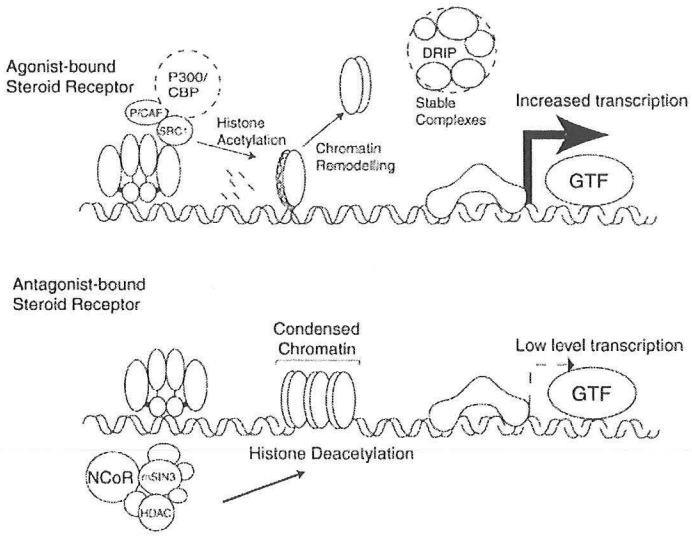

Figure 7 Models for the mechanisms by which the activity of steroid receptors is modulated differentially following the binding of agonists and antagonists.

It is clear from the aforementioned discussion that considerable opportunities exist to explain diversify effects of estrogen on the regulation of gene expression and cellular processes. Several additional potential levels at which such diversity can emerge revolve around the nature of the receptors that bind estrogen and the transformation events leading to the synthesis and degradation of estrogen.

For approximately 30 years, the scientific community perceived that a single receptor protein transduced estrogen signals. Despite a large body of such information, in 1996 the group of Jan-Ake Gustafsson published a report identifying a second distinct receptor protein for estrogen: ER-beta (67). Although sharing a large degree of homology, the tissue levels of distributions and binding specificities of the two proteins were shown to be distinctive.

This situation became even more complex when the group of Giguere identified three proteins related to the action receptor alpha (ERR alpha, ERR beta, ERR gamma) as members of the nuclear receptor family that were capable of being regulated by estrogenic compounds, specifically DES and 4 hydroxy tamoxifen (123, 128). Although the activities and regulation of these proteins by such estrogenic compounds has already been clearly established, it is not yet clear what the relevance of estrogenic regulation of the ERR proteins is to the regulation of gene expression in the context of SERMs.

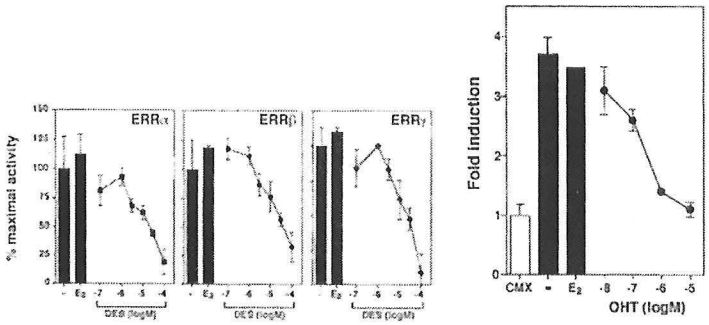

Figure 8 Regulation of members of the ERR family by the estrogenic molecules diethylstilbestrol (DES, left) and 4-hydroxytamoxifen (right)

How do the Mechanisms of Diversity in Estrogen Signaling Explain the Actions of SERMs?

The above insights into the action of nuclear receptors (in general) and the estrogen receptor (in particular) led to a model in which the diversity of the effects of an estrogenic ligand in a particular cell or tissue was postulated to reflect the balance between the molecule (coactivators and corepressors) present in a particular cell that are recruited to a set of estrogen-responsive genes. In this model, variations in the responsiveness of a particular gene might vary considerably, depending on the complement of proteins present to be recruited. In fact, this particular idea had been demonstrated in early experiments using transfection assays (102) These finding have been elegantly confirmed in more native and physiologically relevant contexts by the group of Myles Brown (98).

Selective Androgen Receptor Modulators (SARMS)

Introduction

In contrast to the clear-cut indication that exist for the development of the agents that selectively modify the activity of the estrogen receptor, indications for the development of molecules that selectively modify the activities of androgen receptor in specific tissues and cell types is less clear.

The availability of an agent that can be utilized the treatment of androgen replacement in patients with androgen deficiency caused by either primary or secondary causes are clear. Beyond this clear-cut indication, a number of additional indications are possible. In a subset of men, the decline of testosterone production by the testes is believed to contribute to the diminished muscle mass, increased adiposity, and increased frailty that can be observed in aging men. In addition, androgens had been proposed for use as anabolic agents in a number of wasting diseases.

In contrast to the desired effects of androgen action in individuals with wasting disease, substantial concerns center on the potential that such agents might have in the stimulation of prostate growth leading potentially to the development or progression of prostate cancer or benign prostatic hypertrophy. Such concerns may well be accentuated or mitigated by the results of a large-scale Finasteride trial which is currently under way (20).

Table III Desired Profile of Activity of Potential SARMS

Tissue/Parameter		Indications
	Hypogonadism	Selected indications
Prostate	Stimulatory, but less than DHT	Weak or neutral
Libido	Stimulatory	Stimulatory/Neutral
Gonadotropin Inhibition	Present	Absent/Reduced
Hair Growth	Stimulatory	Neutral
Bone Growth	Stimulatory	Stimulatory
Muscle	Stimulatory	Stimulatory
Fat-free Mass	Increase	Increase
Lipids/CV risk	Neutral	Neutral
Blood Pressure	Neutral	Neutral
Erythropoesis	Weak Stimulatory	Stimulatory
Liver functions	Neutral	Neutral
Breast	Neutral	Neutral

Adapted from Negro-Vilar, 1999

Indications that SARMs are feasible

7 alpha-methyl-19-nortestosterone (MENT)

In much the way that the studies of the properties of Tamoxifen led to the discovery that molecules could preferentially modulate the activity of the estrogen receptor, studies of molecules designed in other areas related to androgen action led to the recognition that selective modulation of androgen receptor function was possible as well. One such agent is 7α-methyl-19-nortestosterone (MENT). This agent was originally developed in testing to identify agents capable of acting as

male contraceptives. Subsequent studies demonstrated that this agent exhibited differential potency when assayed in different tissues. One example of the differential activities observed in monkeys is shown is Figure 9. In these experiments, castrate monkeys were placed with varying doses of either testosterone or MENT delivered by continuous infusion pumps. Although a number of different parameters were assessed in these studies, two representative and contrasting results are depicted. As is evident from the left side of the panel, MENT infusion exerts an effect that is more potent than that of testosterone (compare 0.3 mg/d in the two left panels). By contrast, when prostate growth was assessed using MRI measurements of prostate volume, MENT can be seen to have an effect that is at least three-fold less effective compared to testosterone replacement (compare MENT at 0.1mg/d to testosterone at 0.3mg/d). Parallel assessments of anabolic activity (total body weight) and lipid profiles demonstrated that MENT had a potency 10-12 times that of testosterone. Taken together, these experiments demonstrate that replacement with MENT in castrate monkeys uncover the differential action of this compound in different tissues. These findings have provided impetus to the studies conducted in the pharmaceutical industry to identify molecules capable of modulating the activity of the androgen receptor differentially in different tissues.

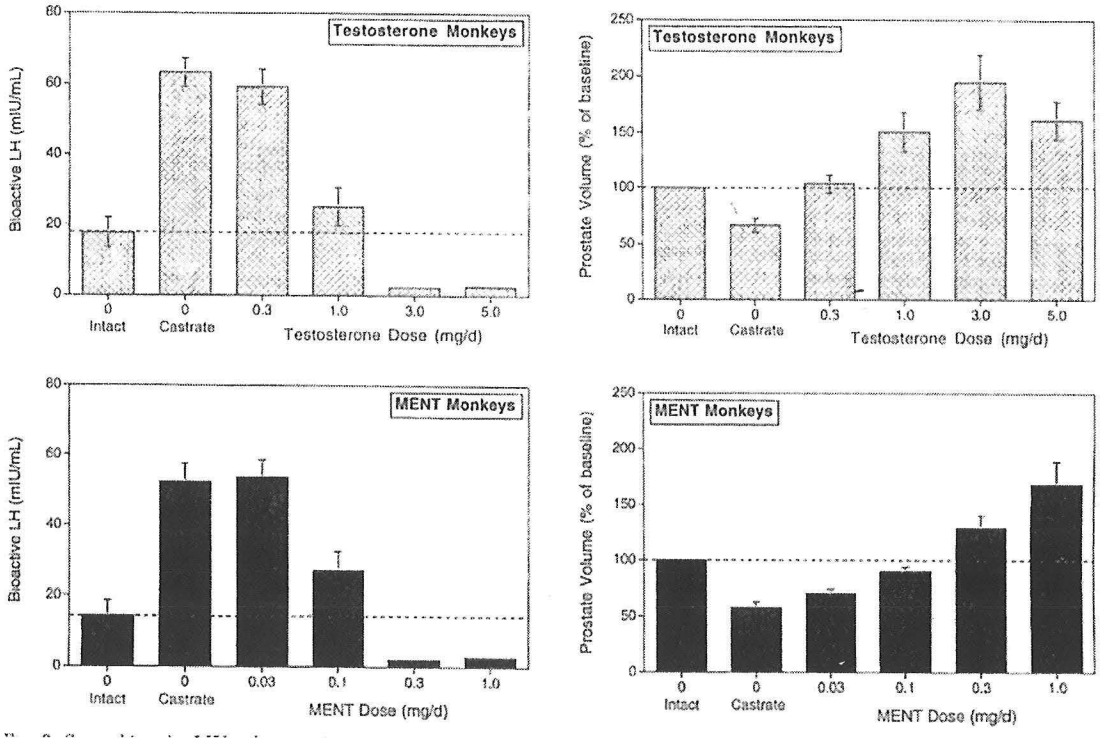

Figure 9 Castrate monkeys were replaced with varying quantities of MENT or testosterone and the effects on LH levels (left) or prostate volume (right) were measured.

Designer SARMs

At present several pharmaceutical companies have attempted to develop agents that display selective activities using *in vitro* or cell-based models of androgen action. Most of these results are still derived from animal-based studies, but movement into human-based clinical trials is likely in the near future.

The compound Andarine, presently under development, displays activities similar to those of testosterone when assessments are made in the action on the levator ani muscle, an androgen-responsive muscle in the rat. Despite equipotency to testosterone in this anabolic model, the same dosing of this compound shows substantially reduced effect in measurements of action in the maintenance of prostate growth. The mechanisms by which these selective results are achieved have not been defined. Despite this lack of insight at the mechanistic level, it is quite clear that in these selected assays a considerable separation has been achieved between the activities measuring anabolic activity, compared to those measuring the effects of these compounds on prostatic growth.

Taken together, these findings represent a "Proof of Principle" that compounds exhibiting the properties of selective androgen receptor modulators are in fact possible.

Future Directions

A considerable amount of information is now available regarding the mechanisms and properties of SERMs. Much of the information relating to the effects and activities of the SERMs that are presently available are in only the earliest stages. A number of large-scale clinical trials are in progress to study the effects of these compounds. The results of the studies will give important direction in how they should be applied in pre and postmenopausal women.

The state of knowledge is even more rudimentary when it comes to molecules capable of selectively altering the activities of other members of the nuclear receptor family. *In vitro* and limited *in vivo* studies suggest that compounds capable of selectively altering the activity of the androgen receptor are possible. Compounds of this type have been developed using cell-based pharmaceutical assays, and several are nearing testing in humans.

In like fashion, agents have been identified that selectively modify the activity of the progesterone and glucocorticoid receptors in specific tissues. Most of these compounds have only been described in the most basic fashion and are likely to be several years away from testing in humans. Nonetheless, it is useful to consider that the nuclear receptor family is one of the largest families of transcriptional activators in the human genome. Its members play critical roles in the regulation of a number of important developmental and homeostatic

processes. It seems quite likely that the insights that have been gained and the progress that has been made in the selective regulation of the estrogen receptor will not be unique. As such, the definition of biologically important end points and functionally workable assays are likely to be the only impediments in the identification of drugs are capable of selectively modifying the activity of any member of the nuclear receptor family.

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