COMMENTARY

Selective Androgen Receptor Modulators (SARMs): A Novel Approach to Androgen Therapy for the New Millennium

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Androgen therapy, using injectable, oral and more recently, transdermal preparations, has been available to physicians for many years to treat a variety of male disorders; to a lesser degree, their use has been extended to some female indications. Unlike female sex hormone therapies, which have found extensive use and applications in the fields of hormone replacement, reproductive disorders, gynecological cancers, and contraception, androgen therapy has not been widespread.

A more widely accepted use of androgen therapy has been hampered by the lack of orally active preparations with good efficacy and, particularly, a safe profile. Progress has been limited over the last three decades in developing synthetic molecules that could separate androgenic activities considered desirable (i.e., anabolic) from others that were undesirable or had dose-limiting side effects (1). The abuse of synthetic anabolic steroids by athletes and body builders has contributed to the general perception of certain negative side effects (1). The abuse of synthetic anabolic steroids by athletes and body builders has contributed to the general perception of certain negative side effects.

Recent advances clearly indicate that androgen therapy is about to experience a fundamental change, both in the extent of use and in the range of applications that may benefit from these upcoming advances. Several factors have and will continue to contribute to this change. First, the significant advances of hormone replacement therapy (HRT) in postmenopausal females and the expansion and application of HRT to treat and prevent major disorders such as osteoporosis, cardiovascular disease, breast cancer, mood and cognition, among others, have clearly established the value of novel HRT therapies for improving women’s health (2–4), and by extrapolation, they clearly point out the potential for similar approaches to address men’s health disorders. Second, the development and marketing of novel selective estrogen receptor modulators (SERMs) has provided both preclinical and clinical proof-of-concept that we can develop molecules with a great degree of tissue selectivity targeting the estrogen receptor to eliminate undesired side effects and to maintain (and in the future to enhance) the positive, protective effects of selective transcriptional receptor activation (3–7). Third, significant advances in our understanding of nuclear receptor activation and function have provided the molecular underpinnings for new drug development efforts to design and bring forward a new generation of tissue-selective molecules targeting steroid and other nuclear receptors. Proof-of-concept for tissue selectivity has now been extended to many compounds interacting with different nuclear receptors, such as the estrogen (ER), progesterone (PR), androgen (AR), retinoid (RAR/RXR), and peroxisome proliferation activated receptors (PPARs), among others (6–11).

With the information described above, we have been able to chart a development path and create a profile of desired activity and selective indications for a new class of molecules targeting the androgen receptor. We have chosen the term selective androgen receptor modulators (SARMs) after the terminology currently used for similar molecules targeting steroid and other nuclear receptors. Below we briefly describe the molecular mechanisms underlying the potential for selective modulation of AR by different ligands and the opportunities that novel SARMs bring to therapies for broad, as well as selective, uses of androgen therapy, in men as well as in women.

Molecular Advances in AR Structure and Function: A Key to Unlocking Tissue Selectivity

The AR is a transcription factor and a member of the extended family of nuclear receptors. As such, it shares significant homology in terms of structure with the other members of the family, including specific protein subdomains that either activate or repress gene activity. Current evidence indicates that these activation domains represent surfaces in the receptor that are induced or exposed upon hormone or ligand-binding in such a manner that they facilitate the interaction of the specific domain or surface with selected proteins named coactivators or corepressors (5, 12). These proteins are part of an expanding family of molecules, and several have been found to bind directly to AR, namely CBP/p300 (13), GRIP1 (14), ARA 54,55 and 70 (15, 16), and Tip60 (17). Each selective ligand, upon binding to the recep-

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tor, may drive it into a distinct conformation that exposes activation or interaction surfaces resulting in recruitment of specific cofactors as revealed by structural studies (12). In addition, tissue expression or relative concentration of different cofactors may vary. Recently, a testis-specific cofactor, ARIP-3, has been described (18) that modulates AR-dependent transcriptional activity. Motif-driven interactions have been described that can modify the affinity of a given cofactor for a nuclear receptor. These motifs, termed nuclear boxes, are contained within distinct segments of conserved sequences in the ligand-binding domain.

The AR is widely distributed among reproductive and nonreproductive tissues, including the prostate and seminal vesicles, male and female external genitalia, skin, testis, ovary, cartilage, sebaceous glands, hair follicles, sweat glands, cardiac muscle, skeletal muscle and smooth muscle, gastrointestinal vesicular cells, thyroid follicular cells, adrenal cortex, liver, pineal, and numerous brain cortical and subcortical regions, including spinal motor neurons. This wide distribution of the receptor needs to be mapped with the particular type and concentration of cofactors that are present in each tissue and cell type. This will provide a more accurate picture of the potential nuclear receptor complex that can be assembled in each case after ligand activation. Availability of this information will help define the types of responses that different SARMs may elicit in a particular tissue.

These multiple mechanisms contribute to the combinatorial recruitment and activity of coactivators and corepressors to provide selective regulation of individual genes in specific tissues by the AR. Because different ligands can provide a myriad of different combinatorial regulations of transcription in different tissues and cells, development of SARMs with intrinsic partial agonist activity offers a unique opportunity to develop new therapeutic agents with distinct activity profiles.

Recently, a novel family of nonsteroidal molecules has been identified with selectivity and specificity for the AR (9, 19). Using molecular screening approaches targeting the transcriptional activation of the human AR, combined with discriminatory cellular assays and medicinal chemistry structure-activity efforts, several series of distinct molecules have been synthesized that possess agonist, agonist, or partial-agonist activity. The latter represent a unique group of molecules that provide the needed diversity of ligands to fully explore the utility and activities of SARMs.

The different series of molecules contain individual members that display selective preferences for certain tissues or activities (i.e., trophic in muscle, strong or very weak gonadotropin feedback) and widely diverse ratios of activity in sex accessory tissues (prostate, seminal vesicles) vs. other peripheral (i.e., muscle) or central nervous system responses. Therefore, groups of molecules are identified that provide a range of activities, from full agonist to partial agonist with distinct tissue selectivity and unique therapeutic potential.

The role of SARMs in androgen therapy and the distinct clinical applications for which they may be targeted are discussed below.

Role of SARMs in Androgen Therapy for Men

Currently used androgenic formulations for replacement therapy are largely restricted to injectable or skin delivery formulations of testosterone or testosterone esters. Marketed injectable forms of testosterone esters (such as testosterone enanthate, propionate, or cypionate) produce undesirable fluctuations in testosterone blood levels, with supraphysiological concentrations early, and subnormal levels towards the end of the period before the next injection, providing an unsatisfactory profile and in some cases undesired side effects. Skin patches do provide a better blood level profile of testosterone, but skin irritation and daily application still limit the usefulness and acceptability of this form of therapy (1, 20–22). Oral preparations such as fluoxymesterone and 17α-methyltestosterone are not currently used due to concerns about liver toxicity linked to the 17α-alkyl group and because of somewhat lower efficacy. Thus, these compounds are considered obsolete (1, 20) and do not represent a viable form of therapy.

The discovery and development of SARMs provides the opportunity to design molecules that are not only orally active, but that target AR in different tissues to elicit the desired activity for each of the key indications benefiting from androgen therapy. The desired activity profile of novel SARMs is described in Table 1. For simplicity, we have listed the desired activity in tissues or specific parameters for one specific indication (i.e., male hypogonadism) side by side with a category for selected indications. The latter provides a menu of choices for the design of molecules that can address very specific needs in the treatment of different disorders. Thus, we envision that an ideal SARM for the treatment of primary or secondary male hypogonadism (Table 1) would have the following profile: orally active, ideally with a pharmacokinetic profile consistent with once a day administration, capable of stimulating prostate, seminal vesicles, and other sex accessory tissues at doses equipotent to those needed to provide increases in muscle mass and strength and fat-free mass, support bone growth, and maintain/restore libido, virilization, and male habitus. Unlike testosterone which, when converted to DHT in the prostate has an enhanced proliferative activity in relation to other peripheral tissues, these SARMs are not substrates for 5α-reductase activity, nor do they affect the activity of the enzyme. Other activities that are considered undesirable should be diminished or eliminated, such as potential liver toxicity, blood pressure effects and fluid retention, induction of gynecomastia, and overstimulation of erythropoiesis. On the other hand, use of SARMs for selected indications provides the rationale for developing molecules with distinct tissue specificity. For example, if the target is bone growth in elderly men with osteopenia or osteoporosis, but with no overt signs of hypogonadism, a more anabolic SARM with clear effects on bone and muscle, but lesser activity on prostate or other sex accessory tissues would be more desirable.

The potential use of androgen therapy utilizing SARMs clearly expands well beyond primary or secondary hypogonadism and into areas including, but not limited to, osteopenia and osteoporosis in elderly men (23, 24), glucocorticoid-induced osteoporosis (23), HIV wasting and cancer cachexia...
The Role of SARMs in Androgen Therapy for Women

If the use of androgens for men has been limited because of the type of preparations available and because of some safety concerns, the application of androgen therapy to women’s health has been hampered by additional factors, namely:

1. The lack of preparations adequately dosed and formulated for use in women;
2. The undesired effects of androgens, such as virilizing effects, that limit their use in many situations; and
3. Perhaps most important, the lack of well controlled, carefully designed studies in women to fully evaluate the potential of androgen therapy for selected indications that validate the many anecdotal or fragmentary reports advocating beneficial effects of androgens in a variety of conditions.

Some recent reviews have covered these issues well (26, 27), clearly outlining the potential benefits of androgen therapy in women, as well as the areas where additional information is needed. We have detailed in Table 2 the desired profile that a SARM should have to represent a novel, attractive approach for hormone replacement therapy in postmenopausal women or for other selected indications. In agreement with Davis and Burger (25, 26), we envision that a SARM for women should be able to enhance or stimulate libido and those parameters of sexuality that androgens can influence alone or in combination with estrogen replacement. This SARM should also provide additional bone protection and/or bone promoting activity, should enhance muscle mass/fat-free mass, and should be free of key side effects, such as virilization and negative impact on lipids (particularly in those parameters such as high- and low-density lipid proteins) that are beneficially affected by estrogens, and should be otherwise clean in terms of liver function.

SARMs for selected indications should provide positive activity in those parameters that are key for a given indication. There are a number of selective indications for androgen therapy in women where SARMs can offer a significant advantage over existing therapies. Among those we list, glucocorticoid-induced osteoporosis, postmenopausal osteoporosis, in conjunction with estrogen therapy, or alone in those cases where estrogens are contraindicated, HIV, or cancer wasting, premature ovarian failure, autoimmune disease in combination with anti-inflammatory regimens, or certain anemias.

Targeting these disorders as primary indications for treating women with SARMs will allow the design of molecules that have the desired profile, dosing, and formulation as well as the supportive clinical data to highlight the advantages of these therapies for addressing women’s health needs.

References

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