Nonsteroidal Selective Androgen Receptors Modulators (SARMs): Designer Androgens with Flexible Structures Provide Clinical Promise

Androgens play an essential role in differentiation and growth of the male reproductive tract, pubertal maturation and development of secondary male sex characteristics, initiation and regulation of spermatogenesis, and male sexual behavior (1). Steroidal androgens increase muscle mass, bone mass, and strength; stimulate male pattern baldness; and alter serum lipid profiles and fat distribution (2). Testosterone (T), synthesized and secreted by the testes, and its more potent 5α-reduced metabolite, dihydrotestosterone (DHT), are the principal biologically active endogenous androgens. T and DHT exert tissue-specific biological effects. For example, T functions to stimulate muscle mass, sexual development, and spermatogenesis, whereas DHT plays critical roles in facial and body hair growth, acne, and prostatic enlargement. The actions of both T and DHT are mediated by the intracellular androgen receptor (AR), a member of the nuclear receptor superfamily of ligand-activated transcription factors (3, 4). Upon binding of T or DHT, AR undergoes a conformational change, binds to specific DNA sequences termed androgen response elements, forms complexes with nuclear coregulatory factors, and modulates the transcription of target genes. For decades, AR has been a target for drug development focused upon the treatment of pathological conditions arising from abnormal androgen levels or altered target tissue responsiveness, the improvement of physical performance, and the regulation of male fertility.

The primary focus for drug design has been the synthesis of chemicals to regulate the transcriptional activity of AR based upon the structural, steroidal or nonsteroidal, and functional androgenic, antiandrogenic, or anabolic properties of ligands. Steroidal androgens, represented by various chemical derivatives of T, have been used clinically to treat a variety of male and female disorders resulting from androgen deficiency (5, 6). The principal clinical indication for androgens is as replacement therapy in hypogonadal men. Androgens have also been used clinically for the treatment of delayed puberty in boys, anemia, primary osteoporosis, hereditary angioneurotic edema, endometriosis, and muscle diseases and wasting. More recently, androgens have been used as hormone replacement therapy in aging men and for regulation of male fertility. The use and abuse of androgens as anabolic agents to enhance physical performance and endurance has been highlighted recently among world-class athletes participating in the Olympic games, as well as among adolescents seeking athletic achievement. Antiandrogens are used to counteract the undesirable actions of excessive androgens to treat acne, hirsutism, and male pattern baldness and to prevent androgen stimulation of prostatic hyperplasia and carcinoma. Nonsteroidal antiandrogens (Fig. 1), such as flutamide (Eulexin; Schering, Kenilworth, NJ), nilutamide (Anandron; Aventis, Kansas City, MO), and bicalutamide (Casodex; AstraZeneca, Wilmington, DE), are referred to as pure antiandrogens because they bind exclusively to AR and thus are devoid of antigonadotropic, anti-estrogenic, and progestational effects (7). These agents have advantages over steroidal antiandrogens such as megestrol acetate or cyproterone acetate in terms of specificity, selectivity, and pharmacokinetic properties.

Whereas nonsteroidal antiandrogens have been used clinically for many years, nonsteroidal androgens have only recently been conceptualized. Better receptor selectivity of nonsteroidal ligands has been achieved from the flexibility by which structural modifications can be used to optimize their physicochemical, pharmacokinetic, and pharmacological properties. As recently demonstrated for the growing class of selective estrogen receptor modulators (SERMs) that includes tamoxifen and raloxifene, these nonsteroidal ligands demonstrate tissue-selective actions and diverse activity profiles that serve specific therapeutic needs (8). In this issue of Endocrinology, Gao et al. (9) report on their continuing progress toward the synthesis, development, and evaluation of nonsteroidal selective androgen receptor modulators (SARMs). Interestingly, this group of investigators has discovered a series of novel derivatives of the nonsteroidal antiandrogens, hydroxyflutamide and bicalutamide, that act as nonsteroidal androgens (10–13). These efforts complement previous reports by other groups describing 2-quinoine, coumarin, and phthalimide analogs that can be converted to AR antagonists or agonists (14–17). These nonsteroidal compounds mark the emergence of a novel category of pharmacological agents with potential applications in androgen therapy. The discovery of nonsteroidal androgens not only provides an opportunity to identify agents with superior therapeutic index and pharmacokinetic profiles compared with steroidal androgens but also presents the reality that tissue-selective ARMs can be effectively developed (18, 19).

The current report by Gao et al. (9) describes the tissue selectivity in intact male rats of two SARMs, designated S1 and S4, that behave as partial agonists in androgen-responsive tissues, such as prostate and seminal vesicles, but full agonists in anabolic tissues such as the levator ani muscle (12). Both S1 and S4 bind with high affinity to AR, with dissociation constant of the ligand inhibitor-receptor complex (Ki) values of 6.1 and 4.0.

Abbreviations: AR, Androgen receptor; DHT, dihydrotestosterone; Ki, dissociation constant of the ligand inhibitor-receptor complex; SARM, selective androgen receptor modulator; T, testosterone.
compared with T propionate. As reported by Gao et al., the efficacy of S1 and S4 in prostate were 12 and 29%, respectively, with partial agonist activity in levator ani muscle but only partial agonist activity in prostate. The relative rates of efficacy of S1 and S4 in prostate were 12 and 29%, respectively, compared with T propionate. As reported by Gao et al. (9) for intact male rats, S1 selectively decreased prostate weight with efficacy similar to that of the 5α-reductase inhibitor finasteride without affecting the levator ani muscle or altering the plasma levels of T, LH, or FSH. By contrast, hydroxyflutamide decreased both the prostate and levator ani muscle weights without selectivity and increased plasma hormone levels in a dose-dependent fashion. Neither S1 nor S4 affected 5α-reductase type I or II isozyme activities. These results show that S1 and S4 act as partial AR agonists with tissue-selective activity that suppresses androgen-dependent prostate growth without influencing the anabolic effects of T on weight of the levator ani muscle. Moreover, the maintenance of normal serum T levels and lack of effect of S1 and S4 on pituitary gonadotropin secretion further exemplify the tissue selectivity of their action.

The derivation of S1 and S4 is based on earlier studies by this group of investigators that focused upon key structural elements previously determined to be important for AR binding of nonsteroidal ligands, such as bicalutamide and hydroxyflutamide (20, 21). In their evaluation of structure-activity relationships for nonsteroidal ligands, AR binding affinity of bicalutamide derivatives was enhanced in the R-isomers defined by the sulfur linkage to the meta-carbon of the B-ring was F (S1), COC₂H₅ (S3), or NHCOCH₃ (S4).

In summary, the novel features of designer androgens may find application in numerous medical situations. The potent anabolic effects on muscle, bone, and mental function may improve the quality of life for those with chronic diseases or for aging men if the potential adverse effects on the cardiovascular system can be divorced. Although the factors that determine tissue selectivity of androgen action remain to be explored, the current report by Gao et al. (9) confirms the critical nature that ligand.
structure plays in regulating AR function in different tissues. The flexibility in design of nonsteroidal AR ligands provides the opportunity to exploit the beneficial effects of androgens while ameliorating their undesirable effects.

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