Inhibition of Androgen Synthesis in Human Testicular and Prostatic Microsomes and in Male Rats by Novel Steroidal Compounds*

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ABSTRACT

The C17,20-lyase and 5α-reductase are key enzymes in the biosynthesis of androgens. The effects of novel steroidal compounds were evaluated as inhibitors against both human C17,20-lyase and 5α-reductase in vitro. The concentrations of testosterone (T) and dihydrotestosterone (DHT) in the prostate, testis and serum and changes in the tissue weights were also determined in rats treated with the novel inhibitors. L-12 and L-26 showed potent inhibition of human testicular C17,20-lyase with IC50 values of 50 and 25 nM, respectively. L-12, L-38, and L-47 showed moderate inhibition of human testicular C17,20-lyase with IC50 values of 75, 108, and 70 nM, respectively similar to ketoconazole (78 nM). Interestingly, L-6, L-26, and L-38 also showed some inhibitory activity against 5α-reductase with IC50 values of 75, 125, and 377 nM, respectively. Finasteride, an inhibitor of 5α-reductase had an IC50 value of 33 nM. However, ketoconazole did not inhibit 5α-reductase nor did finasteride inhibit C17,20-lyase. Treatment of normal male rats with several of these novel inhibitors (50 mg/kg/day, sc, for 14 consecutive days) caused about 45–91% decrease in serum, testicular and prostatic T concentration. Similarly, serum and prostatic DHT concentration were significantly decreased in rats treated with these novel compounds by 50–90% compared with controls. Surgical castration caused almost complete elimination of circulating T and DHT concentration in rat tissues. L-6 and L-12 were the most effective and reduced the wet weight of the prostate by 50%. Although future improvements in their bioavailability are necessary, these novel steroidal compounds show promise as potential agents for reducing T and DHT levels in patients with androgen dependent diseases. (Endocrinology 140: 2891–2897, 1999)
These compounds were demonstrated to be effective dual inhibitors of human testicular C_{17,20} lyase and prostatic 5α-reductase \textit{in vitro} and some also exhibited antiandrogenic activity. In animal studies, the compounds also diminished the levels of circulating T and DHT in male rat tissues. These compounds could be more effective than current therapies in the treatment of prostate cancer due to their multiple activities. In the present investigation, we describe the effects of several other novel steroidal compounds (Fig. 1) on human testicular C_{17,20} lyase and prostatic 5α-reductase \textit{in vitro} and on tissue concentrations of T and DHT in adult male rats. We also examined the changes in tissue weights after administration of these novel compounds to male rats.

Materials and Methods

Chemical inhibitors and reagents

The inhibitors (L-6, L-12, L-26, and L-38) were synthesized in our laboratory according to procedures described by Ling \textit{et al.} (22). L-47 was synthesized as described by Li \textit{et al.} (23). Finasteride was a gift from Merck Research Laboratories (Rahway, NJ), and ketoconazole was purchased from Sigma Chemical Co. (St. Louis, MO). [21-^3H]-17α-hydroxypregnenolone was prepared in our laboratory as previously described (24). [7-^3H]-T (96.5 Ci/mmol) and [1^3C]-DHT (56.5

FIG. 1. Chemical structures of steroidal inhibitors of androgen synthesis evaluated \textit{in vitro} and \textit{in vivo}. 17-(4'-Imidazolyl)androsta-4,16-dien-3-one [L-6]; 3β-Acetoxy-17-(4'-Imidazolyl)androsta-5,16-diene [L-12]; 4,16-Pregnadiene-3,20-dione-20-oxime acetate [L-26]; 17-(5'-Isoxazolyl)androsta-5,16-dien-3β-ol [L-38]; 17β-(4'-Imidazolyl)androst-5-en-3β-ol [I-47].
EFFECTS OF NOVEL STEROIDAL COMPOUNDS

Preparation of microsomes

Human testes and prostate tissue (from patients with benign prostatic hyperplasia, BPH) were obtained from Dr. James Mohler (Director, Urologic Oncology, University of North Carolina at Chapel Hill) and stored at −70°C before use. Testicular and prostatic microsomes were prepared as described previously (19). Briefly, human testis or prostate was washed with saline (0.9%), blotted dry, and weighed. The tissue was minced and homogenized in a blender with two volumes of sucrose (250 mM). The homogenates were added to 50-ml plastic centrifuge tubes and centrifuged at 10,000 × g for 30 min. The resulting supernatant was centrifuged at 109,000 × g for 1 h using an ultracentrifuge. The microsomal pellet was covered with 2 ml of phosphate buffer (0.1 M) and stored at −70°C until required for assay. The microsomal protein content was determined by the Lowry method (25).

C17,20-Lyase activity

The measurement of the activity of the human C17,20-lyase in testicular microsomes, in the absence and presence of inhibitors was performed as described previously (19–22). Briefly, the C17,20-lyase activity was determined by measuring the release of [3H]-acetic acid during the conversion of [21-3H]-17α-hydroxyprogrenolone to dehydroepiandrosterone. The incubations were carried out in a total volume of 1.0 ml. Sample tubes were supplied with 10 μl of propylene glycol, 300,000 dpm of [21-3H]-17α-hydroxyprogrenolone (13.61 mCi/μmol) and the indicated inhibitors. The control incubations were prepared without the addition of the indicated inhibitors. After evaporation of the ethanolic solution, the following were added to each tube: 750 μl of 0.1 mM sodium phosphate buffer (pH 7.4), with 78 μM of dithiothreitol and 50 μl of an NADPH generating system (phosphate buffer containing 6.5 mM of NADP+, 71 mM of glucose-6-phosphate, 1.25 IU of glucose-6-phosphate dehydrogenase). The tubes were preincubated for 15 min at 37°C and the reaction was started by adding 200 μl of human testicular microsomes (300 μg protein per 200 μl of phosphate buffer). The reaction tubes were incubated at 37°C under oxygen. After 1 h, the tubes were placed in an ice bath and the reaction mixture was extracted twice with chloroform (1 ml). The tubes were allowed to stand at 4°C for 20 min, centrifuged at 4°C for 15 min at 2000 × g and then 0.75 ml of the aqueous phase of each tube was placed into a fresh tube. To remove residual steroids, which were present after the chloroform extraction, 0.75 ml of charcoal solution (2.5 g of activated charcoal per 100 ml of distilled water) was added to each tube and vortexed vigorously. After standing for 30 min, the charcoal was pelleted by centrifugation at 7,500 × g for 20 min. Finally, 0.75 ml of the supernatant was analyzed for tritium by liquid scintillation spectrometry. The reaction conditions were optimized with 0.1–6.0 μM of [21-3H]-17α-hydroxyprogrenolone and the Km and Vmax values were determined at the optimum conditions. The IC50 values for inhibitors were calculated using linear regression analysis and the plot of log of potency against log of inhibitor concentration. IC50 values were also determined at the same reaction conditions with addition of appropriate concentrations of inhibitors. The experiments were performed in duplicate and repeated at least twice (i.e. n ≥ 3).

5α-reductase assay

The effects of novel compounds on human prostatic 5α-reductase activity were evaluated as previously described (19–22) with some modifications. Ethanolic solutions of [7-3H]-T (600,000 dpm), cold T (4.8 ng), indicated inhibitors (0–200 nm) and propylene glycol (10 μl) were added to duplicate sample tubes. The control incubations were prepared without the addition of the indicated inhibitors. The ethanol was evaporated to dryness under a gentle stream of air. The samples were reconstituted in phosphate buffer (0.1 M, pH 7.4, 400 μl) containing dithiothreitol (78 μM) and the NADPH generating system (NADP+, 6.5 mM; glucose-6-phosphate, 71 mM; glucose-6-phosphate dehydrogenase, 2.5 IU, in 100 μl of phosphate buffer) was added to each tube. The tubes were preincubated at 37°C for 15 min. The enzymatic reactions were initiated by addition of human BPH microsomes (about 180 μg of microsomal protein in 500 μl of phosphate buffer) in a total volume of 1.0 ml. The incubations were performed for 10 min under oxygen in a shaking water bath at 37°C. The incubations were terminated by placing the sample tubes on ice [14C]-DHT (3000 dpm) and cold DHT (50 μg) were added to each tube as an internal standard and visualization marker, respectively. These additions were immediately followed by ether (1 ml). The steroids were extracted with ether (3 × 1 ml), separated by TLC (chloroform: ether, 80:20) and visualized by exposure to iodine vapor. The extracts were analyzed for [3H] and [14C] using a liquid scintillation counter. The percentage conversion of [7-3H]-T to [7-3H]-DHT was calculated and used to determine 5α-reductase activity. The reaction conditions were optimized with T (0–60 nm) and the Km and Vmax values were estimated at the optimum conditions. The IC50 values were determined from plots of 5α-reductase activity against four different concentrations of the inhibitor. The experiments were performed in duplicate and repeated at least twice (i.e. n ≥ 3).

Animal studies

Adult Male Sprague Dawley rats (240 ± 10 g) were supplied by Charles River Laboratories, Inc. (Wilmington, MA). The animals were maintained in a controlled environment of about 25°C, 50% relative humidity and 12 h of light and 12 h of dark cycles and allowed free access to food and water. The experiments were performed in accordance with guidelines approved by the Veterinary Resources Unit of the University of Maryland School of Medicine, Baltimore. About 6–8 rats were assigned to the different treatment groups. The compounds were suspended in 0.5% hydroxypropylcellulose and administered sc at a dose level of 50 mg/kg for 14 consecutive days. The control group was injected with the vehicle alone. Another group of rats (6–8) was cas-trated and injected with the vehicle alone for 14 days. The rats were killed at the end of the treatment period (1–2 h after the last administered dose) and testes, prostate, epididymis, and seminal vesicles were removed. The organs were cleaned, weighed, and stored at −70°C until analysis. Blood samples were also collected, centrifuged to obtain serum, and stored at −70°C until required.

T RIA assay

Serum, testicular, and prostatic tissues obtained from individual male rats were thawed and placed on ice. Portions (~100 mg) of testicular and prostatic tissues were homogenized in phosphate buffer (pH 7.4, 0.1 M) and the homogenates were centrifuged at 2000 × g for 20 min. Serum (0.4 ml) and aliquots (0.4 ml) of the tissue supernatant were used for the determination of T as described in the 125I-T assay kit supplied by Diagnostic Systems Laboratories, Inc.

DHT RIA assay

Portions (100 mg) of prostatic tissues were homogenized in assay buffer provided with the DHT RIA assay kit obtained from Diagnostic Systems Laboratories, Inc. and the homogenates were centrifuged at 2000 × g for 20 min. Serum (0.4 ml) and aliquots (0.4 ml) of the prostatic supernatant were extracted with 4 ml of hexane/ethanol (98:2) mixture. The extracts were dried under a gentle stream of air, dissolved in sample diluent and used for the determination of DHT as described in the 125I-DHT assay kit.

Statistical analysis

One-way ANOVA on SigmaStat for windows version 1.0 was used to compare different treatment groups at the 95% confidence level. The Bonferroni posthoc test was used for determination of significance. A P value of less than 0.05 was considered as statistically significant.

Results

The Km and Vmax values for C17,20-lyase were 480 nm and 40 pmol/mg protein/min, respectively. L-12 and L-26
showed potent inhibition of human testicular C\textsubscript{17,20}-lyase with IC\textsubscript{50} values of 50 and 25 nM, respectively. L-12, L-38, and I-47 showed moderate inhibition of human testicular C\textsubscript{17,20}-lyase with IC\textsubscript{50} values of 75, 108, and 70 nM, respectively. L-6 and L-12 exhibited noncompetitive inhibition against C\textsubscript{17,20}-lyase with corresponding K\textsubscript{i} values of 23 and 20 nM, respectively (Fig. 2). In comparison, ketoconazole, a competitive inhibitor of C\textsubscript{17,20}-lyase had an IC\textsubscript{50} value of 78 nM and a K\textsubscript{i} of 38 nM (Table 1). The K\textsubscript{m} and V\textsubscript{max} values for 5\alpha-reductase were 40 nM and 2 pmol/mg protein/min, respectively. L-6 and L-26 were moderate inhibitors of human 5\alpha-reductase with IC\textsubscript{50} values of 75 and 125 nM, respectively. L-38 was a weak inhibitor of 5\alpha-reductase (IC\textsubscript{50} = 377 nM). In comparison, finasteride had an IC\textsubscript{50} value of 33 nM against 5\alpha-reductase (Table 1).

Administration of these novel steroidal inhibitors to male Sprague Dawley rats (50 mg/kg daily, sc, for 14 days) significantly reduced the concentrations of T in the serum and testes, as well as DHT in serum by 63–91% with the exception of I-47 (Table 2). Surprisingly, the administration of I-47 increased the concentration of T in rat serum by 24% although it was effective in reducing T by 84% in the testis. L-12, which has similar activity \textit{in vitro} to I-47, was the most effective in lowering T levels and reduced serum and testicular levels by 91% compared with controls. L-6, L-26, and L-38 reduced testicular androgen levels by approximately 65% (Table 2). These three compounds were inhibitors of both the C\textsubscript{17,20}-lyase and 5\alpha-reductase enzymes. DHT levels in serum were reduced 65% by I-47, whereas L-6 and L-12 were more effective and reduced DHT levels by approximately 85% and L-38 by 90%. L-38 (23.95 ± 1.97 pg/ml) reduced serum DHT concentrations to about the level of castrated rats (18.13 ± 7.07 pg/ml). In the prostate, all of the compounds reduced T levels to about the same extent and were similar to the levels in castrated animals. On the other hand, DHT concentrations in the prostate were reduced by approximately 60% by the compounds, whereas DHT levels in castrated animals were minimal (Fig. 3). The effects of these novel steroidal inhibitors on the wet weight of rat prostates and seminal vesicles are shown in Fig. 4. The wet weight of rat prostates were significantly reduced by 17–54% in rats treated with several of these novel steroidal inhibitors. L-6, an inhibitor with dual activity against both the C\textsubscript{17,20}-lyase and 5\alpha-reductase and L-12, which inhibited only the C\textsubscript{17,20}-lyase, were the most effective in this regard and reduced prostatic weight by about 50% (P < 0.05). L-6 also reduced the wet weights of the seminal vesicles, testes, and epididymis by 56%, 22%, and 37%, respectively, in normal male rats. L-12 and L-38 reduced the wet weights of the seminal vesicles by 44.8% and 20.6%, respectively.

**Discussion**

C\textsubscript{17,20}-lyase catalyzes the early step in the biosynthesis of T and other androgens in both the testes and the adrenal

**TABLE 1. Kinetic constants of novel steroidal compounds against human C\textsubscript{17,20}-lyase and 5\alpha-reductase**

<table>
<thead>
<tr>
<th>Compound</th>
<th>C\textsubscript{17,20}-Lyase</th>
<th>5\alpha-Reductase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC\textsubscript{50} (nM)</td>
<td>K\textsubscript{i} (nM)</td>
</tr>
<tr>
<td>L-6</td>
<td>50 ± 1.2</td>
<td>23 ± 1.6</td>
</tr>
<tr>
<td>L-12</td>
<td>75 ± 1.0</td>
<td>20 ± 1.1</td>
</tr>
<tr>
<td>L-26</td>
<td>25 ± 0.8</td>
<td>ND</td>
</tr>
<tr>
<td>L-38</td>
<td>108 ± 2.9</td>
<td>ND</td>
</tr>
<tr>
<td>I-47</td>
<td>70 ± 2.8</td>
<td>ND</td>
</tr>
<tr>
<td>Finasteride</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>78 ± 2.0</td>
<td>38 ± 1.0</td>
</tr>
</tbody>
</table>

IC\textsubscript{50} and K\textsubscript{i} values of these steroidal compounds against human testicular C\textsubscript{17,20}-lyase and prostatic 5\alpha-reductase from human BPH microsomes were determined as described in Materials and Methods. The control incubations were prepared without the indicated inhibitors. Values are the means ± sës from three experiments (n = 3). ND, Not determined; NI, no inhibition.
Materials and Methods

Normal adult male rats (240 ± 10 g) were injected with the compounds listed (50 mg/kg/day, s.c., for 14 consecutive days). Blood was collected and the testes were removed. The concentrations of testosterone (T) and dihydrotestosterone (DHT) in tissues were determined by RIA, as described in Materials and Methods. Values are the means ± SE from six to eight rats. * P < 0.05, and ** P < 0.01, compared with the control group.

TABLE 2. Effects of novel steroidal compounds on testosterone and dihydrotestosterone levels in tissues of normal adult male rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>T Levels</th>
<th>DHT levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum (ng/ml)</td>
<td>Testis (ng/g · wt)</td>
</tr>
<tr>
<td>Control</td>
<td>2.38 ± 0.69</td>
<td>398.2 ± 57.4</td>
</tr>
<tr>
<td>Castrated</td>
<td>0.63 ± 0.008a</td>
<td>146.50 ± 38.71b</td>
</tr>
<tr>
<td>L-6</td>
<td>0.45 ± 0.16a</td>
<td>34.01 ± 9.17b</td>
</tr>
<tr>
<td>L-12</td>
<td>0.22 ± 0.02a</td>
<td>143.01 ± 20.98a</td>
</tr>
<tr>
<td>L-26</td>
<td>0.87 ± 0.06a</td>
<td>102.02 ± 16.67b</td>
</tr>
<tr>
<td>L-38</td>
<td>0.83 ± 0.02a</td>
<td>62.60 ± 27.53a</td>
</tr>
<tr>
<td>I-47</td>
<td>2.97 ± 0.58</td>
<td>84.53 ± 25.15a</td>
</tr>
</tbody>
</table>

Normal adult male rats (240 ± 10 g) were injected with the compounds listed (50 mg/kg/day, s.c., for 14 consecutive days). Blood was collected and the testes were removed. The concentrations of testosterone (T) and dihydrotestosterone (DHT) in tissues were determined by RIA, as described in Materials and Methods. Values are the means ± SE from six to eight rats. * P < 0.05, and ** P < 0.01, compared with the control group.

Fig. 3. Effects of novel steroidal compounds on T and DHT levels in prostates of normal adult male rats. Normal adult male rats (240 ± 10 g) were injected with the compounds listed (50 mg/kg/day, sc, for 14 consecutive days). Prostates were removed and the prostatic concentrations of T and DHT were determined by RIA as described under Materials and Methods. Values are the means ± SE from six to eight rats. * P < 0.05, and ** P < 0.01, compared with the control group.

Fig. 4. The effects of androgen synthesis inhibitors on tissue weight in normal adult male rats. Rats were injected sc with 50 mg/kg/day suspension of inhibitors in 0.5% hydroxypropylcellulose or vehicle alone (controls). Animals were autopsied after 2 weeks and the following tissues were weighed: prostate, testes, seminal vesicles, epididymis, adrenals, liver, and kidneys. There were no significant changes in the weights of adrenals, liver, kidneys, or total body weight between different treatment group. Values are the means ± SEs from six to eight rats. *, P < 0.05 and ***, P < 0.01 compared with controls.

glands, whereas 5α-reductase converts T to DHT in the prostate gland (4). Both T and its metabolite, DHT, promote prostatic growth and cancer. Thus, inhibition of both enzymes would be expected to result in diminished levels of circulating T and DHT and therefore serve as a useful strategy for developing new treatments for prostate cancer (26, 27). Several inhibitors of C17,20-lyase and/or 5α-reductase have been described previously, however, they have a number of limitations. Ketoconazole is currently the only inhibitor used in the treatment of prostate cancer (16). This compound inhibits P-450 enzymes including C17,20-lyase but is not selective (15). Finasteride, an inhibitor of 5α-reductase, induces accumulation of T (18) and has no activity against C17,20-lyase (21). Literature reports have indicated that selective inhibitors of 5α-reductase reduced tissue DHT levels but also produced an accumulation of T (28–30). Several of the compounds described in this study are dual inhibitors of C17,20-lyase and 5α-reductase and were effective in reducing the levels of both T and DHT in rat tissues. In addition these novel compounds exhibit antiandrogenic activity in LNCaP cell cultures by displacing the synthetic androgen [3H]R1881 from the androgen receptor. The compounds have also been shown recently to reduce the growth of LNCaP tumors in SCID mice (31).

In the present study, we determined the inhibitory potency of these compounds on C17,20-lyase only using the [3H]acetic acid release method. In previous studies we used an HPLC assay to determine the relative ability of our compounds to block 17α-hydroxylase and C17,20-lyase activities (20). The results obtained with several of our compounds indicate that the steroids show similar inhibitory potencies for both enzymes. However, the HPLC method is cumbersome and less rapid (20). Hence, we routinely use the simple and rapid [3H]acetic acid release method for assessing the inhibitory potencies of the compounds on C17,20-lyase. The enzyme, 5α-reductase, occurs in two isoforms namely, type I and type...
II. The predominant isoform of 5α-reductase that converts T to DHT in the human prostate is the type II. DHT is the main androgen involved in prostate development and growth. In this study, we did not attempt to determine the inhibitory potency of these compounds on the type I isozyme because this isozyme is mainly expressed in the skin and liver and plays a limited role in prostate homeostasis (5).

The results obtained from the present investigation show that L-6, L-12, L-26, and I-47 exhibit inhibitory action against human C17,20-lyase. L-6, for example, showed potent inhibition of human C17,20-lyase with an IC₅₀ value of 50 nm and a Kᵣ value of 23 nm. In comparison, the IC₅₀ value for ketoconazole was 78 nm and the Kᵣ was 38 nm (Table 1 and Fig. 2). The compounds are also potent inhibitors of rat testicular C17,20-lyase (22). L-6 and L-12 showed noncompetitive inhibition and probably binds strongly to the active site and the apoprotein of C17,20-lyase (Fig. 2). A more detailed study on the mechanism of enzyme inhibition of these compounds will be carried out in our future studies. L-6 and L-12 have similar Kᵣ values for the C17,20-lyase, although, L-6 was also a moderate inhibitor of 5α-reductase (IC₅₀ 75 ± 3 nm) compared with finasteride (33 ± 1.1 nm). Both L-6 and L-12 were the most effective compounds in reducing prostatic weights. Surprisingly, L-38, which was the least potent of the dual inhibitors, was the most effective in reducing serum DHT levels. I-47, which is not an inhibitor of 5α-reductase and actually increased serum T levels, reduced DHT levels and caused a 30% reduction in prostate weight (Table 2 and Fig. 3). It would appear from the results that other properties of the compounds influence their effectiveness in vivo. Surgical castration is the traditional approach to lower androgen levels in vivo (7) and was used in this investigation as the standard for comparison. These novel steroids were as effective as castration in reducing T concentration in the prostate and were potent inhibitors of the C17,20-lyase. However, DHT concentrations in rat prostates were reduced by 50–65% of intact controls by the novel compounds compared with about 99% reduction by castration. Prostatic growth and weight are regulated by both T and DHT, albeit to a greater extent by the latter (5, 6). Although the significant reduction in the levels of androgens by these compounds may explain the corresponding reduction in prostate size observed after treatment with some of these compounds, other compounds such as L-26 and I-47 were ineffective in reducing prostatic weight. None of the compounds were as effective as castration. While it would appear that reduction in concentration of DHT in the prostate is critical to reducing prostatic weight in normal rats, other activities of the compounds in vivo may be important. Our results indicate that although these novel inhibitors are effective in reducing serum and tissue androgen concentrations, their effectiveness in vivo does not strongly correlate the potencies of these compounds on the enzyme systems in vitro. The possibility that the compounds interact with the androgen receptor or are converted to androgenic metabolites requires investigation. Also, the bioavailability of the compounds may be limiting their efficacy. Further studies on the uptake, distribution, and metabolism of the compounds are required. Another consideration is the specificity of inhibition shown by these compounds. Although studies with related steroid compounds suggest that these compounds are dual inhibitors of C17,20-lyase and 5α-reductase, we plan to ascertain their enzyme (especially their effects on adrenal steroids and other P-450 enzymes) and receptor specificity of action in our future studies.

In conclusion, the present investigation demonstrates that several of these novel steroidal inhibitors of androgen synthesis are effective at reducing the circulating levels of T and DHT in adult male rats. L-6, L-12, L-38, and I-47 were also effective at inducing a significant reduction in the weights of rat prostates. Although further improvements in their bioavailability and other mechanism of action in vivo are necessary, these novel steroidal compounds show promise as potential agents for reducing androgen levels in patients.

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