5α-Reductase Type 1 Modulates Insulin Sensitivity in Men


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CONTEXT: 5α-Reductase (5αR) types 1 and 2 catalyze the A-ring reduction of steroids, including androgens and glucocorticoids. 5α-R inhibitors lower dihydrotestosterone in benign prostatic hyperplasia; finasteride inhibits 5αR2, and dutasteride inhibits both 5αR2 and 5αR1. In rodents, loss of 5αR1 promotes fatty liver.

OBJECTIVE: Our objective was to test the hypothesis that inhibition of 5αR1 causes metabolic dysfunction in humans.

DESIGN, SETTING, AND PARTICIPANTS: This double-blind randomized controlled parallel group study at a clinical research facility included 46 men (20-85 years) studied before and after intervention.

INTERVENTION: Oral dutasteride (0.5 mg daily; n = 16), finasteride (5 mg daily; n = 16), or control (tamsulosin; 0.4 mg daily; n = 14) was administered for 3 months.

MAIN OUTCOME MEASURE: Glucose disposal was measured during a stepwise hyperinsulinemic-euglycemic clamp. Data are mean (SEM).

RESULTS: Dutasteride and finasteride had similar effects on steroid profiles, with reduced urinary androgens and glucocorticoid metabolites and reduced circulating DHT but no change in plasma or salivary cortisol. Dutasteride, but not finasteride, reduced stimulation of glucose disposal by high-dose insulin (dutasteride by -5.7 [3.2] μmol/kg fat-free mass/min, versus finasteride +7.2 [3.0], and tamsulosin +7.0 [2.0]). Dutasteride also reduced suppression of nonesterified fatty acids by insulin and increased body fat (by 1.6% [0.6%]). Glucose production and glycerol turnover were unchanged. Consistent with metabolic effects of dutasteride being mediated in peripheral tissues, mRNA for 5αR1 but not 5αR2 was detected in human adipose tissue.

CONCLUSION: Dual inhibition of 5αRs, but not inhibition of 5αR2 alone, modulates insulin sensitivity in human peripheral tissues rather than liver. This may have important implications for patients prescribed dutasteride for prostatic disease.