Dual 5-alpha reductase inhibition promotes hepatic lipid accumulation in man

Jonathan M. Hazlehurst,1,2 Andrei I. Opruesci,2 Nikolaos Nikolakou,2 Riccardo Di Guida,3 Annabell E. K. Grinberg,6 Nigel P. Davies3, Robert B. Flintham,6 Angela E. Taylor,2 Beverly A. Hughes,6 Jingfei Yu,5 Leanne Hudson,1 Warwick B. Dunn1,5 and Jeremy W. Tomlinson1

1University of Oxford, Oxford Centre for Diabetes, Endocrinology and Metabolism, UK
2University of Birmingham, Centre for Endocrinology, Diabetes and Metabolism, UK
3University of Birmingham, School of Biosciences, UK
4NHF Wellcome Trust Clinical Research Facility, Queen Elizabeth Hospital Birmingham, UK
5Medical Physics, Queen Elizabeth Hospital Birmingham, UK
6University of Birmingham, School of Sports and Exercise Sciences, UK

Background

Non-alcoholic fatty liver disease (NAFLD) is increasingly prevalent and is associated with significant morbidity and mortality. Both glucocorticoids (GCs) and androgens have been implicated in its pathogenesis. Tissue-specific availability of these hormones is controlled at a pre-receptor level by a series of enzymes including the A-ring reductions 5α-reductase type 1 (5αR1) and 2 (5αR2). These enzymes inactivate cortisol as well as activating testosterone to the more potent androgen dihydrotestosterone. 5αR1 and 5αR2 are both expressed in the liver with only 5αR1 expressed in adipose. Several studies have highlighted a link between metabolic phenotype and 5α-reductase activity. The metabolic impact of inhibiting these enzymes with the dual inhibitor (Dutasteride) and selective SRD5A2 inhibitor (Finasteride) (both drugs commonly used for prostate disease) has begun to be elucidated. Our study extends this observations to examine lipid metabolism within the liver and the mechanisms underlying these observations.

Methods

Twelve healthy male volunteers (mean age 36.3±4.4 years, body mass index (BMI) 26.8±1.2 kg/m²) (LREC ref 12/WM/10122) were recruited. All were non-diabetic and not on medications that regulate GC metabolism. Volunteers had a series of detailed metabolic investigations pre and post 3 weeks of treatment with either Dutasteride (0.5mg od) or Finasteride (5mg od). Investigations included hepatic magnetic resonance spectroscopy to evaluate intrahepatic lipid, 2-step-hyperinsulinaemic euglycaemic clamps incorporating stable isotopes with concomitant adipose tissue microdialysis to evaluate tissue-specific carbohydrate and lipid flux as well as an analysis of the serum lipid profile using ultra performance liquid chromatography mass spectrometry. Serum and urinary steroids were analysed by liquid chromatography and gas chromatography respectively.

Results

Changes to the serum metabolome

A smaller number of metabolites showing a greater magnitude of change observed in serum with Dutasteride treatment compared to Finasteride (Figures 3A-D). Dutasteride has a greater effect on the serum metabolome than Finasteride (Figures 3A, B). A specific effect on the metabolism of the liver is observed with Dutasteride (Figure 3A, D). Dutasteride has a greater effect on lipid metabolites than Finasteride with increased glycerophospholipids and other lipid metabolites (Figure 3B, D).

Figure 1. The effect of Dutasteride (A) and Finasteride (B) on hepatic lipid content (% as measured by MRS) (a) and (b) and de novo lipogenesis (DNL) (c) and (d) and glucose production (Ra) (e) and (f). Open bars represent pre-treatment and filled bars represent the effect of 3-weeks of drug treatment (black=Dutasteride, shaded=Finasteride). *p<0.05 vs pre-treatment.

Figure 2. The impact of Dutasteride (A) and Finasteride (B) on hepatic lipid content (% as measured by MRS) (a) and (b) and de novo lipogenesis (DNL) (c) and (d). Open circles/squares represent pre-treatment and filled circles/squares represent the effect of 3-weeks of drug treatment (white=Dutasteride, squares=Finasteride). *p<0.05 vs pre-treatment. The change in rate of DNL is positively correlated with the fall in hepatic lipid content after treatment with Dutasteride (e) but not Finasteride.

Figure 3. A: Dutasteride has a greater effect on the serum metabolome than Finasteride with a particular effect on perturbation of lipid metabolism (left hand panel, black=Dutasteride, shaded=Finasteride). Figure 3B: Dutasteride has a greater effect on lipid metabolites than Finasteride with increased glycerophospholipids and other lipid metabolites.