Morphology of the testis and the epididymis in rats with dihydrotestosterone (DHT) deficiency

Kolasa A, Marchlewicz M, Wenda-Różewicka L, Wiszniewska B

Department of Histology and Embryology, Pomeranian Medical University Szczecin, Poland

Abstract

The aim of the study was to estimate morphology in the testis and epididymis of adult rats, treated with finasteride for 28 days (the time period of two seminiferous epithelium cycles) and 56 days (the time period of one spermatogenesis). A 28 days long DHT deficiency did not significantly influence the structure of seminiferous epithelium. After 56 days of treatment, finasteride induced sloughing of immature germinal cells (spermatids and rarely pachytene spermatocytes) into the lumen of the seminiferous tubules. A reduced content of spermatozoa was observed in the lumen of rat epididymis in rats with 56-day-long deficiency. The results indicated that 5α-reductase 2 activity is important for the maintenance of spermatogenesis. The decreased content of spermatozoa in the epididymal lumen of rats, treated with finasteride during one course of spermatogenesis, could reflect seminiferous epithelium condition.

Key words: testis, epididymis, DHT deficiency.

Introduction

Spermatogenesis, including meiosis, as well as germinal cell survival and the differentiation of round spermatids to elongated spermatids is known to be testosterone-dependent [1, 2]. Also epididymis function, in areas of maturation, transport and storage of spermatozoa is under testosterone control. In androgen target tissues, T can be intracellularly converted into DHT, the most potent androgen. Testicular and epididymal epithelial cells contain enzymes which control the ratio of testosterone to androgen metabolites and of androgens to other hormones, employed to regulate the male reproductive tract function (intracrine modulation). The irreversible conversion of T into DHT is catalyzed by steroid 5α-reductase (5α-red). Two isoforms of 5α-red were identified: type 1 (5α-red1) and type 2 (5α-red2), which are encoded by two different genes. 5α-red2 is more often expressed in male reproductive organs than 5α-red1 [3]. Finasteride is one of several steroid-based inhibitors, which has a higher affinity to 5α-red2, and is used in the treatment of aberrant prostate growth and prostate cancer. Therefore, one can create an experimental animal model to study the morphology of the testis and epididymis of rats with DHT deficiency, using finasteride as the inhibitor.

ADDRESS FOR CORRESPONDENCE:
Barbara Wiszniewska
Department of Histology and Embryology
Pomeranian Medical University
Al. Powstańców Wlkp. 72, 70-111 Szczecin, Poland
Tel/Fax 0-91 466-16-77,
e-mail: barbwisz@sci.pam.szczecin.pl

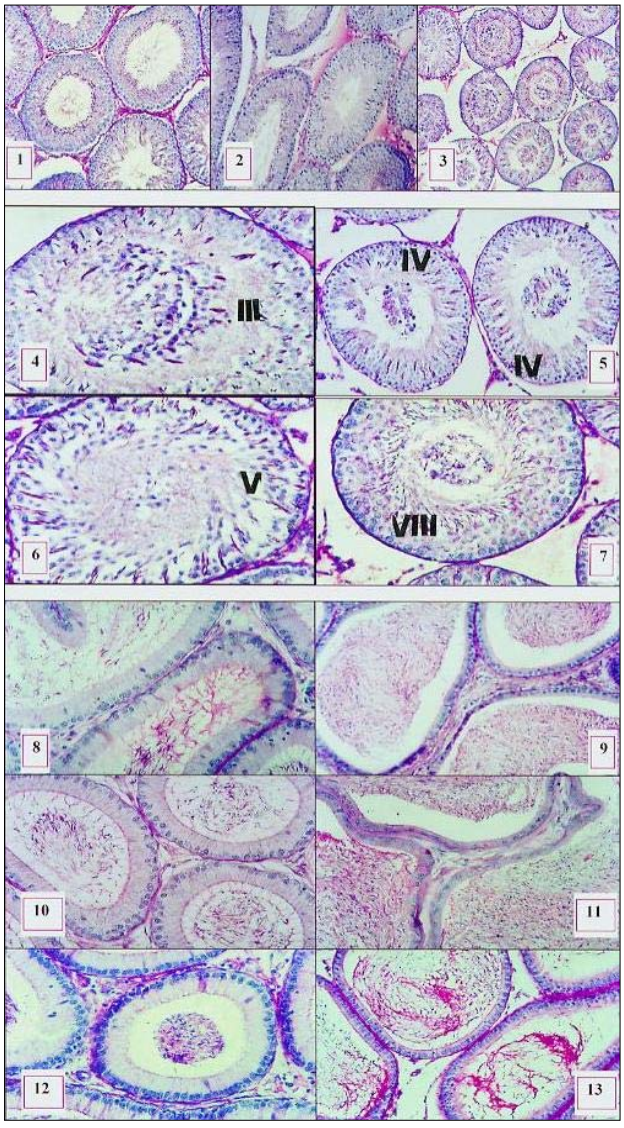
Material and methods

The study was performed in adult, male Wistar rats. The rats were randomly divided into 3 groups (with 5 animals in each): control and two experimental (I, II). The animals in the experimental groups received *per os* inhibitor of 5α-red2 (finasteride; Proscar®, MSD Sweden), during 28 days (Group I; the time period of two seminiferous epithelium cycles) and 56 days (Group II; the time period of one spermatogenesis) in 5mg/kg body weight doses. Sections of testis and epididymis, fixed in Bouin's solution and embedded in paraffin, were stained by the PAS method. The study was approved by the Local Ethics Committee and Animals Research.

Results

There were no changes in the morphology of testis of the rats, treated with finasteride during the time period of two seminiferous epithelium cycles (Fig. 2). Similarly as in testes from the control rats (Fig. 1), the seminiferous epithelium contained all the generations of germinal cells, corresponding to the stages of seminiferous epithelium cycle. In contrast, the inhibition of

Figures 1, 2, 3. Cross-section of seminiferous tubules of the testes from the control and the experimental rats. Seminiferous epithelium of the control rats contains all germinal cell generations, suitable for each cycle of seminiferous epithelium stage (1). Unchanged morphology of seminiferous epithelium of a rat with DHT deficiency through two seminiferous epithelium cycles (2). Sloughing of immature germinal cells into the lumens of the seminiferous tubules of rats with DHT deficiency during the time period of one spermatogenesis (3).
Figures 4, 5, 6, 7. Cross-section of seminiferous tubules of the testes from the rats with DHT deficiency during the time period of one spermatogenesis. The sloughing of spermatids in stages 3 and 16 (4); spermatid stages 4 (left tubule), and 17 and late pachyten spermatocytes (right tubule) (5); spermatids step 5 (6) and spermatids step 8 (7). Empty areas are seen in the seminiferous epithelium (5, 6).
Figures 8, 9, 10, 11, 12. 13. Cross-section of epididymis from the control rats (8, 9) and from the rats with 28-day (10, 11). The decrease content of spermatozoa in the lumen of caput (12) and cauda (13) epididymis of the rats with 56-day DHT deficiency.
PAS: 3 - x 160; 1, 2, 5 - x 320; 4, 6-13 - x 670.
Stages of seminiferous epithelium cycle in Figs. 4-7 are designated by Roman numbers.



5α-red2 activity through the time period of one spermatogenesis duration altered the morphology of rat testis (Fig. 3). DHT deficiency resulted in sloughing of immature germinal cells. In the lumen of the tubules, there were mainly spermatids in different developmental stages (Figs. 4-7) and, rarely, late pachytene spermatocytes (Fig. 5). Moreover, empty areas within the seminiferous epithelium were observed as a result of cell sloughing (Fig. 6). The morphology of epithelial cells of the rat epididymides from Group I and Group II (the experimental groups) was not changed during finasteride treatment (Figs. 10-13), in comparison to the values in the control rats epididymides (Figs. 8, 9). A smaller amount of sperm was found in the lumen of epididymides of the rats with DHT deficiency throughout the time period of one spermatogenesis (56 days) (Figs. 12, 13).

Discussion

Changes in morphology were observed only in the testes of rats, receiving finasteride during the course of one spermatogenesis. An unchanged structure of testes of the rats, treated with finasteride through the time of two cycles of seminiferous epithelium, could be maintained by DHT, which was produced by 5α-red1 activity, the other type of enzyme presented in the testis [4], not inhibited by finasteride. It is possible that this pathway of T reduction is an alternative but short-term solution. On the other hand, the lack of morphological changes in the rats from the 28-day experiment could result from oxidative activity of 3α-hydroxysteroid dehydrogenase (3α-HSD), which catalyses the conversion of 3α-androstendiol into DHT [3]. Thus, the 28-day inhibition of 5α-red2 activity was too short to alter the morphology of the testis. Changes in morphology, observed in seminiferous epithelium of the rats with 56-day DHT deficiency, including the sloughing of immature germinal cells, are in agreement with other authors. O'Donnell et al. [5] have shown that 5α-reduction of testosterone is particularly important for the progression through midspermatogenesis (the transition of stage VII to stage VIII, in which the transition of round spermatids from step 7 to step 8 takes place). An alteration of testis morphology could result from the antyproliferative and apoptotic effects of finasteride [6, 7, 8]. A study of prostatic epithelial cells has shown finasteride-dependent changes of MAP kinase and Akt-1 factor expression, a decrease of Bcl-2 family peptide expression, Insulin-like Growth Factor I (IGF-I) and IGF-I receptor gene suppression [6, 7]. It is suggested that DHT initiates [9] and supports the process of spermatogenesis in rats [2, 5]. Normal morphology of rat epididymides, observed during finasteride treatment, could suggest that the organ develops an additional mechanism of protection. The reduced content of spermatozoa in the lumen, especially in cauda epididymis from the rats of Group II, could reflect seminiferous epithelium condition in those animals. It has been shown that men, receiving finasteride during 12 weeks, had semen quantity reduced by 25%. Moreover, the decrease of 5α-red activity causes oligoasthenozoospermia, oligozoospermia and even azoospermia.

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