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ADJUVANT-INDUCED ARTHRITIS AFFECTS TESTES OF WISTAR RATS

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Abstract

In the testes, AIA promoted histopathological changes characterized by an increase in the percentage of abnormal tubules and reduction in the height of the seminiferous epithelium, daily production of spermatozoa, and cellular proliferation. In the prostate, AIA decreased the luminal volume of the secretory ducts. In condition of androgenic deprivation due to the orchiectomy, AIA induced proliferation of the prostatic epithelium.

Keywords: histopathological changes, cell proliferation, prostate gland, secretory pathways, androgenic deficiency.

ADYUVANT-INDUKSIYALANGAN ARTRITDA WISTAR KALAMUSHLARINING MOYAKLARIDA O`ZGARISHLAR

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Annotatsiya

Moyaklarda AIA gistopatologik o'zgarishlarni keltirib chiqardi, bu g'ayritabiiy tubulalar foizining oshishi va urug' epiteliyasi balandligining pasayishi, kunlik sperma ishlab chiqarish va hujayra proliferatsiyasi bilan tavsiflanadi. Prostata bezida AIA sekretor kanallarning lümenini kamaytiradi. Orxiektomiya natijasida kelib chiqqan androgen etishmovchiligi sharoitida AIA prostata epiteliyasining ko'payishini keltirib chiqaradi.

Kalit so’zlar: gistopatologik o‘zgarishlar, hujayra proliferatsiyasi, prostata bezi, sekretor yo‘llar, androgenik yetishmovchilik.

ВОЗДЕЙСТВИЯ АДЬЮВАНТ ИНДУЦИРОВАННОГО АРТРИТА У СЕМЕННИКОВ КРЫС ЛИНИИ ВИСТАР

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Аннотация

В яичках AIA вызывал гистопатологические изменения, характеризующиеся увеличением процента аномальных канальцев и уменьшением высоты семенного эпителия, ежедневной продукцией сперматозоидов и клеточной пролиферацией. В предстательной железе AIA уменьшает просвет секреторных протоков. В условиях андрогенной депривации, вызванной орхиэктомией, AIA индуцирует пролиферацию эпителия предстательной железы.

Ключевые слова: гистопатологические изменения, клеточная пролиферация, предстательная железа, секреторные протоки, андрогенная депривация.

Introduction. Rheumatoid arthritis (RA) is a chronic, autoimmune, and destructive inflammatory arthropathy, manifested by severe pain, edema, loss of mobility, and disability. The etiology of RA is not completely understood, but it is known that this disease affects approximately 0.5 to 1% of the world population, predominantly women in the age-group of 30 to 50 years [2, 4].

The RA-related joint damage begins with infiltration of macrophages and activation of CD4 + T lymphocytes, leading to hyperplasia and increased vascularization of the synovial membrane. In addition, cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-a), and other inflammatory mediators such as prostaglandins and free radicals are produced in the synovial fluid. This inflammatory process in synovium is aggravated by the action of enzymes such as metalloproteinases, hyaluronidases, and cyclooxygenases.

Adjuvant-induced arthritis—AIA protocol. Arthritis was induced in rats by an intradermal injection of 100 lL of heat-inactivated Mycobacterium tuberculosis (Difco, Detroit, MI, USA) in mineral oil at 50 mg/mL, in the right hind paw under 2,2,2-tribromoethanol anesthesia (250 mg/kg, i.p.). Sham-immunized animals were submitted to the same procedure, but only received the mineral oil. The earliest inflammatory signs of AIA in the contralateral hind paw, characterized by mild erythema as well as paws' diameter and mass, were usually observed around 15–20 days post-immunization.

The animals that showed no inflammation signs on the hind paw 20 days post-AIA induction were excluded.

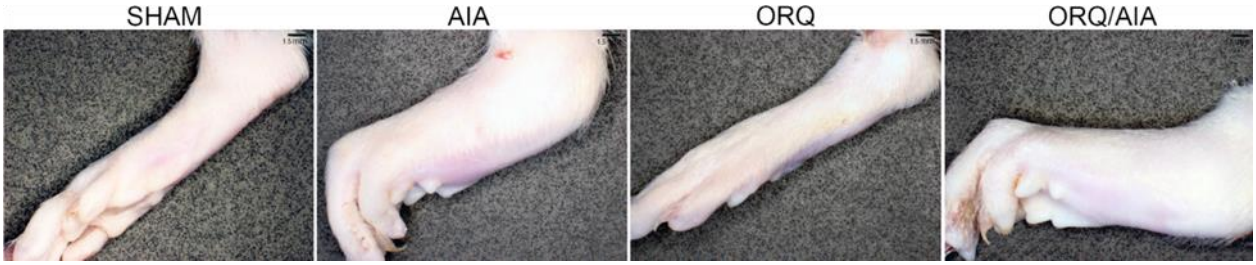
The effectiveness of the AIA induction was verified by the increment in the diameter of the left tibiotarsal joint, quantified by an analog pachymeter (0.05 mm

accuracy) on the 40th day post-AIA induction, immediately after the animals' death. In order to confirm the articular inflammation, left hind paws were also dissected just before of the tibiotarsal joint and weighed in analytical balance (0.1 mg accuracy).

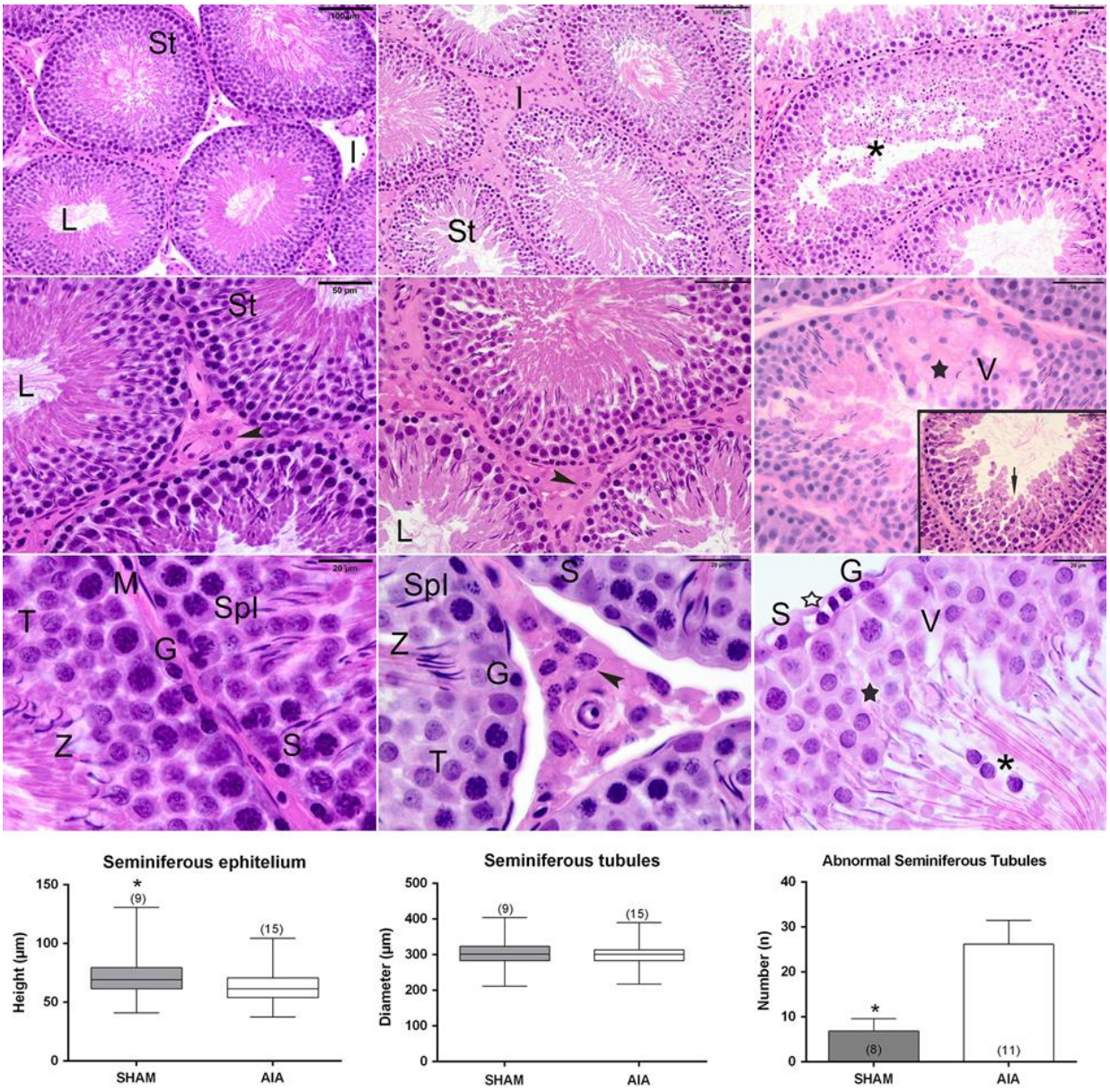
Morphometric-stereological analyses of the testes. In each testis, belonging to SHAM and AIA animals, at least two hundred seminiferous tubules (stage IX of the seminiferous epithelium cycle) were randomly selected [5]. The tubular in the testes, one hundred random tubules per experimental group were also captured, independently of the stage of the spermatogenic cycle. Abnormalities as immature germ cells in the lumen, presence of vacuoles in the seminiferous epithelium, and cellular disaggregation were considered in the analysis [1]. To evaluate the Leydig cell density in the interstitium, 10 histological fields per testis were randomly captured from sections stained with 1% toluidine blue in 1% borax. The Leydig cell number was counted at 10009 magnification in the fixed total area of 14.24 lm [3] considering for its identification the morphological characteristics as nucleus with chromatin of heterogeneous aspect, evident nucleoli and aggregation around to blood vessels.

Results. Biometric analysis**.** AIA and orchiectomy promoted significant decreasing in body weight in relation to the SHAM. Significant decrease in ventral prostate wet weight was observed in the ORQ and ORQ/AIA groups. On the other hand, the arthritis only did not significantly influence the reduction in prostate wet weight. Significant increase in left hind paw wet weight and diameter (contralateral to the paw that underwent induction) was observed in the AIA and ORQ/AIA groups. The AIA promoted significant increase in gonadosomatic index in relation to the SHAM (table 1, picture 1).

Histopathological and morphometrical analyses of the testes. The testes from the SHAM animals exhibited normal and regular histological organization, with the presence of seminiferous tubules exhibited the classic structure with a central lumen and seminiferous epithelium, which contained all spermatogenic lineage cells and Sertoli cells in the tubular periphery (picture 2 a, d, g). Leydig cell aggregates were observed in the interstitial tissue and exhibited a normal morphologic pattern (picture 2 d).



Picture 1. Daily sperm production and Leydig cell density.



Picture 2. Photomicrographs of global histology of testis from sham rats (a, d, g) and, arthritic rats (b, c, e, f, h, i); morphometry of the seminiferous tubules (j, k); percentage of abnormal tubules (l). In the SHAM groups, the testis exhibited morphologically normal seminiferous tubules (St), with spermatozoa (Z), and standard interstitial tissue (I) with Leydig cells (arrowhead). In the AIA group, seminiferous tubules with normal morphology were observed in the testes (b, e, h). Despite this, note that several seminiferous tubules of the AIA rats exhibited damage signals, characterized by cell desquamation of the seminiferous epithelium into the tubular lumen (*) (c, f-inset), loss of some germ cells (filled star), vacuolization in spermatogonia and Sertoli cell (non-filled star) and presence of vacuoles (V), and disaggregation of germ cells in the seminiferous epithelium (arrow) (1f, f-inset, i). Abbreviations: G = spermatogonia; L = lumen; S = Sertoli cells; T = spermatids; SpI = primary spermatocytes; M = peritubular cells. Staining: hematoxylin and eosin. Legend: Data of height and diameter of seminiferous tubules are expressed as median (Min to Max) and were analyzed by Mann–Whitney test. Data of abnormality of seminiferous tubules are expressed as meanDP and were analyzed by t test. *p ≤ 0.05 significant difference in relation to the AIA group. In parentheses, number of independent determinations.

In the AIA group, the testicular tissue exhibited the same structural organization and classic structure in several seminiferous tubules as observed in the SHAM group (picture 2 b, e, h). The interstitial tissue exhibited also the same structural pattern observed in testes of sham rats (picture 2 h). However, many

seminiferous tubules of the arthritis rats exhibited cell desquamation of the seminiferous epithelium into the tubular lumen, indicating the premature detachment of germ cells (picture 2 c, f-inset). The arthritis also induced other alterations such as depletion of some germ cells, spermatogonia and Sertoli cell vacuolization, and disaggregation of germ cells in the epithelium germinative, indicating the broke of the cytoplasmic bridges (picture 2 f, f-inset, i).

Morphometrical analysis of the testes revealed that AIA led to a significant reduction in height of seminiferous epithelium (picture 2 j). On the other hand, no significant difference was observed in diameter of the seminiferous tubules (picture 2 k). In addition, the percentage of abnormal seminiferous tubules exhibiting damages increased significantly in AIA when compared to the SHAM group (picture 2 l).

Daily sperm production and Leydig cell density. In the AIA group, a significant reduction in daily sperm production per testis was observed relative to the sham rats cells in the epithelium germinative, indicating the broke of the cytoplasmic bridges (picture 2 f, f-inset, i).

Morphometrical analysis of the testes revealed that AIA led to a significant reduction in height of seminiferous epithelium (picture 2 j). On the other hand, no significant difference was observed in diameter of the seminiferous tubules (picture 2 k). In addition, the percentage of abnormal seminiferous tubules exhibiting damages increased significantly in AIA when compared to the SHAM group (picture 2 l).

In conclusion, the AIA promoted an increase in abnormal seminiferous tubules and reduction in the cellular proliferation, leading to a decrease in both the height of the seminiferous epithelium and daily production of spermatozoa with impact, therefore, in the spermatogenic efficiency. In the prostate, the arthritis mainly decreased the luminal volume of the secretory ducts, suggesting a decrease in its secretory activity and, consequently, promoting a mild dilation of the stromal tissue. These effects on male genital system, that are present on the 40th day post-AIA induction, probably are a consequence of a transitory hypoandrogenism, which is quite evident around the 15th day. On the other hand, in long-lasting androgenic deprivation condition due to the orchiectomy, AIA induced proliferation of the prostatic epithelium. This suggests that the articular inflammatory process may have direct repercussions upon the prostate, regardless of the AIA-induced hypoandrogenism.

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