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Effects of telmisartan and losartan on irradiated testes

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ABSTRACT

Aims: To analyze the effects of radiation on the reproductive tissue of male *Wistar* rats and to evaluate whether treatment with the Ang II AT1 receptor antagonists telmisartan and losartan mitigate the dysfunctions resulting from this exposure.

Main methods: Rats were randomly divided into groups: Control, Irradiated, Telmisartan, Losartan, Irradiated + Telmisartan, and Irradiated + Losartan. Single dose of 5Gy was administered directly into the scrotum, followed by treatment with telmisartan (12 mg/kg/day) or losartan (34 mg/kg/two times/day) for 60 days. Testicular function parameters were evaluated from spermatozoa of the vas deferens. Testes were processed for histopathological and morphometric-stereological analysis. Proliferating cell nuclear antigen (PCNA) immunohistochemistry was evaluated.

Key findings: Radiation significantly reduced sperm motility, concentration, vitality, and increased the number of abnormal spermatozoa. Telmisartan and losartan did not significantly prevent these radiation-induced disorders. Seminiferous tubules were atrophied in both untreated and treated irradiated testes, and exhibited vacuoles, increased interstitial tissue and high number of blood vessels. However, several seminiferous tubules in recuperation were founded among damaged tubules in the testes of treated animals. The PCNA immunohistochemistry confirmed these outcomes. PCNA-positive cells were detected in dividing spermatogonia and spermatocytes from irradiated telmisartan and losartan treated rats whereas in the only-irradiated group, PCNA staining was observed in the nuclei of only the surviving spermatogonia.

Significance: Under these experimental conditions, the testicular function parameters showed that radiation produced marked damage that was not reversed by treatments. However, gonadal restructuring and recovery of spermatogenesis in treated animals may to reflect attenuation of radiation-induced damages and potential start of recovery.

1. Introduction

Radiotherapy has become one of the most common treatments for cancer patients. Although this therapy has increased the number of survivors, it produces significant tissue damage, which is reflected in patient quality of life [1–3].

Previous studies have shown the impact of radiation in male fertility [4–9]. The effects on gonadal tissue are due to the cytotoxic action of radiotherapy in the seminiferous epithelium; it causes the elimination of spermatogonia in differentiation and a substantial reduction in spermatogenic cell counts in the later stages of spermatogenesis [6,7]. Male germ cells are extremely sensitive to radiation, and infertility following partial or total body irradiation has become a common problem [3,10].

As the use of radiotherapy has spread, radioprotectors have begun to receive notoriety, and many studies argue that renin-angiotensin system (RAS) inhibitors offer great potential for reducing damages caused by ionizing radiation [11–15]. The pathogenic role of the RAS in irradiated tissue has been shown through its modulation of effects. Angiotensin II and ionizing radiation mediate biological responses either directly through the generation of reactive oxygen species or indirectly through the activation of proinflammatory mediators, which induce cell dysfunction [6,16].

Interest in investigating the effect of Ang II AT1 receptor inhibitors

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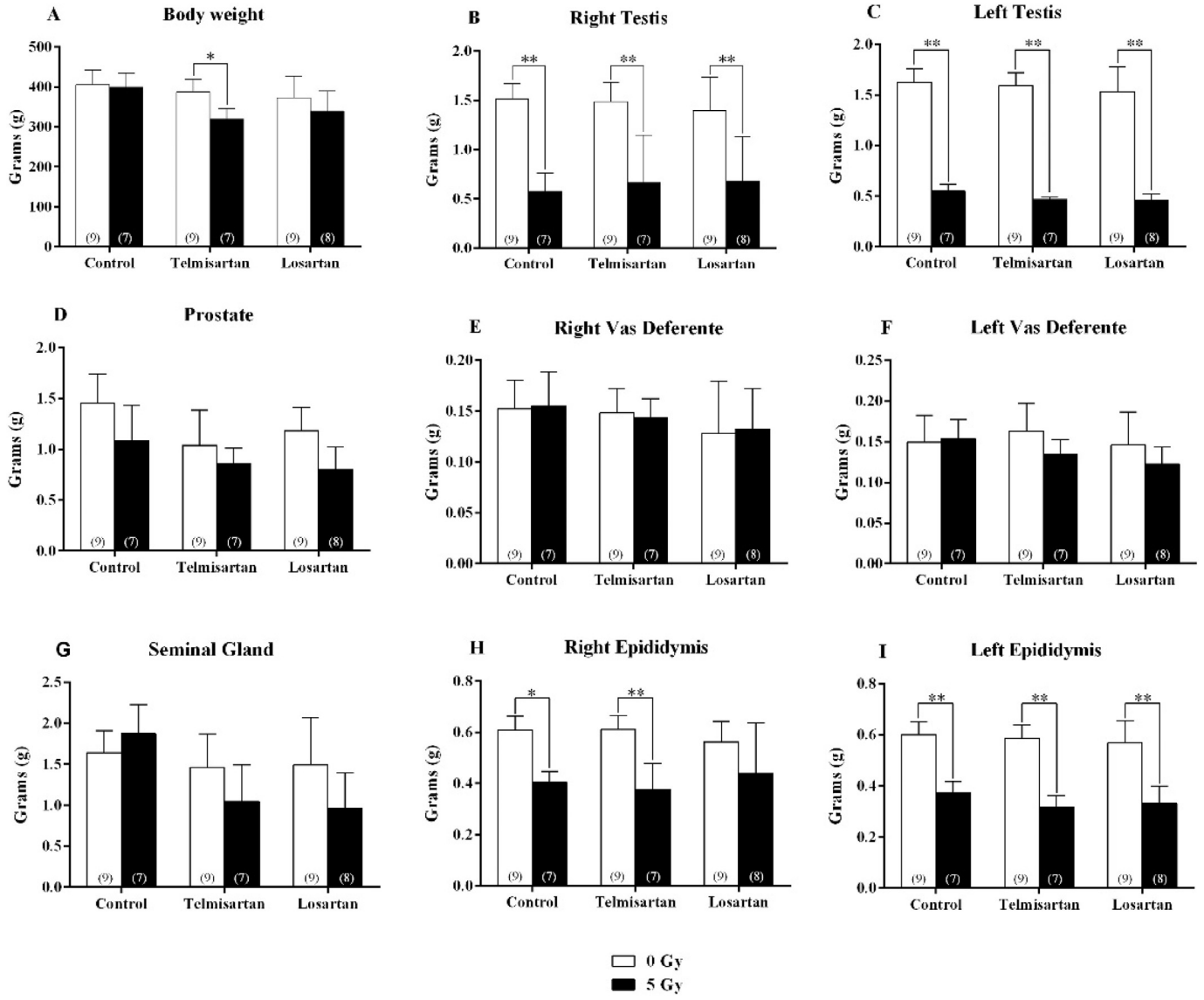

Fig. 1. Body weight and wet weight of reproductive organs in each experimental group. Values expressed as means ± SD. *$p < 0.05$, **$p < 0.001$; parametric two-way ANOVA followed by the Tukey test. In parenthesis, number of independent determinations. Group comparisons: Control vs. Group I; Group T vs. Group IT, and Group L vs. Group IL.

on irradiated reproductive tissues has increased since the potential radioprotective effect of these drugs was observed in other irradiated tissues, such as renal, cerebral, and pulmonary tissues; they were found to act against oxidative stress by blocking the formation of free radicals and reducing inflammation [17,18]. However, the role of RAS inhibitors has not been investigated in irradiated male genital organs.

Thus, the aim of this study was to investigate the histopathological and morphometric-stereological effects of ionizing radiation on the testes and sperm, as well as to evaluate whether AT1 receptor antagonists telmisartan and losartan mitigate the reproductive dysfunctions that result from this exposure.

2. Materials and methods

2.1. Animals

Fifty-one male Wistar rats 8 to 9 weeks of age were obtained from the Central Vivarium of Marília Medical School (Famema) in Marília, São Paulo State, Brazil. The animals were housed at 23 °C ± 1 °C on a 12-h light/dark cycle with free access to water and pelleted rodent chow. This study was approved by the institution's Animal Experimentation Ethics Committee (CEUA/Famema, protocol number 552/14).

2.2. Experimental groups

The rats were randomly divided into six groups: in addition to the control group ($n = 9$), Group I was irradiated ($n = 7$), Group T received treatment with telmisartan alone ($n = 9$), Group L received treatment only with losartan ($n = 9$), Group I/T was irradiated and treated with telmisartan ($n = 9$), and Group I/L was irradiated and treated with losartan ($n = 8$).

2.3. Irradiation protocol

Prior to irradiation, the rats were weighed and anesthetized using Ketamine-xylazine (70/7 mg/kg body weight, i.p.) [19] and affixed to a tray through the immobilization of their four extremities. Irradiation was delivered from a distance of 65 cm using a Clinic 6EX linear accelerator at 6MV (Varian, California, USA). A single irradiation dose of 5 Gy was administered at a dose rate of 1.05 Gy/min immediately surrounding the 5 × 5 cm scrotal field in the antero-posterior direction