Radioprotective Effects of Losartan on Testicular Damage Against Acute and Late Effects of Irradiation

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Testicular dysfunction is a common side effect of radiotherapy due to off-target damage. Germ cells are highly vulnerable, and while Sertoli and Leydig cells are more resistant, they are still affected, impairing spermatogenesis and steroidogenesis. With rising youth cancer rates, strategies to preserve fertility are crucial. Losartan (LOS) has shown potential to mitigate this damage. This work aimed to determine if radiotherapy induces acute and late alterations in testicular metabolism and if LOS can restore this function. Male Wistar rats (n=47, 12 weeks old) received 2.5 Gy of ionizing radiation to the scrotum (1.05 Gy/min; Varian Clinic 6EX). LOS-treated rats received 34 mg/kg twice daily by gavage for 7 days before, during and after irradiation. Animals were euthanized at 2 and 60 days post-exposure, to represent acute and late effects, respectively. Reproductive organs were weighed, serum hormones assessed (ELISA), sperm parameters analyzed following World Health Organization guidelines, testicular mRNA expression quantified (qPCR) and oxidative stress markers, such as lipid peroxidation, protein carbonylation, and protein nitration (slot-blot) measured. Metabolomic profiles were obtained via 1H-NMR. Acute irradiation reduced seminal vesicle weight, increased FSH, and decreased sperm concentration. Late effects included reduced testicular and epididymal weight, impaired sperm quality, increased protein carbonylation, and altered metabolic profiles. LOS mitigated acute weight loss but not sperm decline. Long-term, LOS improved sperm quality, reduced oxidative stress, and promoted adaptive metabolic responses. Irradiation-based cancer therapy causes structural and functional testicular damage and changes the testicular metabolome of rats, while LOS has the potential to be used as a radioprotector to mitigate the adverse acute and late effects of radiation on male fertility.