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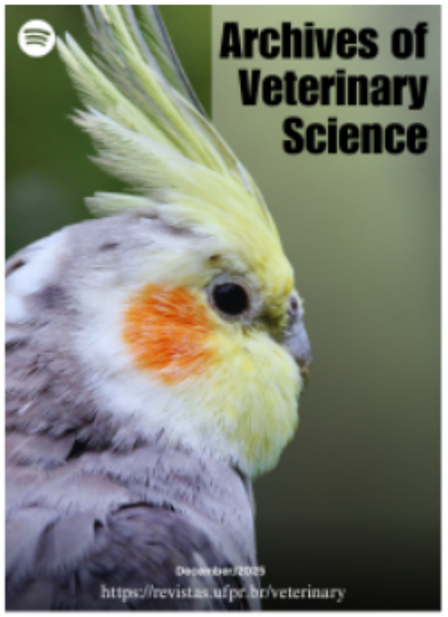

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Impact of increased expression of testicular caspase-3 in early ages of rats exposed to Ivermectin

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Abstract: Studies from our group have revealed that treatment with a therapeutic dose of ivermectin in adult rats increases the expression of caspase-3 and the number of tubules with labeled cells in the tubular lumen, thereby affecting the testicular natural homeostasis process. These effects resulted in impairments of spermatogenesis and spermiogenesis. The present study investigated whether exposure to a therapeutic dose of ivermectin at young and peripubertal ages affected spermatogenesis, spermiogenesis, and the expression of caspase-3 in the testes of rats. Methods: Wistar rats received two doses of 1.0 mg/kg IVM or 0.9% saline solution at 29 and 44 days of age. At 45 days of age, these groups were euthanized, and the rats and testicles were weighed. We conducted a macroscopic evaluation of the animals and a microscopic morphometry evaluation of the seminiferous epithelium. The testis tissue apoptosis was made using Caspase's methodology. The rat's body weight, testicular volume, relative weight, the major and minor axes, and the frequency of Leydig cells did not differ between groups. The epithelium tubular height increased in ivermectin-treated rats compared to the control group. In the IVM group, histopathological analysis revealed disorganization of the germinal epithelium, vacuolation, desquamation of cells into the tubular lumen, and cell nuclei with pyknotic aspects. Ivermectin increased the expression of caspase-3 in median and strongly labeled tubules, suggesting possible testicular damage at young and peripubertal ages in male rats.
Keywords: Avermectins; Morphometry; Testis histological analysis; Seminiferous epithelium; Apoptosis

1. Introduction

Ivermectin (IVM) is a macrocyclic lactone used to treat parasitic diseases and is widely used in veterinary medicine as an insecticide, as well as in humans to treat parasitic infections. IVM interacts with GABAergic receptors on vertebrate (mammal) neurons. However, it has a greater affinity (approximately 100 times more) for invertebrate receptors; in invertebrates, IVM also acts on glutamate receptors (Sears and Hewett 2021). Currently, three classes of GABAergic receptors are known: GABAA(Kim and Hibbs 2021), GABAB(Xie et al. 2025), and GABAC (Johnston et al. 2010). The GABA A receptor in the central nervous system is responsible for the behavioral effects producing central depression(Hu et al. 2023; Michałowski et al. 2025).

In addition, GABA and its receptors are also present in several non-neural tissues, including the endocrine organs of the pituitary, pancreas, and testis(Gajić Bojić et al. 2025). In the case of rat testis, GABA appears to be linked to the regulation of steroid synthesis by Leydig cells through GABA(A) receptors. Still, neither the testicular sources of GABA nor the precise nature of testicular GABA receptors is fully known. In male gonads and accessory reproductive organs, it was reported that GABA could mimic and potentiate the action of progesterone in initiating the acrosome reaction of mammalian sperm, indicating that sperm contain receptors for GABA(Gürsoy Gürgen et al. 2021). In this respect, the GABAA (Geigerseder et al. 2003), GABAB (He et al. 2003), and GABA C (Li et al. 2008) receptors occur in rat testis and sperm. In addition, the GABAergic system plays a modulatory role in spermiogenesis, as the expression of glutamate decarboxylase mRNAs, the enzymes responsible for GABA synthesis, has been observed in both round and elongated spermatids (Kanbara et al., 2005, 2010). Moreover, the GABAergic system has been found in adult Leydig cells in rodents and humans. These data suggest that the regulation of steroid synthesis by Leydig cells is linked via local GABAA receptors(Geigerseder et al. 2004; Hauet et al. 2005).

Cordeiro et al.(2018) showed that acute IVM therapeutic doses impair spermatogenesis and spermiogenesis in adult rats, but they have no effects on Leydig cells and testosterone levels. Despite negatively affecting the adult rat testis, evaluations of the temporal effects of the low and high therapeutic doses of IVM were reversible and correlated with the IVM plasmatic levels. More recently, these authors revealed that ivermectin treatment increased the expression of caspase-3 (labeled seminiferous tubules and strongly labeled tubules), as well as increased the number of tubules that presented labeled cells in the tubular lumen, compared to the control group (Cordeiro et al. 2023). Thus, the impairments in spermatogenesis and spermiogenesis affecting testicular homeostasis were attributed to the expressed apoptosis in cells of the seminiferous tubules of rats.

The histologic appearance in the male reproductive tract in response to exposure to several drugs and toxicants is affected by age. However, testing the testis during maturation is hampered because, in immature testis, these effects are superimposed by normal growth and development changes. In this respect, postnatal development of the rat testes can be divided into four recognized stages: neonatal (birth to postnatal day, PND 7), infantile (PND 8–20), young (PND 21–32), and peripubertal (PND 33–55). Although IVM is indicated to treat children parasitosis, it is contraindicated in children who are younger than five years old or who weigh <15 kg because the use of this type of drug during brain periods of maturation can lead to several adverse disorders(Wilkins et al. 2018; Jittamala et al. 2021). IVM exposure in the early stages of life has been shown to have several adverse effects, including acute vision changes and ataxia(Bhardwaj et al., 2023), mildly elevated creatine kinase levels, eczema flare-ups, diarrhea, vomiting, irritability, pruritus, and pustular skin reactions(Lobo and Wheller 2021), nephrotoxicity with histological damages, and ultrastructure

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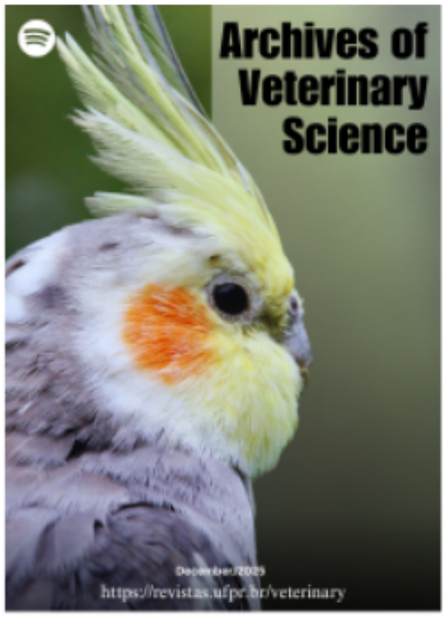

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