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A Mini Review on Reproductive Toxicity of Cyclosporine in Male Animals

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Abstract

Cyclosporine is an immunosuppressive drug that is widely used in organ transplantation and autoimmune diseases. However, its potential reproductive toxicity in male animals is not fully understood. This mini-review aims to provide an overview of the current knowledge on the reproductive toxicity of cyclosporine in male animals, focusing on its effects on spermatogenesis, sperm quality, and fertility. A literature search was conducted using PubMed, Google Scholar, and other databases to identify relevant studies. Studies have shown that cyclosporine can have various adverse effects on spermatogenesis in male animals, including decreased sperm production, impaired sperm motility, and increased sperm abnormalities. Cyclosporine can also affect sperm quality by reducing sperm concentration, viability, and DNA integrity. These effects may result in decreased fertility in male animals. The available evidence suggests that cyclosporine has reproductive toxic effects in male animals. Further research is needed to fully elucidate the mechanisms of action and to develop strategies to mitigate these effects.

Keywords: Reproduction; Toxicity; Cyclosporine; Oxidative Stress; Inflammation; Immunosuppression

Abbreviations: GnRH: Gonadotropin-Releasing Hormone; LH: Luteinizing Hormone; HPG: Hypothalamus-Pituitary-Gonadal; FSH: Follicle-Stimulating Hormone; ROS: Reactive Oxygen Species; MAPK: Mitogen-Activated Protein Kinase; STAT: Signal Transducer and Activator of Transcription.

Introduction

Cyclosporine is a potent immunosuppressive drug used to prevent rejection in organ transplantation, treat autoimmune diseases such as rheumatoid arthritis and psoriasis, and manage severe allergic reactions [1]. Its discovery revolutionized organ transplantation, significantly improving patient outcomes. However, concerns have emerged regarding cyclosporine's potential reproductive effects. This review aims to summarize the current knowledge on the reproductive effects of cyclosporine in male animals.

Evidence from Research from Animal studies has shown that cyclosporine inhibits spermatogenesis, reducing sperm count and motility [2-4]. In humans, cyclosporine therapy has been associated with azoospermia (absence of sperm) and decreased sperm quality [5,6]. Cyclosporine can disrupt the menstrual cycle, causing irregular periods or amenorrhea (absence of periods) [7]. It may also damage ovarian follicles, leading to premature ovarian failure and infertility.

Cyclosporine exerts its reproductive toxicity primarily through its effects on the hypothalamus-pituitary-gonadal (HPG) axis [4,8]. It inhibits the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which in turn suppresses the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary

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gland [4]. As a result, testosterone production by the testes is decreased [9]. In addition to its effects on the HPG axis, Cyclosporine has also been shown to directly affect testicular function [10]. It can induce apoptosis (programmed cell death) in Leydig cells, which are responsible for testosterone production Drobnis, et al. Cyclosporine can also disrupt spermatogenesis, leading to reduced sperm count and motility [4]. Cyclosporine is known to inhibit calcineurin, a key enzyme involved in immune cell signaling [11]. Calcineurin inhibition can disrupt cellular processes in the testes, leading to impaired spermatogenesis and sperm function [12].

Cyclosporine and Male Reproductive System

Cyclosporine is primarily metabolized by cytochrome P450 enzymes, particularly CYP3A4, in the liver [13]. The main metabolite is M17 (AMO1), which is further metabolized to M21 (AMO2) [13]. Both M17 and M21 have immunosuppressive activity, but to a lesser extent than cyclosporine. Studies have shown that cyclosporine and its metabolites distribute to various tissues and organs, including the male reproductive system [3,14]. In the testes, cyclosporine concentrates in the seminiferous tubules, where spermatogenesis occurs [15]. It also accumulates in the epididymis and seminal vesicles.

Cyclosporine has been shown to inhibit spermatogenesis, the process of sperm production. Studies have demonstrated a dose-dependent decrease in sperm count and seminiferous tubule diameter in men treated with cyclosporine [16,17]. This inhibition is believed to occur through various mechanisms, including: Inhibition of testosterone synthesis, Induction of oxidative stress, and Alteration of Sertoli cell function [4]. In addition to impaired spermatogenesis, cyclosporine can also affect sperm morphology and motility [4]. Although, Men treated with cyclosporine have been found not to have an incidence of abnormal sperm quality [18].

Cyclosporine inhibits the synthesis of testosterone by Leydig cells [19,20]. This effect is dose-dependent, with higher doses leading to more pronounced suppression. The reduced testosterone levels can result in hypogonadism, a condition characterized by low testosterone levels and its associated symptoms, such as decreased libido, erectile dysfunction, and infertility [4,21]. Cyclosporine disrupts the steroidogenesis pathway in Leydig cells, which is responsible for the synthesis of testosterone [3,10]. It inhibits the activity of enzymes involved in the production of precursors to testosterone, such as cholesterol and pregnenolone [4]. This disruption leads to a decline in testosterone production and an accumulation of intermediates in the steroidogenesis pathway. In addition to reducing testosterone production and impairing steroidogenesis, cyclosporine has been associated with other effects on Leydig cells, including: Decreased cell viability, Alterations in gene expression and Reduced responsiveness to luteinizing hormone (LH), the hormone that stimulates testosterone production.

Animal Studies on Cyclosporine's Reproductive Toxicity

Studies in rats and mice have demonstrated that cyclosporine administration leads to dose-dependent alterations in spermatogenesis [4,10,22,23]. High doses of cyclosporine (e.g., 50-100 mg/kg/day) result in significant reductions in sperm count, motility, and normal morphology [24,25]. These effects are attributed to cyclosporine's inhibition of spermatid maturation and Sertoli cell function. Animal studies have also explored the impact of cyclosporine on fertility and reproductive parameters [3]. Administration of cyclosporine has been shown to decrease fertility rates in male rodents Oyovwi, et al. [26,27]. This is associated with impaired sperm quality and reduced sperm transport. Additionally, cyclosporine can alter hormone levels (e.g., testosterone, luteinizing hormone) involved in reproductive function [28-30]. Beyond its effects on spermatogenesis and fertility, cyclosporine has been linked to other reproductive abnormalities in rodents. These include testicular atrophy, decreased libido, and alterations in epididymal sperm maturation [4]. The mechanisms underlying these effects are not fully understood but may involve oxidative stress, inflammation, impaired androgenic hormones and enzymes and immune dysregulation [3,4,31].

Mechanism of Cyclosporine-Induced reproductive Toxicity

Immunosuppressive Effects

Cyclosporine primarily targets T lymphocytes, inhibiting their activation and proliferation [32]. This immunosuppressive action can disrupt the immune tolerance required for successful reproduction. It may impair the development of regulatory immune cells, leading to an imbalance between pro- and anti-inflammatory responses. Notably, Cyclosporine exerts its immunosuppressive action by inhibiting calcineurin, a phosphatase that plays a crucial role in T-cell activation [33-36]. By blocking calcineurin, cyclosporine suppresses the production of interleukin-2 (IL-2), a cytokine essential for T-cell proliferation and differentiation [37]. This immunosuppressive effect has implications for reproductive function.

Oxidative Stress

Oxidative stress occurs when the production of reactive oxygen species (ROS) exceeds the body's antioxidant

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defenses. Cyclosporine increases the production of reactive oxygen species (ROS) in the reproductive organs [38,39]. Cyclosporine can impair mitochondrial function, leading to increased ROS production [40,41]. Cyclosporine activates NADPH oxidase, an enzyme that generates ROS in immune cells [42,43]. Excessive ROS can damage cellular components, including DNA, proteins, and lipids [44]. This oxidative stress can impair gamete function, embryo development, and placental integrity [45,46]. Cyclosporine can reduce the activity of antioxidant enzymes, such as glutathione peroxidase and superoxide dismutase, making cells more susceptible to oxidative damage [4,47]. Oxidative stress can damage sperm, oocytes, and reproductive tissues [4]. In male rats, cyclosporine-induced oxidative stress has been associated with decreased sperm motility, morphology, and viability [4].

Inflammatory Responses

Cyclosporine triggers inflammatory responses by activating pro-inflammatory cytokines and suppressing anti-inflammatory mediators [48]. Chronic inflammation in the reproductive organs can damage tissues, disrupt hormonal balance, and inhibit reproductive processes [49]. Cyclosporine inhibits the nuclear factor kappa B (NF-κB), a transcription factor that regulates the expression of pro-inflammatory cytokines [50,51]. By inhibiting NF-κB, cyclosporine promotes the release of inflammatory mediators. Cyclosporine activates mitogen-activated protein kinase (MAPK) pathways, which are involved in the production of inflammatory cytokines and chemokines [51]. Cyclosporine also activates signal transducer and activator of transcription (STAT) proteins, which regulate the expression of genes involved in inflammation and immune responses [52]. Cyclosporine treatment increases the levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interferon-gamma (IFN-γ) [53]. Cyclosporine also stimulates the production of chemokines, which attract immune cells to the site of inflammation [54]. Cyclosporine-induced inflammation is associated with increased production of ROS, which can damage cellular components and contribute to oxidative stress [4]. Cyclosporine-induced inflammation leads to testicular damage, including germ cell apoptosis, Leydig cell dysfunction, and impaired spermatogenesis [4]. Cyclosporine has been linked to ovarian toxicity, including follicular atresia, disruption of ovulation, and reduced fertility [55]. More so, Cyclosporine treatment can cause endometrial inflammation, which may interfere with implantation and pregnancy maintenance [56].

Hormonal Imbalances

Cyclosporine can interfere with the hypothalamic-pituitary-gonadal axis, leading to hormonal imbalances [4]. It may suppress the release of gonadotropins (LH and FSH), which are essential for fertility [3]. Additionally, it can alter the production of sex hormones (estrogen, progesterone, and testosterone), affecting fertility [3,57]. In male rats, cyclosporine has been shown to inhibit the synthesis of testosterone by Leydig cells in the testes [16]. This leads to decreased serum testosterone levels, resulting in impaired spermatogenesis and reduced sperm counts [3,4]. Cyclosporine can affect the pituitary-gonadal axis, which regulates hormone production [58,59]. It has been found to inhibit the hypothalamic hypophyseal gonadal axis in transplant patients Watkins PB, et al. [60] which may alter the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, leading to decreased LH and FSH secretion from the pituitary gland. This disruption of the axis further contributes to gonadal hormone imbalances. Cyclosporine has been shown to interfere with steroidogenesis, the process of hormone production in the gonads [3]. It inhibits the activity of key enzymes involved in steroid synthesis, such as cytochrome P450 enzymes [61]. This impairment can lead to decreased production of testosterone, estrogen, and other sex hormones. Cyclosporine's immunosuppressive effects can also contribute to reproductive toxicity [4]. It suppresses the immune system, which can lead to inflammation and damage to reproductive tissues. This inflammation can disrupt hormone production and impair fertility [56]. In addition to hormonal imbalances, cyclosporine has been linked to other mechanisms of reproductive toxicity, such as oxidative stress, mitochondrial dysfunction, and changes in gene expression [62-64]. These mechanisms can further contribute to impaired spermatogenesis, oogenesis, and fertility.

Mitochondrial Dysfunction

Mitochondria are the energy powerhouses of cells and play a crucial role in spermatogenesis. Cyclosporine has been shown to impair mitochondrial function in reproductive tissues [63]. Mitochondria are responsible for energy production and play a crucial role in gamete maturation, fertilization, and embryo development [65]. Mitochondrial dysfunction can lead to reduced ATP levels, and oxidative stress .ATP depletion and oxidative stress impair sperm maturation and motility. Mitochondrial damage triggers apoptotic pathways in developing sperm. Oxidative stress damages sperm DNA, compromising fertility.

Conclusion

Cyclosporine exhibits reproductive toxicity in male animals, primarily affecting testicular function, sexual behavior, and the prostate gland. These effects are likely mediated by the inhibition of steroidogenesis, alterations in hormonal balance, and oxidative stress. Further research is

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needed to fully understand the mechanisms of cyclosporine's reproductive toxicity and to develop strategies to mitigate its adverse effects.

Ethical Clearance Statement

This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all authors included in the study.

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Author Contribution

Oyovwi Mega Obukohwo participated in sorting and conceptualizing the manuscript and wrote the manuscript. Oyovwi Mega Obukohwo Tang organized the literature and presented ideas. Oyovwi Mega Obukohwo read and approved the submitted version. Oyovwi Mega Obukohwo is responsible for the contribution. The author contributed to the revision of the manuscript, read and approved the submitted version.

CRediT Authorship Contribution Statement

Oyovwi Mega Obukohwo: Resources. Oyovwi Mega Obukohwo: Investigation. Oyovwi Mega Obukohwo: Writing – review & editing. Oyovwi Mega Obukohwo: Writing – review & editing. Oyovwi Mega Obukohwo: Writing – original draft. Oyovwi Mega Obukohwo: Writing – original draft Oyovwi Mega Obukohwo: Writing – review & editing.

Declaration of Competing Interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability

No data was used for the research described in the article.

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